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(54) Title: COMBINATION THERAPY OF A PATIENT SUBGROUP

(57) Abstract: This disclosure relates to methods of treating a defined subgroup of subjects having neoplastic disorders with a combination of an AXL-kinase inhibitor and an immune- regulatory agent. The disclosure also relates to the inhibitors and agents for use in such methods, as well as further methods for identifying and selecting subjects suitable for treatment.



COMBINATION THERAPY OF A PATIENT SUBGROUP

EARLIER APPLICATION

This application claims priority from United Kingdom application GB1912059.1 filed on 22 August 2019.

FIELD

This disclosure relates to methods of treating a defined subgroup of subjects having neoplastic disorders with a combination of an AXL-kinase inhibitor and an immune-regulatory agent. The disclosure also relates to the inhibitors and agents for use in such methods, as well as further methods for identifying and selecting subjects suitable for treatment.

BACKGROUND

AXL

All of the protein kinases that have been identified to date in the human genome share a highly conserved catalytic domain of around 300 amino acids. This domain folds into a bi-lobed structure in which resides ATP-binding and catalytic sites. The complexity of protein kinase regulation allows many potential mechanisms of inhibition including competition with activating ligands, modulation of positive and negative regulators, interference with protein dimerization, and allosteric or competitive inhibition at the substrate or ATP binding sites.

AXL (also known as UFO, ARK, and Tyro7; nucleotide accession numbers NM_021913 and NM_001699; protein accession numbers NP_068713 and NP_001690) is a receptor protein tyrosine kinase (RTK) that comprises a C-terminal extracellular ligand binding domain and N-terminal cytoplasmic region containing the catalytic domain. The extracellular domain of AXL has a unique structure that juxtaposes immunoglobulin and fibronectin Type III repeats and is reminiscent of the structure of neural cell adhesion molecules. AXL and its two close relatives, Mer /Nyk and Sky (Tyro3 / Rse / Dtk), collectively known as the Tyro3 family of RTK's, all bind and are stimulated to varying degrees by the same ligand, GAS6 (growth arrest specific-6), a ~76kDa secreted protein with significant homology to the coagulation cascade regulator, Protein S. In addition to binding to ligands, the AXL extracellular domain has been shown to undergo homophilic interactions that mediate cell aggregation, suggesting that one important function of AXL may be to mediate cell-cell adhesion.

AXL is predominantly expressed in the vasculature in both endothelial cells (EC's) and vascular smooth muscle cells (VSMC's) and in cells of the myeloid lineage and is also detected in breast epithelial cells, chondrocytes, Sertoli cells and neurons. Several functions including protection from apoptosis induced by serum starvation, TNF- α or the viral protein E1A, as well as migration and cell differentiation have been ascribed to AXL signalling in cell culture. However, *Axl*^{-/-} mice exhibit no overt developmental phenotype and the physiological function of AXL in vivo is not clearly established in the literature.

AXL pathology

The overexpression of AXL and/or its ligand has also been reported in a wide variety of solid tumor types including, but not limited to, breast, renal, endometrial, ovarian, thyroid, non-small cell lung carcinoma, and uveal melanoma as well as in myeloid leukemias. Furthermore, it possesses transforming activity in NIH3T3 and 32D cells. It has been demonstrated that loss of Axl expression in tumor cells blocks the growth of solid human neoplasms in an *in vivo* MDA-MB-231 breast carcinoma xenograft model. Taken together, these data suggest AXL signalling can independently regulate EC angiogenesis and tumor growth and thus represents a novel target class for tumor therapeutic development.

The expression of AXL and GAS6 proteins is upregulated in a variety of other disease states including endometriosis, vascular injury and kidney disease and AXL signalling is functionally implicated in the latter two indications. AXL-GAS6 signalling amplifies platelet responses and is implicated in thrombus formation. AXL may thus potentially represent a therapeutic target for a number of diverse pathological conditions including solid tumors, including, but not limited to, breast, renal, endometrial, ovarian, thyroid, non-small cell lung carcinoma and uveal melanoma; liquid tumors, including but not limited to, leukemias (particularly myeloid leukemias) and lymphomas; endometriosis, vascular disease / injury (including but not limited to restenosis, atherosclerosis and thrombosis), psoriasis; visual impairment due to macular degeneration; diabetic retinopathy and retinopathy of prematurity; kidney disease (including but not limited to glomerulonephritis, diabetic nephropathy and renal transplant rejection), rheumatoid arthritis; osteoporosis, osteoarthritis and cataracts.

AXL inhibitors

In view of the role played by AXL in numerous pathological conditions, the development of safe and effective AXL inhibitors has been a topic of interest in recent years. Different groups of AXL inhibitors are discussed in, *inter alia*, US20070213375, US 20080153815, US20080188454, US20080176847, US20080188455, US20080182862, US20080188474, US20080117789, US20090111816, WO2007/0030680, WO2008/045978, WO2008/083353, WO2008/0083357, WO2008/083354, WO2008/083356, WO2008/080134, WO2009/054864, and WO/2008/083367.

Combination therapies using AXL inhibitors

The combination of one or more of the above cited AXL inhibitors with one or more other agents is discussed in, for example, WO/2010/083465 and WO/2016/193680, with WO/2016/193680 focussing on combinations of AXL inhibitors with agent having immune-regulatory or modulatory activity. In many cases it is possible to hypothesise about the possible therapeutic advantages that may accompany the use of such combinations.

The complexity of tumour biology and its interaction with the immune system, along with the potential for serious side-effects inherent in such powerful therapies, means that research is ongoing to identify the specific disorders and/or subjects that will benefit most from treatment.

SUMMARY

Through studying the cellular mechanisms and processes through which neoplastic disorders acquire resistance to anti-proliferative drugs, the present authors have determined that AXL signalling plays a vital role in allowing neoplastic cells to enter a drug-tolerant state that appears to precede the emergence of permanent drug resistance through manifestation of genetic resistance mechanisms (a so-called 'persister cell phenotype'). Further investigation of this AXL -signalling supported drug-tolerant state indicated a cyto-protective AXL -dependent autophagy-related mechanism that supports a robust drug-tolerant state from which permanent resistance can emerge.

A key observation was that abrogation of this cyto-protective autophagic flux by the use of AXL inhibitors resulted in a switch in the persister cells' immune profile by, for example, promoting the release of Damage-Associated Molecular Pattern molecules (DAMPs) such as HMGB1 and ATP, and the cell-surface translocation of calreticulin. This switch in immune profile is in turn expected to increase the immunogenicity of the tumor cells, particularly by increasing the adjuvanticity, which will aid in the recruitment of antigen-presenting dendritic cells and immune effector cells to the tumor site. This is the first step of the cancer-immunity cycle bridging the innate and adaptive arms of the immune system. Accordingly, the use of AXL -inhibitors in subjects having neoplastic disorders characterized by the presence of cells having the persister cell phenotype should lead to increased activation of both the innate and adaptive arms of the immune system by stimulating the cancer immunity cycle.

Based on their observations, the authors reasoned that any stimulation of the immune system caused by the treatment of neoplastic persister cells with AXL inhibitors could be potentiated by administering the AXL inhibitor in combination with an immune regulatory agent (IR) – for example, an immune checkpoint inhibitor (ICI) – that increases the sensitivity of the immune system to stimulation and/or amplifies the strength of the resulting immune response.

Accordingly, in a first aspect the present disclosure provides a method for treating a neoplastic disorder in a subject with a combination of an AXLi and an IR, the method comprising:

- (i) administering a combination of an AXLi and an IR to the subject;
 - (ii) administering an AXLi to the subject, wherein an IR has been, is, or will be, administered to the subject; or
 - (iii) administering an IR to the subject, wherein an AXLi has been, is, or will be, administered to the subject;
- wherein the neoplastic disorder is characterized by the presence of cells having a persister-cell phenotype.

The cells having a persister-cell phenotype have increased AXL -signalling, CD44 expression, autophagic flux, or resistance to staurosporine-induced apoptosis as compared to a control. The cells may have decreased expression of spry1, spry2, spry4, pPLCg, pSTAT5, EGFR, and/or pEGFR as compared to a control.

The cells having a persister-cell phenotype may exhibit a cobblestone-to-spindle morphological switch. The cells may comprise a receptor-activating mutation; for example, an EGFR-activating mutation such as an in-frame deletion in exon 19 deleting L747 to E749, or a L858R substitution. The cells may not comprise an anti-proliferative agent resistance mutation in a receptor; for example an EGFR-inhibitor resistance mutation such as a T790M substitution or a D761Y substitution.

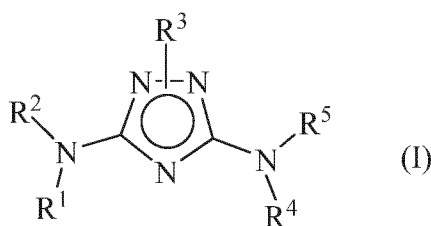
The cells having a persister-cell phenotype may be neoplastic cells, such as cancer cells.

The neoplastic disorder may be cancer. For example, lung cancer such as NSCLC. The neoplastic disorder may be a solid tumour.

The neoplastic disorder may be resistant to treatment with an anti-proliferative agent. For example, resistant to an EGFR inhibitor such as erlotinib.

The AXLi and/or IR may be administered in further combination with an anti-proliferative agent. The agent may be an agent to which the neoplastic disorder is resistant to. The AXLi and/or IR may be administered in further combination with a chemotherapeutic agent and/or radiation.

The AXLi may be a compound of formula (I): as described in more detail elsewhere herein.



The AXLi may be bemcentinib. The AXLi may also be an antibody; for example, an antibody comprising the 6 CDRs having the sequences of SEQ ID Nos. 1 to 6, or the 6 CDRs having the sequences of SEQ ID Nos. 7 to 12.

The IR may be an immune checkpoint inhibitor (ICI), or a T-cell co-stimulatory agonist. For example, the IR may be selected from the group consisting of: anti-CTLA-4 antibodies, anti-PD-1 antibodies, anti-PD-L1 antibodies, anti-4-1BB antibodies, anti-OX-40 antibodies, anti-GITR antibodies, anti-CD27 antibodies, anti-CD28 antibodies, anti-CD40 antibodies, anti-LAG3 antibodies, anti-ICOS antibodies, anti-TWEAKR antibodies, anti-HVEM antibodies, anti-TIM-1 antibodies, anti-TIM-3 antibodies, anti-VISTA antibodies, and anti-TIGIT antibodies.

The anti-proliferative agent may be a receptor signalling inhibitor; for example, an EGFR inhibitor such Gefitinib, Erlotinib, osimertinib, Lapatinib, Brigatinib, rociletinib, olmutinib, nazartinib, naquotinib, and mavelertinib.

In a second aspect the present disclosure provides a method for identifying a subject having a neoplastic disorder characterized by the presence of cells having a persister-cell phenotype, the method comprising the steps of (i) determining whether the cells, disorder, and/or subject are as defined as described above for the first aspect, and (ii) identifying the subject as having a neoplastic disorder characterized by the presence of cells having a persister-cell phenotype if the cells, disorder, and/or subject are as defined as described above for the first aspect.

In a third aspect, the present disclosure provides a method for diagnosing a subject having a neoplastic disorder characterized by the presence of cells having a persister-cell phenotype, the method comprising the step of: (i) identifying a subject as described in the second aspect; and (ii) diagnosing the subject as having a neoplastic disorder characterized by the presence of cells having a persister-cell phenotype identified.

In a fourth aspect, the present disclosure provides the method as described in the first aspect wherein: (i) the subject has been identified by a method according to second aspect; or (ii) the subject has been diagnosed by a method according to the third aspect.

In a fifth aspect, the present disclosure provides a method as described in the first aspect, wherein the treatment comprises the step of: (i) identifying the subject according to a method of the second aspect; or (ii) diagnosing the subject according to a method of the third aspect.

In a sixth aspect, the disclosure provides an AXLi, IR, or combination thereof, or a composition comprising an AXLi, IR, or combination thereof, for use in a method of treatment according to the first, fourth, or fifth aspects.

Also included in the sixth aspect is the use of an AXLi, IR, or combination thereof in the manufacture of a medicament for treating a disorder in a subject, wherein the treatment comprises the method of treatment of the first, fourth, or fifth aspects.

DETAILED DESCRIPTION

The present authors have studied the cellular mechanisms and processes through which neoplastic disorders acquire resistance to anti-proliferative drugs. They have demonstrated the existence of a cyto-protective AXL -dependent autophagy-related mechanism that supports a robust drug-tolerant state from which permanent resistance can emerge. Investigation of this drug-tolerant 'persister phenotype' revealed that treatment with AXL inhibitors resulted in a switch to a more antigenic profile, with the release of DAMPs and other molecules having adjuvant activity. Building on these observations, the authors reasoned that the stimulation of the immune system by this adjuvant activity would be potentiated by administering the AXL inhibitor in combination with an immune regulatory agent – for example, an immune checkpoint inhibitor – that increases the sensitivity of the immune system to stimulation and/or amplifies the strength of the resulting immune response.

Accordingly, in a first aspect the present disclosure provides a method for treating a neoplastic disorder in a subject with a combination of an AXLi and an IR, the method comprising: administering a combination of an AXLi and an IR to the subject; administering an AXLi to the subject, wherein an IR has been, is, or will be, administered to the subject; or administering an IR to the subject, wherein an AXLi has been, is, or will be, administered to the subject; wherein the neoplastic disorder is characterized by the presence of cells having a persister-cell phenotype.

Persister cell phenotype

In some embodiments the cells having a persister-cell phenotype have increased AXL -signalling as compared to a control. The increased AXL -signalling may be characterized by – for example – increased AXL expression, increased AXL phosphorylation (ie. phosphoAXL expression), and/or increased Akt phosphorylation. In some cases, any non-negligible expression of phosphoAXL is indicative of a persister-cell phenotype. That is, in some embodiments the cells having a persister-cell phenotype express phosphoAXL.

In some embodiments the cells having a persister-cell phenotype have increased CD44 expression as compared to a control. In some cases, any non-negligible expression of CD44 is indicative of a persister-cell phenotype. That is, in some embodiments the cells having a persister-cell phenotype express CD44.

In some embodiments the cells having a persister-cell phenotype have decreased expression of pPLCg and/or pSTAT5 as compared to a control. In some embodiments the cells having a persister-cell phenotype have decreased expression of pPLCg, pSTAT5, EGFR, and/or pEGFR as compared to a control. In some cases cells having a persister-cell phenotype do not express pPLCg, pSTAT5, EGFR, and/or pEGFR. In some cases cells having a persister-cell phenotype do not express pPLCg or pSTAT5.

In some embodiments the cells having a persister-cell phenotype have decreased expression of *spry1*, *spry2*, and/or *spry4* as compared to a control.

In some embodiments the cells having a persister-cell phenotype have increased autophagic flux as compared to a control. This may be measured by, for example, the CYTO-ID assay described herein. In some cases the increased autophagic flux is indicated by increased expression of LC3A/B. In some cases the increased autophagic flux is indicated by increased expression levels of membrane-bound LC3-II assessed, for example, by the methods described herein.

In some embodiments the cells having a persister-cell phenotype are characterised by enrichment of genes associated with established autophagy gene expression signatures downloaded from GSEA Molecular signature database v6.1 (see Subramanian A. et al., PNAS 2005;102:15545-50 ; Kumar D. et al., Cell 2010;140:731-43), the Autophagy database (see Homma K. et al., Nucleic Acids Res 2011;39:D986-90), and HADb (last accessed: 2019 Apr 22; <http://autophagy.lu/index.html>). The enrichment scores may be calculated by Bioconductor (see Hanzelmann S., et al., BMC Bioinformatics 2013;14:7).

In some embodiments the cells having a persister-cell phenotype exhibit a cobblestone-to-spindle morphological switch.

In some embodiments the cells having a persister-cell phenotype have increased resistance to staurosporine induced apoptosis as compared to a control. In some embodiments the increased resistance to staurosporine induced apoptosis is indicated by decreased luminescence in luminescence-based caspase 3/7 assay described herein. For example, a luminescence below 20,000 units when exposed to 1 μ M staurosporine and measured as described in Example 3 herein. In some embodiments the increased resistance to staurosporine induced apoptosis is indicated by decreased expression of by Western blot of cleaved caspase 3, cleaved caspase 8, and/or cleaved PARP.

Typically, the cells having a persister-cell phenotype are neoplastic cells, such as cancer cells.

Suitable controls are discussed in more detail in the dedicated section elsewhere herein.

Typically, the term “increased” as used herein is used to denote a significant increase in the stated parameter, with significant meaning $P \leq 0.05$ as calculated by the methods set out in the “Statistics” section herein. In some embodiments $P \leq 0.01$ is used as the significance threshold. In other embodiments $P \leq 0.001$ is used as the significance threshold. With reference to gene expression, in preferred embodiments, (phospho)protein expression levels are quantified using the technique described herein in the “Western blotting” section of the materials & methods.

Receptor-activating mutations

In some embodiments the cells having a persister-cell phenotype comprise a receptor-activating mutation.

In some cases, the receptor-activating mutation is an EGFR-activating mutation, such as an EGFR-activating mutation is a mutation in the EGFR tyrosine-kinase domain. The EGFR-activating mutation may be one or more of:

- (i) an in-frame deletion in exon 19, optionally wherein L747 to E749 are deleted;
- (ii) a L858R substitution;
- (iii) a G719S/A/C substitution;
- (iv) a V765A substitution;
- (v) a T783A substitution;
- (vi) a C797S substitution; or
- (vii) an in-frame duplication and/or insertion in exon 20.

In some embodiments the cells having a persister-cell phenotype do not comprise an anti-proliferative agent resistance mutation in a receptor. In some cases, the cells having a persister-cell phenotype do not comprise an anti-proliferative agent resistance mutation in EGFR, such as a T790M substitution and/or a D761Y substitution.

Neoplastic disorders

In some embodiments, the neoplastic disorder is cancer. The cancer may be selected from the group consisting of: histiocytoma, glioma, astrocytoma, osteoma, lung cancer, small-cell lung cancer, non-small-cell lung cancer, gastrointestinal cancer, bowel cancer, colon cancer, breast carcinoma, ovarian carcinoma, prostate cancer, testicular cancer, liver cancer, kidney cancer, bladder cancer, pancreas cancer, brain cancer, sarcoma, osteosarcoma, Kaposi's sarcoma, melanoma, lymphomas, and leukemias.

In preferred embodiments the cancer lung cancer. NSCLC is particularly preferred.

In some embodiments the cancer is a solid tumour. Typically, the solid tumour comprises the cells having persister-cell phenotype. In some cases the solid tumour also comprises cells not having a persister-cell phenotype.

Typically, the neoplastic disorder is resistant to treatment with an anti-proliferative agent.

In some embodiments, a neoplastic disorder is considered resistant to an anti-proliferative agent if administration of the agent at normal therapeutic dosing levels does not significantly reduce tumour growth.

In some embodiments, a neoplastic disorder is considered resistant to an anti-proliferative agent when relapse from treatment with the anti-proliferative agent is observed. For example, typically initial treatment with an anti-proliferative agent leads to a degree of disease regression. For example, the reduction in size of solid tumours. In some cases, relapse is considered to have occurred when tumour growth resumes despite continued treatment with the anti-proliferative agent.

Pattern of AXLi and IR administration

The advantage of the combined treatment is achieved when the increased tumour immunogenicity resulting from administration of the AXLi stimulates an immune system activated by and IR. Accordingly, since it can be envisioned that each individual agent may (1) require some time before its full level of inhibition/activation is achieved, and/or (2) persist in the subject for a time depending upon the pharmacokinetics of agent and subject, it may not be strictly required to administer the AXLi and IR to the subject simultaneously in order to achieve the enhanced efficacy discussed herein.

Thus, in some embodiments the AXLi and IR are administered concurrently. In other embodiments the AXLi and IR are administered separately and/or sequentially. In embodiments where the AXLi and IR are not administered concurrently, typically the AXLi and IR are administered to the subject no more than 3 weeks apart, such as no more than 1 week apart, no more than 48 hours apart, or no more than 24 hours apart.

Similarly, in embodiments where only one agent is administered as part of the described method (ie. methods involving administering an AXLi to the subject wherein an IR has been or will be administered to the subject, or administering an IR to the subject wherein an AXLi has been or will be administered to the subject) the method typically involves administering the AXLi (or IR) to the subject no more than 3 weeks before/after the IR (or AXLi) has been or will be administered, such as no more than 1 week before/after, no more than 48 hours before/after, or no more than 24 hours before/after.

Further combination with an anti-proliferative agent

A further anti-proliferative agent may be administered in combination with the AXLi and/or IR. In particular, it is envisioned that in embodiments where the neoplastic disorder is resistant to treatment with an anti-proliferative agent, it may be preferable to continue treating the subject with the same anti-proliferative agent. This is in order to maintain the persister cell phenotype which has developed and so maintain the tumour-adjuvant effects of administering the AXLi.

In some embodiments the anti-proliferative agent is administered concurrently with the AXLi and/or IR. In other embodiments the anti-proliferative agent is administered separately and/or sequentially to the AXLi and/or IR.

In some embodiments the treatment further comprises administering a chemotherapeutic agent and/or radiation, optionally wherein the radiation is ionizing radiation. Such additional treatments are known to further increase the tumour-immunogenicity by causing localised tumour cell death and the release of tumour antigens.

In some embodiments the subject has been, is being, or will be treated with an anti-proliferative agent. For example, in some cases the subject has been treated with an anti-proliferative agent no more than 3 months before treatment with the AXLi and IR

combination, such as no more than 1 month before treatment with the AXLi and IR combination.

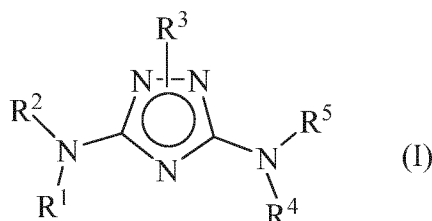
In some embodiments the subject responds to the treatment with by reaching an improved clinical outcome as compared to an otherwise comparable subject whose neoplastic disorder is not characterized by the presence of cells having a persister-cell phenotype. In some embodiments the comparison is between a group of subjects treated according to the present methods and a group of otherwise comparable subjects whose neoplastic disorders are not characterized by the presence of cells having a persister-cell phenotype. In some cases the improved clinical outcome is progression free survival (PFS), overall survival (OS) and/or event free survival (EFS).

AXL inhibitors (AXLi)

Small molecule AXL inhibitors

General formula

In some embodiments the AXL inhibitor is a compound of formula (I):



wherein:

R¹, R⁴ and R⁵ are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, aralkyl, -C(O)R⁸, -C(O)N(R⁶)R⁷, and -C(=NR⁶)N(R⁶)R⁷;

R² and R³ are each independently a polycyclic heteroaryl containing more than 14 ring atoms optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, -R⁹-OR⁸, -R⁹-O-R¹⁰-OR⁸, -R⁹-O-R¹⁰-O-R¹⁰-OR⁸, -R⁹-O-R¹⁰-CN, -R⁹-O-R¹⁰-C(O)OR⁸, -R⁹-O-R¹⁰-C(O)N(R⁶)R⁷, -R⁹-O-R¹⁰-S(O)_pR⁸ (where p is 0, 1 or 2), -R⁹-O-R¹⁰-N(R⁶)R⁷, -R⁹-O-R¹⁰-C(NR¹¹)N(R¹¹)H, -R⁹-OC(O)-R⁸, -R⁹-N(R⁶)R⁷, -R⁹-C(O)R⁸, -R⁹-C(O)OR⁸, -R⁹-C(O)N(R⁶)R⁷, -R⁹-N(R⁶)C(O)OR⁸, -R⁹-N(R⁶)C(O)R⁸, -R⁹-N(R⁶)S(O)_tR⁸ (where t is 1 or 2), -R⁹-S(O)_tOR⁸ (where t is 1 or 2), -R⁹-S(O)_pR⁸ (where p is 0, 1 or 2), and -R⁹-S(O)_tN(R⁶)R⁷ (where t is 1 or 2);

or R² is a polycyclic heteroaryl containing more than 14 ring atoms as described above and R³ is selected from the group consisting of aryl and heteroaryl, where the aryl and the heteroaryl are each independently optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted

heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, $-R^{13}-OR^{12}$, $-R^{13}-OC(O)-R^{12}$, $-R^{13}-O-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)OR^{12}$, $-R^{13}-C(O)N(R^{12})_2$, $-R^{13}-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}$, $-R^{13}-C(O)N(R^{12})-R^{14}-OR^{12}$, $-R^{13}-N(R^{12})C(O)OR^{12}$, $-R^{13}-N(R^{12})C(O)R^{12}$, $-R^{13}-N(R^{12})S(O)_tR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_tOR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_pR^{12}$ (where p is 0, 1 or 2), and $-R^{13}-S(O)_tN(R^{12})_2$ (where t is 1 or 2);

or R^3 is a polycyclic heteroaryl containing more than 14 ring atoms as described above, and R^2 is selected from the group consisting of aryl and heteroaryl, where the aryl and the heteroaryl are each independently optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, $-R^{13}-OR^{12}$, $-R^{13}-OC(O)-R^{12}$, $-R^{13}-O-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)OR^{12}$, $-R^{13}-C(O)N(R^{12})_2$, $-R^{13}-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}$, $-R^{13}-C(O)N(R^{12})-R^{14}-OR^{12}$, $-R^{13}-N(R^{12})C(O)OR^{12}$, $-R^{13}-N(R^{12})C(O)R^{12}$, $-R^{13}-N(R^{12})S(O)_tR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_tOR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_pR^{12}$ (where p is 0, 1 or 2), and $-R^{13}-S(O)_tN(R^{12})_2$ (where t is 1 or 2);

each R^6 and R^7 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, hydroxyalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, $-R^{10}-OR^8$, $-R^{10}-CN$, $-R^{10}-NO_2$, $-R^{10}-N(R^8)_2$, $-R^{10}-C(O)OR^8$ and $-R^{10}-C(O)N(R^8)_2$, or any R^6 and R^7 , together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heteroaryl or an optionally substituted *N*-heterocyclyl;

each R^8 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, and optionally substituted heteroarylalkynyl;

each R^9 is independently selected from the group consisting of a direct bond, an optionally substituted straight or branched alkylene chain, an optionally substituted straight or branched alkenylene chain and an optionally substituted straight or branched alkynylene

chain;

each R^{10} is independently selected from the group consisting of an optionally substituted straight or branched alkylene chain, an optionally substituted straight or branched alkenylene chain and an optionally substituted straight or branched alkynylene chain;

each R^{11} is independently selected from the group consisting of hydrogen, alkyl, cyano, nitro and $-OR^8$;

each R^{12} is independently selected from the group consisting of hydrogen, alkyl, alkenyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^{10}-OR^8$, $-R^{10}-CN$, $-R^{10}-NO_2$, $-R^{10}-N(R^8)_2$, $-R^{10}-C(O)OR^8$ and $-R^{10}-C(O)N(R^8)_2$, or two R^{12s} , together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heterocyclyl or an optionally substituted *N*-heteroaryl;

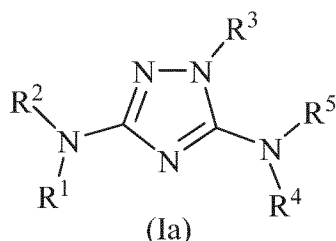
each R^{13} is independently selected from the group consisting of a direct bond, an optionally substituted straight or branched alkylene chain and an optionally substituted straight or branched alkenylene chain; and

each R^{14} is independently selected from the group consisting of an optionally substituted straight or branched alkylene chain and an optionally substituted straight or branched alkenylene chain;

as an isolated stereoisomer or mixture thereof or as a tautomer or mixture thereof, or a pharmaceutically acceptable salt or *N*-oxide thereof.

Some embodiments

In some embodiments of the use of the present disclosure, the compound of formula (I) is a compound of formula (Ia):



wherein R^1 , R^2 , R^3 , R^4 and R^5 are as described above for compounds of formula (I), as an isolated stereoisomer or mixture thereof or as a tautomer or mixture thereof, or a pharmaceutically acceptable salt or *N*-oxide thereof.

In some embodiments in the compound of formula (Ia) as set forth above, R^2 and R^3 are each independently a polycyclic heteroaryl containing more than 14 ring atoms optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-R^9-OR^8$, $-R^9-O-R^{10}-OR^8$, $-R^9-O-R^{10}-O-R^{10}-OR^8$, $-R^9-O-R^{10}-CN$, $-R^9-O-R^{10}-C(O)OR^8$, $-R^9-O-R^{10}-C(O)N(R^6)R^7$,

$-R^9-O-R^{10}-S(O)_pR^8$ (where p is 0, 1 or 2), $-R^9-O-R^{10}-N(R^6)R^7$, $-R^9-O-R^{10}-C(NR^{11})N(R^{11})H$, $-R^9-OC(O)-R^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)R^8$, $-R^9-C(O)OR^8$, $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)OR^{12}$, $-R^9-N(R^6)C(O)R^8$, $-R^9-N(R^6)S(O)_tR^8$ (where t is 1 or 2), $-R^9-S(O)_tOR^8$ (where t is 1 or 2), $-R^9-S(O)_pR^8$ (where p is 0, 1 or 2), and $-R^9-S(O)_tN(R^6)R^7$ (where t is 1 or 2); and R^1 , R^4 , R^5 , each R^6 , each R^7 , each R^8 , each R^9 , each R^{10} , each R^{11} and R^{12} are as described above for compounds of formula (Ia).

Another embodiment is the use where, in the compound of formula (Ia) as set forth above:

R^1 , R^4 and R^5 are each hydrogen;

each R^6 and R^7 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, hydroxyalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^{10}-OR^8$, $-R^{10}-CN$, $-R^{10}-NO_2$, $-R^{10}-N(R^8)_2$, $-R^{10}-C(O)OR^8$ and $-R^{10}-C(O)N(R^8)_2$, or any R^6 and R^7 , together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heteroaryl or an optionally substituted *N*-heterocyclyl;

each R^8 is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, and optionally substituted heteroarylalkyl;

each R^9 is independently selected from the group consisting of a direct bond and an optionally substituted straight or branched alkylene chain;

each R^{10} is an optionally substituted straight or branched alkylene chain; and

each R^{11} is independently selected from the group consisting of hydrogen, alkyl, cyano, nitro and $-OR^8$.

In some embodiments the compound of formula (Ia) as set forth above:

R^2 and R^3 are each independently a polycyclic heteroaryl containing more than 14 ring atoms selected from the group consisting of 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl, 6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl, 6,7,8,9-tetrahydro-5*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[2,3]azepino[4,5-*c*]pyridazin-3-yl, (Z)-dibenzo[*b*,*f*][1,4]thiazepin-11-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[4,5-*c*]pyridazin-2-yl, 6,7-dihydro-5*H*-benzo[2,3]oxepino[4,5-*c*]pyridazin-3-yl, spiro[chromeno[4,3-*c*]pyridazine-5,1'-cyclopentane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 5,6,8,9-tetrahydrospiro[benzo[7]annulene-7,2'-[1,3]dioxolane]-3-yl, 5,7,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-6,2'-[1,3]dioxolane]-3-yl, 6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-2-yl, 5,6,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxane]-3-yl and 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridin-2-yl, each optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-R^9-OR^8$, $-R^9-OC(O)-R^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)R^8$, $-R^9-C(O)OR^8$,

$-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)OR^{12}$, $-R^9-N(R^6)C(O)R^8$, $-R^9-N(R^6)S(O)_tR^8$ (where t is 1 or 2), $-R^9-S(O)_tOR^8$ (where t is 1 or 2), $-R^9-S(O)_pR^8$ (where p is 0, 1 or 2), and $-R^9-S(O)_tN(R^6)R^7$ (where t is 1 or 2).

In some embodiments in the compound of formula (Ia) is 1-(6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazin-3-yl)-*N*³-(5',5'-dimethyl-6,8,9,10-tetrahydro-5H-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxane]-3-yl)-1*H*-1,2,4-triazole-3,5-diamine.

In some embodiments in the compound of formula (Ia) as set forth above, R^2 is a polycyclic heteroaryl containing more than 14 ring atoms optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-R^9-OR^8$, $-R^9-O-R^{10}-OR^8$, $-R^9-O-R^{10}-O-R^{10}-OR^8$, $-R^9-O-R^{10}-CN$, $-R^9-O-R^{10}-C(O)OR^8$, $-R^9-O-R^{10}-C(O)N(R^6)R^7$, $-R^9-O-R^{10}-S(O)_pR^8$ (where p is 0, 1 or 2), $-R^9-O-R^{10}-N(R^6)R^7$, $-R^9-O-R^{10}-C(NR^{11})N(R^{11})H$, $-R^9-OC(O)-R^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)R^8$, $-R^9-C(O)OR^8$, $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)OR^{12}$, $-R^9-N(R^6)C(O)R^8$, $-R^9-N(R^6)S(O)_tR^8$ (where t is 1 or 2), $-R^9-S(O)_tOR^8$ (where t is 1 or 2), $-R^9-S(O)_pR^8$ (where p is 0, 1 or 2), and $-R^9-S(O)_tN(R^6)R^7$ (where t is 1 or 2); R^3 is selected from the group consisting of aryl and heteroaryl, where the aryl and the heteroaryl are each independently optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, $-R^{13}-OR^{12}$, $-R^{13}-OC(O)-R^{12}$, $-R^{13}-O-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)OR^{12}$, $-R^{13}-C(O)N(R^{12})_2$, $-R^{13}-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}$, $-R^{13}-C(O)N(R^{12})-R^{14}-OR^{12}$, $-R^{13}-N(R^{12})C(O)OR^{12}$, $-R^{13}-N(R^{12})C(O)R^{12}$, $-R^{13}-N(R^{12})S(O)_tR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_tOR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_pR^{12}$ (where p is 0, 1 or 2), and $-R^{13}-S(O)_tN(R^{12})_2$ (where t is 1 or 2); and R^1 , R^4 , R^5 , each R^6 , each R^7 , each R^8 , each R^9 , each R^{10} , each R^{11} , each R^{12} , each R^{13} and each R^{14} are as described above for compounds of formula (Ia).

In some embodiments in the compound of formula (Ia) as set forth above:

R^1 , R^4 and R^5 are each hydrogen;

each R^6 and R^7 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, hydroxyalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^{10}-OR^8$, $-R^{10}-CN$, $-R^{10}-NO_2$, $-R^{10}-N(R^8)_2$, $-R^{10}-C(O)OR^8$ and $-R^{10}-C(O)N(R^8)_2$, or any R^6 and R^7 , together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heteroaryl or an optionally substituted *N*-heterocyclyl;

each R⁸ is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclalkyl, optionally substituted heteroaryl, and optionally substituted heteroarylalkyl;

each R⁹ is independently selected from the group consisting of a direct bond and an optionally substituted straight or branched alkylene chain;

each R¹⁰ is an optionally substituted straight or branched alkylene chain;

each R¹¹ is independently selected from the group consisting of hydrogen, alkyl, cyano, nitro and -OR⁸;

each R¹² is independently selected from the group consisting of hydrogen, alkyl, alkenyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl, or two R^{12s}, together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heterocyclyl or an optionally substituted *N*-heteroaryl;

each R¹³ is independently selected from the group consisting of a direct bond and an optionally substituted straight or branched alkylene chain; and

each R¹⁴ is an optionally substituted straight or branched alkylene chain.

Another embodiment is the use where, in the compound of formula (Ia) as set forth above:

R¹, R⁴ and R⁵ are each hydrogen;

R² is a polycyclic heteroaryl containing more than 14 ring atoms selected from the group consisting of 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl, 6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl, 6,7,8,9-tetrahydro-5*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[2,3]azepino[4,5-*c*]pyridazin-3-yl, (Z)-dibenzo[*b,f*][1,4]thiazepin-11-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[4,5-*c*]pyridazin-2-yl, 6,7-dihydro-5*H*-benzo[2,3]oxepino[4,5-*c*]pyridazin-3-yl, spiro[chromeno[4,3-*c*]pyridazine-5,1'-cyclopentane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 5,6,8,9-tetrahydrospiro[benzo[7]annulene-7,2'-[1,3]dioxolane]-3-yl, 5,7,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-6,2'-[1,3]dioxolane]-3-yl, 6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-2-yl, 5,6,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxane]-3-yl and 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridin-2-yl, each optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, -R⁹-OR⁸, -R⁹-OC(O)-R⁸, -R⁹-N(R⁶)R⁷, -R⁹-C(O)R⁸, -R⁹-C(O)OR⁸, -R⁹-C(O)N(R⁶)R⁷, -R⁹-N(R⁶)C(O)OR¹², -R⁹-N(R⁶)C(O)R⁸, -R⁹-N(R⁶)S(O)_tR⁸ (where *t* is 1 or 2), -R⁹-S(O)_tOR⁸ (where *t* is 1 or 2), -R⁹-S(O)_pR⁸ (where *p* is 0, 1 or 2), and -R⁹-S(O)_tN(R⁶)R⁷ (where *t* is 1 or 2);

each R⁶ and R⁷ is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, hydroxyalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally

substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^{10}-OR^8$, $-R^{10}-CN$, $-R^{10}-NO_2$, $-R^{10}-N(R^8)_2$, $-R^{10}-C(O)OR^8$ and $-R^{10}-C(O)N(R^8)_2$, or any R^6 and R^7 , together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heteroaryl or an optionally substituted *N*-heterocyclyl;

each R^8 is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, and optionally substituted heteroarylalkyl;

each R^9 is independently selected from the group consisting of a direct bond and an optionally substituted straight or branched alkylene chain;

each R^{10} is an optionally substituted straight or branched alkylene chain;

each R^{12} is independently selected from the group consisting of hydrogen, alkyl, alkenyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl, or two R^{12s} , together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heterocyclyl or an optionally substituted *N*-heteroaryl;

each R^{13} is independently selected from the group consisting of a direct bond and an optionally substituted straight or branched alkylene chain; and

each R^{14} is an optionally substituted straight or branched alkylene chain.

In some embodiments in the compound of formula (Ia) as set forth above:

R^2 is a polycyclic heteroaryl containing more than 14 ring atoms selected from the group consisting of 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl, 6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl, 6,7,8,9-tetrahydro-5*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[2,3]azepino[4,5-*c*]pyridazin-3-yl, (Z)-dibenzo[*b,f*][1,4]thiazepin-11-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[4,5-*c*]pyridazin-2-yl, 6,7-dihydro-5*H*-benzo[2,3]oxepino[4,5-*c*]pyridazin-3-yl, spiro[chromeno[4,3-*c*]pyridazine-5,1'-cyclopentane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 5,6,8,9-tetrahydrospiro[benzo[7]annulene-7,2'-[1,3]dioxolane]-3-yl, 5,7,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-6,2'-[1,3]dioxolane]-3-yl, 6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-2-yl, 5,6,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxane]-3-yl and 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridin-2-yl, each optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-R^9-OR^8$, $-R^9-OC(O)-R^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)R^8$, $-R^9-C(O)OR^8$, $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)OR^{12}$, $-R^9-N(R^6)C(O)R^8$, $-R^9-N(R^6)S(O)_tR^8$ (where *t* is 1 or 2), $-R^9-S(O)_tOR^8$ (where *t* is 1 or 2), $-R^9-S(O)_pR^8$ (where *p* is 0, 1 or 2), and $-R^9-S(O)_tN(R^6)R^7$ (where *t* is 1 or 2); and

R³ is heteroaryl selected from the group consisting of pyridinyl, pyrimidinyl, 4,5-dihydro-1*H*-benzo[*b*]azepin-2(3*H*)-on-8-yl, benzo[*d*]imidazolyl, 6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*d*]azepin-3-yl, 6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*c*]azepin-3-yl, 5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl, 5,6,7,8-tetrahydroquinolin-3-yl, 1,2,3,4-tetrahydroisoquinolin-7-yl, 2,3,4,5-tetrahydrobenzo[*b*]oxepin-7-yl, 3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepin-7-yl, benzo[*d*]oxazol-5-yl, 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-7-yl, benzo[*b*]thiophenyl, thieno[3,2-*d*]pyrimidinyl and 6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-3-yl, each optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, -R¹³-OR¹², -R¹³-OC(O)-R¹², -R¹³-O-R¹⁴-N(R¹²)₂, -R¹³-N(R¹²)₂, -R¹³-C(O)R¹², -R¹³-C(O)OR¹², -R¹³-C(O)N(R¹²)₂, -R¹³-C(O)N(R¹²)-R¹⁴-N(R¹²)R¹³, -R¹³-C(O)N(R¹²)-R¹⁴-OR¹², -R¹³-N(R¹²)C(O)OR¹², -R¹³-N(R¹²)C(O)R¹², -R¹³-N(R¹²)S(O)_tR¹² (where *t* is 1 or 2), -R¹³-S(O)_tOR¹² (where *t* is 1 or 2), -R¹³-S(O)_pR¹² (where *p* is 0, 1 or 2), and -R¹³-S(O)_tN(R¹²)₂ (where *t* is 1 or 2).

In some embodiments the compound of formula (Ia), as set forth above, is selected from the group consisting of:

- 1-(6,7-dimethoxy-quinazolin-4-yl)-N³-(5,7,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-6,2'-[1,3]dioxolane]-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;
- 1-(2-chloro-7-methylthieno[3,2-*d*]pyrimidin-4-yl)-N³-(5,7,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-6,2'-[1,3]dioxolane]-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;
- 1-(2-chloro-7-methylthieno[3,2-*d*]pyrimidin-4-yl)-N³-(5,6,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl)-1*H*-1,2,4-triazole-3,5-diamine; and
- 1-(2-chloro-7-methylthieno[3,2-*d*]pyrimidin-4-yl)-N³-(5',5'-dimethyl-6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxane]-3-yl)-1*H*-1,2,4-triazole-3,5-diamine.

In some embodiments in the compound of formula (Ia) as set forth above, R² is selected from the group consisting of aryl and heteroaryl, where the aryl and the heteroaryl are each independently optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, -R¹³-OR¹², -R¹³-OC(O)-R¹²,

$-R^{13}-O-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)OR^{12}$,
 $-R^{13}-C(O)N(R^{12})_2$, $-R^{13}-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}$, $-R^{13}-C(O)N(R^{12})-R^{14}-OR^{12}$,
 $-R^{13}-N(R^{12})C(O)OR^{12}$, $-R^{13}-N(R^{12})C(O)R^{12}$, $-R^{13}-N(R^{12})S(O)_tR^{12}$ (where t is 1 or 2),
 $-R^{13}-S(O)_tOR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_pR^{12}$ (where p is 0, 1 or 2), and $-R^{13}-S(O)_tN(R^{12})_2$
 (where t is 1 or 2); R^3 is a polycyclic heteroaryl containing more than 14 ring atoms optionally
 substituted by one or more substituents selected from the group consisting of oxo, thio, cyano,
 nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted
 cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted
 heteroaryl, optionally substituted heterocyclyl, $-R^9-OR^8$, $-R^9-O-R^{10}-OR^8$,
 $-R^9-O-R^{10}-O-R^{10}-OR^8$, $-R^9-O-R^{10}-CN$, $-R^9-O-R^{10}-C(O)OR^8$, $-R^9-O-R^{10}-C(O)N(R^6)R^7$,
 $-R^9-O-R^{10}-S(O)_pR^8$ (where p is 0, 1 or 2), $-R^9-O-R^{10}-N(R^6)R^7$, $-R^9-O-R^{10}-C(NR^{11})N(R^{11})H$,
 $-R^9-OC(O)-R^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)R^8$, $-R^9-C(O)OR^8$, $-R^9-C(O)N(R^6)R^7$,
 $-R^9-N(R^6)C(O)OR^{12}$, $-R^9-N(R^6)C(O)R^8$, $-R^9-N(R^6)S(O)_tR^8$ (where t is 1 or 2), $-R^9-S(O)_tOR^8$
 (where t is 1 or 2), $-R^9-S(O)_pR^8$ (where p is 0, 1 or 2), and $-R^9-S(O)_tN(R^6)R^7$ (where t is 1 or
 2); and R^1 , R^4 , R^5 , each R^6 , each R^7 , each R^8 , each R^9 , each R^{10} , each R^{11} , each R^{12} , each
 R^{13} and each R^{14} are as described above for compounds of formula (I).

In some embodiments in the compound of formula (Ia) as set forth above:

R^1 , R^4 and R^5 are each independently hydrogen;

each R^6 and R^7 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, hydroxyalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^{10}-OR^8$, $-R^{10}-CN$, $-R^{10}-NO_2$, $-R^{10}-N(R^8)_2$, $-R^{10}-C(O)OR^8$ and $-R^{10}-C(O)N(R^8)_2$, or any R^6 and R^7 , together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heteroaryl or an optionally substituted *N*-heterocyclyl;

each R^8 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, and optionally substituted heteroarylalkyl;

each R^9 is independently selected from the group consisting of a direct bond and an optionally substituted straight or branched alkylene chain;

each R^{10} is an optionally substituted straight or branched alkylene chain;

each R^{11} is independently selected from the group consisting of hydrogen, alkyl, cyano, nitro and $-OR^8$;

each R^{12} is independently selected from the group consisting of hydrogen, alkyl, alkenyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^{10}-OR^8$, $-R^{10}-CN$, $-R^{10}-NO_2$, $-R^{10}-N(R^8)_2$, $-R^{10}-C(O)OR^8$ and $-R^{10}-C(O)N(R^8)_2$, or two R^{12} s, together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heterocyclyl or an optionally substituted *N*-heteroaryl;

each R^{13} is independently selected from the group consisting of a direct bond and an optionally substituted straight or branched alkylene chain; and

each R^{14} is an optionally substituted straight or branched alkylene chain.

In some embodiments in the compound of formula (Ia) as set forth above:

R^2 is aryl optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thio, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, $-R^{13}-OR^{12}$, $-R^{13}-OC(O)-R^{12}$, $-R^{13}-O-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)OR^{12}$, $-R^{13}-C(O)N(R^{12})_2$, $-R^{13}-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}$, $-R^{13}-C(O)N(R^{12})-R^{14}-OR^{12}$, $-R^{13}-N(R^{12})C(O)OR^{12}$, $-R^{13}-N(R^{12})C(O)R^{12}$, $-R^{13}-N(R^{12})S(O)_tR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_tOR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_pR^{12}$ (where p is 0, 1 or 2), and $-R^{13}-S(O)_tN(R^{12})_2$ (where t is 1 or 2).

In some embodiments in the compound of formula (Ia) as set forth above:

R^2 is aryl selected from the group consisting of phenyl and 6,7,8,9-tetrahydro-5H-benzo[7]annulene-2-yl, each optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thio, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, $-R^{13}-OR^{12}$, $-R^{13}-OC(O)-R^{12}$, $-R^{13}-O-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)OR^{12}$, $-R^{13}-C(O)N(R^{12})_2$, $-R^{13}-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}$, $-R^{13}-C(O)N(R^{12})-R^{14}-OR^{12}$, $-R^{13}-N(R^{12})C(O)OR^{12}$, $-R^{13}-N(R^{12})C(O)R^{12}$, $-R^{13}-N(R^{12})S(O)_tR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_tOR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_pR^{12}$ (where p is 0, 1 or 2), and $-R^{13}-S(O)_tN(R^{12})_2$ (where t is 1 or 2); and

R^3 is a polycyclic heteroaryl containing more than 14 ring atoms selected from the group consisting of 6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazin-3-yl, 6,7-dihydro-5H-pyrido[2',3':6,7]cyclohepta[1,2-c]pyridazin-3-yl, 6,7,8,9-tetrahydro-5H-cyclohepta[4,5]thieno[2,3-d]pyrimidin-4-yl, 6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-d]pyrimidin-4-yl, 6,7-dihydro-5H-benzo[2,3]azepino[4,5-c]pyridazin-3-yl, (Z)-dibenzo[b,f][1,4]thiazepin-11-yl, 6,7-dihydro-5H-benzo[6,7]cyclohepta[4,5-c]pyridazin-2-yl, 6,7-dihydro-5H-benzo[2,3]oxepino[4,5-c]pyridazin-3-yl, spiro[chromeno[4,3-c]pyridazine-5,1'-cyclopentane]-3-yl, 6,8,9,10-tetrahydro-5H-spiro[cycloocta[b]pyridine-7,2'-[1,3]dioxolane]-3-yl, 5,6,8,9-tetrahydrospiro[benzo[7]annulene-7,2'-[1,3]dioxolane]-3-yl, 5,7,8,9-tetrahydrospiro[cyclohepta[b]pyridine-6,2'-[1,3]dioxolane]-3-yl, 6,7-dihydro-5H-

benzo[2,3]thiopheno[4,5-*c*]pyridazin-3-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-2-yl, 5,6,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxane]-3-yl and 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridin-2-yl, each optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-R^9-OR^8$, $-R^9-OC(O)-R^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)R^8$, $-R^9-C(O)OR^8$, $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)OR^{12}$, $-R^9-N(R^6)C(O)R^8$, $-R^9-N(R^6)S(O)_tR^8$ (where *t* is 1 or 2), $-R^9-S(O)_tOR^8$ (where *t* is 1 or 2), $-R^9-S(O)_pR^8$ (where *p* is 0, 1 or 2), and $-R^9-S(O)_tN(R^6)R^7$ (where *t* is 1 or 2).

In some embodiments in the compound of formula (Ia) as set forth above:

R^2 is phenyl optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, $-R^{13}-OR^{12}$, $-R^{13}-OC(O)-R^{12}$, $-R^{13}-O-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)OR^{12}$, $-R^{13}-C(O)N(R^{12})_2$, $-R^{13}-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}$, $-R^{13}-C(O)N(R^{12})-R^{14}-OR^{12}$, $-R^{13}-N(R^{12})C(O)OR^{12}$, $-R^{13}-N(R^{12})C(O)R^{12}$, $-R^{13}-N(R^{12})S(O)_tR^{12}$ (where *t* is 1 or 2), $-R^{13}-S(O)_tOR^{12}$ (where *t* is 1 or 2), $-R^{13}-S(O)_pR^{12}$ (where *p* is 0, 1 or 2), and $-R^{13}-S(O)_tN(R^{12})_2$ (where *t* is 1 or 2).

In some embodiments in the compound of formula (Ia) as set forth above:

R^2 is phenyl optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, cyano, and optionally substituted heterocyclyl where the optionally substituted heterocyclyl is selected from the group consisting of piperidinyl, piperazinyl, pyrrolidinyl, azepanyl, decahydropyrazino[1,2-*a*]azepinyl, octahydropyrrolo[3,4-*c*]pyrrolyl, azabicyclo[3.2.1]octyl, octahydropyrrolo[3,4-*b*]pyrrolyl, octahydropyrrolo[3,2-*c*]pyridinyl, 2,7-diazaspiro[4.4]nonanyl and azetidiny; each independently optionally substituted by one or two substituents selected from the group consisting of $-R^9-OR^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)OR^8$, $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)R^7$, $-R^9-N(R^6)C(O)OR^7$, alkyl, halo, haloalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, and optionally substituted heteroarylalkyl;

R^3 is selected from the group consisting of 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl, 6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridin-2-yl, 6,7-dihydro-5*H*-benzo[2,3]thiopheno[4,5-*c*]pyridazin-3-yl, spiro[chromeno[4,3-*c*]pyridazine-5,1'-cyclopentane]-3-yl and 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[4,5-*c*]pyridazin-3-yl, each optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, halo and $-R^9-OR^8$.

In some embodiments the compound of formula (Ia), as set forth above, is selected from the group consisting of:

*N*³-(4-(4-cyclohexanylpiperazin-1-yl)phenyl)-1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(4-(pyrrolidin-1-yl)piperidin-1-yl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(4-methyl-3-phenylpiperazin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(4-piperidin-1-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(4-(indolin-2-on-1-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(4-(morpholin-4-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(4-(4-cyclopentyl-2-methylpiperazin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(4-(3,5-dimethylpiperazin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(4-(4-(pyrrolidin-1-yl)piperidin-1-yl)-3-cyanophenyl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(3-(diethylamino)pyrrolidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(4-(4-(bicyclo[2.2.1]heptan-2-yl)piperazin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(4-(4-methylpiperazin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(4-(diethylamino)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-9-methoxybenzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(4-(pyrrolidin-1-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-10-fluorobenzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(4-(pyrrolidin-1-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-10-fluorobenzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(4-(cyclohexyl)piperazin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-9-methoxybenzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(4-(cyclohexyl)piperazin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(4-(4-methylpiperazin-1-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(4-(4-methylpiperidin-1-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(4-dimethylaminopiperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-chloro-4-(4-pyrrolidin-1-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-trifluoromethyl-4-(4-pyrrolidin-1-yl-piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-9,10-dimethoxybenzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(4-pyrrolidin-1-yl-piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-9,10,11-trimethoxybenzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(4-pyrrolidin-1-yl-piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(5-methyloctahydropyrrolo[3,4-*c*]pyrrolyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(3-pyrrolidin-1-yl-piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(3-pyrrolidin-1-yl-azepan-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(4-*N*-methylpiperidin-4-yl-piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[4,5-*c*]pyridazin-2-yl)-*N*³-(3-fluoro-4-(4-(pyrrolidinyl)piperidinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(5-propyloctahydropyrrolo[3,4-*c*]pyrrolyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(decahydropyrazino[1,2-*a*]azepin-2-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(5-cyclopentyloctahydropyrrolo[3,4-*c*]pyrrolyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(3-(pyrrolidin-1-yl)-8-azabicyclo[3.2.1]oct-8-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(4-pyrrolidin-1-yl-azepan-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(4-(4-methylpiperazin-1-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(4-(4-isopropylpiperazin-1-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(1-methyloctahydropyrrolo[3,4-*b*]pyrrol-5-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(4-(*N*-methylcyclopentylamino)piperidinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(4-(dipropylamino)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(1-propyloctahydro-1*H*-pyrrolo[3,2-*c*]pyridine-5-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[4,5-*c*]pyridazin-2-yl)-*N*³-(3-fluoro-4-(4-(*N*-methylpiperazin-1-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(4-(tert-butyloxycarbonylamino)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(4-aminopiperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(4-(5-cyclohexyloctahydropyrrolo[3,4-*c*]pyrrolyl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(4-(methylpiperidin-4-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(4-(4-pyrrolidin-1-yl)piperidinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(4-pyrrolidin-1-yl)piperidinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-methyl-4-(4-pyrrolidin-1-yl)piperidinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(4-cyclopentylpiperazinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(4-*N*-methylpiperidin-4-yl)piperazinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(*N*-isopropylpiperazin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(3-pyrrolidin-1-ylazetidiny)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-methyl-4-(4-(*N*-methylpiperazin-4-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-((*S*)-3-(pyrrolidin-1-ylmethyl)pyrrolidinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(4-(pyrrolidinylmethyl)piperidinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-((4*aR*,8*aS*)-decahydroisoquinolin-2-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(octahydro-1*H*-pyrido[1,2-*a*]pyrazin-2-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(3-pyrrolidin-1-yl)pyrrolidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(4-(5-methyloctahydropyrrolo[3,4-*c*]pyrrolyl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(octahydropyrrolo[3,4-*c*]pyrrolyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-9-chloro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(4-pyrrolidin-1-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-9-chloro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(4-(*N*-methylpiperazin-1-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(4-iodophenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(spiro[chromeno[4,3-*c*]pyridazine-5,1'-cyclopentane]-3-yl)-*N*³-(3-fluoro-4-(4-methylpiperazin-1-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(spiro[chromeno[4,3-*c*]pyridazine-5,1'-cyclopentane]-3-yl)-*N*³-(3-fluoro-4-(pyrrolidin-1-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(4-pyrrolidin-1-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[4,5-*c*]pyridazin-2-yl)-*N*³-(3-fluoro-4-(4-pyrrolidin-1-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(4-(4-methylpiperazin-1-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(3-(3*R*)-dimethylaminopyrrolidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[4,5-*c*]pyridazin-2-yl)-*N*³-(3-methyl-4-(4-pyrrolidin-1-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[4,5-*c*]pyridazin-2-yl)-*N*³-(3-fluoro-4-(4-pyrrolidin-1-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(4-phenyl-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridin-2-yl)-*N*³-(3-fluoro-4-(4-cyclohexylpiperazin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(4-phenyl-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridin-2-yl)-*N*³-(4-(4-methylpiperazin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(4-methylpiperazin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(4-(1-bicyclo[2.2.1]heptan-2-yl)-piperidin-4-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(4-(1-cyclopropylmethylpiperidin-4-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(4-cyclopropylmethylpiperazin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl)-*N*³-(4-(1-bicyclo[2.2.1]heptan-2-yl)-piperidin-4-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(4-phenyl-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridin-2-yl)-*N*³-(3-fluoro-4-(4-pyrrolidin-1-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine, and

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(4-(pyrrolidin-1-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine.

In some embodiments in the compound of formula (Ia) as set forth above:

R² is phenyl optionally substituted by one or more substituents selected from the group consisting of halo, alkyl, heterocyclalkenyl, -R¹³-OR¹², -R¹³-O-R¹⁴-N(R¹²)₂, -R¹³-N(R¹²)-R¹⁴-N(R¹²)₂, -R¹³-N(R¹²)₂, -R¹³-C(O)R¹², -R¹³-C(O)N(R¹²)₂, and -R¹³-N(R¹²)C(O)R¹²;

R³ is selected from the group consisting of 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl and 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[4,5-*c*]pyridazin-3-yl, each optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, halo and -R⁹-OR⁸.

In some embodiments the compound of formula (Ia), as set forth above, is selected from the group consisting of:

- 1-(6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazin-3-yl)-N³-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-1H-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazin-3-yl)-N³-(4-(4-(cyclopentyl)piperazin-1-ylcarbonyl)phenyl)-1H-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazin-3-yl)-N³-(4-((2-pyrrolidin-1-ylethyl)aminocarbonyl)phenyl)-1H-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazin-3-yl)-N³-(4-(2,2,6,6-tetramethylpiperidin-1-yl)ethoxyphenyl)-1H-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazin-3-yl)-N³-(4-((2-(dimethylamino)ethyl)aminocarbonyl)phenyl)-1H-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazin-3-yl)-N³-(4-((2-(methoxy)ethyl)aminocarbonyl)phenyl)-1H-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazin-3-yl)-N³-(4-((2-(pyrrolidin-1-yl)ethyl)aminocarbonyl)phenyl)-1H-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazin-3-yl)-N³-(4-((4-(pyrrolidin-1-yl)piperidin-1-yl)carbonyl)phenyl)-1H-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazin-3-yl)-N³-(3-chloro-4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-1H-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazin-3-yl)-N³-(3-fluoro-4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-1H-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5H-10-fluorobenzo[6,7]cyclohepta[1,2-c]pyridazin-3-yl)-N³-(3-fluoro-4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-1H-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5H-9-methoxybenzo[6,7]cyclohepta[1,2-c]pyridazin-3-yl)-N³-(3-fluoro-4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-1H-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazin-3-yl)-N³-(4-(2-(N-methylcyclopentylamino)ethoxy)phenyl)-1H-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazin-3-yl)-N³-(3-fluoro-4-(N-methylpiperidin-4-yl-N-methylamino)phenyl)-1H-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazin-3-yl)-N³-(4-((N-butyl-N-acetoamino)methyl)phenyl)-1H-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazin-3-yl)-N³-(4-(4-(4-methylpiperazin-1-yl)piperidin-1-ylprop-1-enyl)phenyl)-1H-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazin-3-yl)-N³-(4-(4-(piperidin-1-yl)piperidin-1-ylprop-1-enyl)phenyl)-1H-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazin-3-yl)-N³-(4-(piperidin-1-ylprop-1-enyl)phenyl)-1H-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazin-3-yl)-N³-(4-(pyrrolidin-1-ylprop-1-enyl)phenyl)-1H-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazin-3-yl)-N³-(4-(3-dimethylaminopyrrolidin-1-ylprop-1-enyl)phenyl)-1H-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazin-3-yl)-N³-(4-(3-diethylaminopyrrolidin-1-ylprop-1-enyl)phenyl)-1H-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(4-(4-pyrrolidin-1-yl)piperidin-1-ylprop-1-enyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(4-(4-methylpiperazin-1-ylprop-1-enyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(4-(4-isopropylpiperazin-1-ylprop-1-enyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(4-(4-cyclopentylpiperazin-1-ylprop-1-enyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(4-(morpholin-4-ylprop-1-enyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine; and
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(4-(1-methylpiperidin-3-yl-oxy)phenyl)-1*H*-1,2,4-triazole-3,5-diamine.

In some embodiments in the compound of formula (Ia) as set forth above:

R² is phenyl optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, cyano, and optionally substituted heterocyclyl where the optionally substituted heterocyclyl is selected from the group consisting of piperidinyl, piperazinyl, pyrrolidinyl, azepanyl, decahydropyrazino[1,2-*a*]azepinyl, octahydropyrrolo[3,4-*c*]pyrrolyl, azabicyclo[3.2.1]octyl, octahydropyrrolo[3,4-*b*]pyrrolyl, octahydropyrrolo[3,2-*c*]pyridinyl, 2,7-diazaspiro[4.4]nonanyl and azetidiny; each independently optionally substituted by one or two substituents selected from the group consisting of -R⁹-OR⁸, -R⁹-N(R⁶)R⁷, -R⁹-C(O)OR⁶, -R⁹-C(O)N(R⁶)R⁷, -R⁹-N(R⁶)C(O)R⁷, -R⁹-N(R⁶)C(O)OR⁷, alkyl, halo, haloalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, and optionally substituted heteroarylalkyl; and

R³ is selected from the group consisting of 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl and 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-2-yl, each optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, halo and -R⁹-OR⁸.

In some embodiments the compound of formula (Ia), as set forth above, is selected from the group consisting of:

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl)-*N*³-(4-(4-(bicyclo[2.2.1]heptan-2-yl)piperazin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl)-*N*³-(3-fluoro-4-(4-(diethylamino)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-2-yl)-*N*³-(4-(*N*-methylpiperazin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-2-yl)-*N*³-(3-fluoro-4-(4-cyclohexylpiperazinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine; and
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-2-yl)-*N*³-(4-(4-(2*S*)-bicyclo[2.2.1]heptan-2-yl)-piperazinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine.

In some embodiments in the compound of formula (Ia) as set forth above:

R² is phenyl optionally substituted by one or more substituents selected from the group consisting of halo, alkyl, heterocyclalkenyl, -R¹³-OR¹², -R¹³-O-R¹⁴-N(R¹²)₂, -R¹³-N(R¹²)-R¹⁴-N(R¹²)₂, -R¹³-N(R¹²)₂, -R¹³-C(O)R¹², -R¹³-C(O)N(R¹²)₂, and -R¹³-N(R¹²)C(O)R¹²; and

R³ is selected from the group consisting of 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl and 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-2-yl, each optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, halo and -R⁹-OR⁸.

In some embodiments the compound of formula (Ia), as set forth above, is selected from the group consisting of:

- 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-2-yl)-N³-(3-fluoro-4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-1*H*-1,2,4-triazole-3,5-diamine; and
- 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl)-N³-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-1*H*-1,2,4-triazole-3,5-diamine.

In some embodiments in the compound of formula (Ia) as set forth above:

R² is phenyl optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, cyano, and optionally substituted heterocycl where the optionally substituted heterocycl is selected from the group consisting of piperidinyl, piperazinyl, pyrrolidinyl, azepanyl, decahydropyrazino[1,2-*a*]azepinyl, octahydropyrrolo[3,4-*c*]pyrrolyl, azabicyclo[3.2.1]octyl, octahydropyrrolo[3,4-*b*]pyrrolyl, octahydropyrrolo[3,2-*c*]pyridinyl, 2,7-diazaspiro[4.4]nonanyl and azetidyl; each independently optionally substituted by one or two substituents selected from the group consisting of -R⁹-OR⁸, -R⁹-N(R⁶)R⁷, -R⁹-C(O)OR⁶, -R⁹-C(O)N(R⁶)R⁷, -R⁹-N(R⁶)C(O)R⁷, -R⁹-N(R⁶)C(O)OR⁷, alkyl, halo, haloalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocycl, optionally substituted heterocyclalkyl, optionally substituted heteroaryl, and optionally substituted heteroarylalkyl; and

R³ is selected from the group consisting of 6,7-dihydro-5*H*-benzo[2,3]azepino[4,5-*c*]pyridazin-3-yl, (Z)-dibenzo[*b,f*][1,4]thiazepin-11-yl, 6,7-dihydro-5*H*-benzo[2,3]oxepino[4,5-*c*]pyridazin-3-yl, and 6,7-dihydro-5*H*-benzo[2,3]thiepin[4,5-*c*]pyridazin-3-yl, each optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, halo and -R⁹-OR⁸.

In some embodiments the compound of formula (Ia), as set forth above, is selected from the group consisting of:

- 1-(7-methyl-6,7-dihydro-5*H*-benzo[2,3]azepino[4,5-*c*]pyridazin-3-yl)-N³-(4-(N-methylpiperazin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
- 1-(7-methyl-6,7-dihydro-5*H*-benzo[2,3]azepino[4,5-*c*]pyridazin-3-yl)-N³-(3-fluoro-4-(4-cyclohexylpiperazinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
- 1-((Z)-dibenzo[*b,f*][1,4]thiazepin-11-yl)-N³-(4-(4-N-methylpiperazinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
- 1-((Z)-dibenzo[*b,f*][1,4]thiazepin-11-yl)-N³-(3-fluoro-4-(4-diethylaminopiperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[2,3]oxepino[4,5-*c*]pyridazin-3-yl)-*N*³-(4-(4-pyrrolidin-1-yl)piperidinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[2,3]oxepino[4,5-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(4-pyrrolidin-1-yl)piperidinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(4-pyrrolidin-1-yl)piperidinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl)-*N*³-(4-(4-pyrrolidin-1-yl)piperidinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(pyrrolidinylmethyl)piperidinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-((4*aR*,8*aS*)-decahydroisoquinolin-2-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine; and
 1-(6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(octahydro-1*H*-pyrido[1,2-*a*]pyrazin-2-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine.

In some embodiments in the compound of formula (Ia) as set forth above:

R² is phenyl optionally substituted by one or more substituents selected from the group consisting of halo, alkyl, heterocyclalkenyl, -R¹³-OR¹², -R¹³-O-R¹⁴-N(R¹²)₂, -R¹³-N(R¹²)-R¹⁴-N(R¹²)₂, -R¹³-N(R¹²)₂, -R¹³-C(O)R¹², -R¹³-C(O)N(R¹²)₂, and -R¹³-N(R¹²)C(O)R¹²; and

R³ is selected from the group consisting of 6,7-dihydro-5*H*-benzo[2,3]azepino[4,5-*c*]pyridazin-3-yl, (Z)-dibenzo[*b,f*][1,4]thiazepin-11-yl, 6,7-dihydro-5*H*-benzo[2,3]oxepino[4,5-*c*]pyridazin-3-yl, and 6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl, each optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclalkyl, -R⁹-OR⁸, -R⁹-OC(O)-R⁸, -R⁹-N(R⁶)R⁷, -R⁹-C(O)R⁸, -R⁹-C(O)OR⁸, -R⁹-C(O)N(R⁶)R⁷, -R⁹-N(R⁶)C(O)OR¹², -R⁹-N(R⁶)C(O)R⁸, -R⁹-N(R⁶)S(O)_tR⁸ (where *t* is 1 or 2), -R⁹-S(O)_tOR⁸ (where *t* is 1 or 2), -R⁹-S(O)_pR⁸ (where *p* is 0, 1 or 2), and -R⁹-S(O)_tN(R⁶)R⁷ (where *t* is 1 or 2).

In some embodiments the compound of formula (Ia), as set forth above, is selected from the group consisting of:

1-(7-methyl-6,7-dihydro-5*H*-benzo[2,3]azepino[4,5-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-1*H*-1,2,4-triazole-3,5-diamine; and
 1-((Z)-dibenzo[*b,f*][1,4]thiazepin-11-yl)-*N*³-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-1*H*-1,2,4-triazole-3,5-diamine.

In some embodiments in the compound of formula (Ia) as set forth above:

R² is phenyl optionally substituted by a substituent selected from the group consisting of optionally substituted heterocyclalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl;

R³ is selected from the group consisting of 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl and 6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl, each optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted

cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-R^9-OR^8$, $-R^9-OC(O)-R^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)R^8$, $-R^9-C(O)OR^8$, $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)OR^{12}$, $-R^9-N(R^6)C(O)R^8$, $-R^9-N(R^6)S(O)_tR^8$ (where t is 1 or 2), $-R^9-S(O)_tOR^8$ (where t is 1 or 2), $-R^9-S(O)_pR^8$ (where p is 0, 1 or 2), and $-R^9-S(O)_tN(R^6)R^7$ (where t is 1 or 2)

each R^6 and R^7 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, hydroxyalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^{10}-OR^8$, $-R^{10}-CN$, $-R^{10}-NO_2$, $-R^{10}-N(R^8)_2$, $-R^{10}-C(O)OR^8$ and $-R^{10}-C(O)N(R^8)_2$, or any R^6 and R^7 , together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heteroaryl or an optionally substituted *N*-heterocyclyl;

each R^8 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, and optionally substituted heteroarylalkyl;

each R^9 is independently selected from the group consisting of a direct bond and an optionally substituted straight or branched alkylene chain;

each R^{10} is an optionally substituted straight or branched alkylene chain; and R^{12} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, alkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl.

In some embodiments the compound of formula (Ia), as set forth above, is selected from the group consisting of:

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(4-((4-methylpiperazin-1-yl)methyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(4-((5-fluoroindolin-2-on-3-yl)methyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(4-((4-pyrrolidin-1-ylpiperidinyl)methyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(4-((4-cyclopentylpiperazinyl)methyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(4-((4-isopropylpiperazinyl)methyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine; and
 1-(6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(isoindolin-2-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine.

In some embodiments in the compound of formula (Ia) as set forth above:

R^1 , R^4 and R^5 are each independently hydrogen;

R^2 is 6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl,

optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, $-R^{13}-OR^{12}$, $-R^{13}-OC(O)-R^{12}$, $-R^{13}-O-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)OR^{12}$, $-R^{13}-C(O)N(R^{12})_2$, $-R^{13}-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}$, $-R^{13}-C(O)N(R^{12})-R^{14}-OR^{12}$, $-R^{13}-N(R^{12})C(O)OR^{12}$, $-R^{13}-N(R^{12})C(O)R^{12}$, $-R^{13}-N(R^{12})S(O)_tR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_tOR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_pR^{12}$ (where p is 0, 1 or 2), and $-R^{13}-S(O)_tN(R^{12})_2$ (where t is 1 or 2); and

R^3 is a polycyclic heteroaryl containing more than 14 ring atoms selected from the group consisting of 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl, 6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl, 6,7,8,9-tetrahydro-5*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[2,3]azepino[4,5-*c*]pyridazin-3-yl, (Z)-dibenzo[*b,f*][1,4]thiazepin-11-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[4,5-*c*]pyridazin-2-yl, 6,7-dihydro-5*H*-benzo[2,3]oxepino[4,5-*c*]pyridazin-3-yl, spiro[chromeno[4,3-*c*]pyridazine-5,1'-cyclopentane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 5,6,8,9-tetrahydrospiro[benzo[7]annulene-7,2'-[1,3]dioxolane]-3-yl, 5,7,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-6,2'-[1,3]dioxolane]-3-yl, 6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-2-yl, 5,6,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxane]-3-yl and 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridin-2-yl, each optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-R^9-OR^8$, $-R^9-OC(O)-R^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)R^8$, $-R^9-C(O)OR^8$, $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)OR^{12}$, $-R^9-N(R^6)C(O)R^8$, $-R^9-N(R^6)S(O)_tR^8$ (where t is 1 or 2), $-R^9-S(O)_tOR^8$ (where t is 1 or 2), $-R^9-S(O)_pR^8$ (where p is 0, 1 or 2), and $-R^9-S(O)_tN(R^6)R^7$ (where t is 1 or 2); and each R^6 , each R^7 , each R^8 , each R^9 , each R^{12} , each R^{13} and each R^{14} are as described above for compounds of formula (Ia).

In some embodiments the compound of formula (Ia), as set forth above, is selected from the group consisting of:

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)- N^3 -(7-(pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)- N^3 -(7-((bicyclo[2.2.1]heptan-2-yl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)- N^3 -(7-((bicyclo[2.2.1]heptan-2-yl)(methyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)- N^3 -((7-piperidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7-azetidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7-(*R*)-pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-diethylamino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-cyclopentylamino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7-(*S*)-pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7-(2-(*S*)-methyloxycarbonyl)pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7-(2-(*S*)-carboxy)pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(8-diethylaminoethyl-9hydroxy-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-(3-(*S*)-fluoropyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-(2-(*S*)-methylpyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-(3-(*R*)-hydroxypyrrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-(2-(*R*)-methylpyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-(3-(*S*)-hydroxypyrrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-(3-(*R*)-fluoropyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-oxo-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-cyclohexylamino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-cyclopropylamino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-hydroxy-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-(4-methylpiperazin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-(tetrahydrofuran-2-ylmethyl)amino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-cyclobutylamino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-(cyclopropylmethyl)amino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-(2-(diethylamino)ethyl)methylamino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-(4-pyrrolidin-1-yl)piperidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-(4-(piperidin-1-ylmethyl)piperidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-amino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-(2-(dimethylamino)ethyl)amino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-(carboxymethyl)amino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(*t*-butoxycarbonylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-(acetamido)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-((2*R*)-2-(methoxycarbonyl)pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-(4,4-difluoropiperidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-((methoxycarbonylmethyl)(methyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-((2*R*)-2-(carboxy)pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-(4-(ethoxycarbonyl)piperidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-(4-(carboxy)piperidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-((carboxymethyl)(methyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-(4-(ethoxycarbonylmethyl)piperazin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-(4-(carboxymethyl)piperazin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-(pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-1-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-((7*S*)-7-amino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-(di(cyclopropylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-((2-methylpropyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-((propyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-((7*S*)-7-(dipropylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-((7*S*)-7-(diethylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-((7*S*)-7-(cyclohexylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-((7*S*)-7-(cyclopentylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-((1-cyclopentylethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(2-propylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-((3,3-dimethylbut-2-yl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-((cyclohexylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(di(cyclohexylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-((5-chlorothien-2-yl)methyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-((2-carboxyphenyl)methyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-((3-bromophenyl)methyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(dimethylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(cyclobutylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(3-pentylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-((2,2-dimethylpropyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(di(cyclopentylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-((cyclopentylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(di(bicyclo[2.2.1]hept-2-en-5-ylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-((bicyclo[2.2.1]hept-2-en-5-ylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(3-methylbutylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(di(3-methylbutyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(2-ethylbutylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(but-2-enylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(butyl(but-2-enyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*⁵-((7*S*)-7-(*t*-butoxycarbonylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-amino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(dimethylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(diethylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(dipropylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(di(cyclopropylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(di(3-methylbutyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(cyclobutylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(cyclohexylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-((methylethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(cyclopentylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine; and

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(2-butylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine.

In some embodiments in the compound of formula (Ia) as set forth above:

R¹, R⁴ and R⁵ are each independently hydrogen;

R² is heteroaryl optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thiooxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, -R¹³-OR¹², -R¹³-OC(O)-R¹², -R¹³-O-R¹⁴-N(R¹²)₂, -R¹³-N(R¹²)-R¹⁴-N(R¹²)₂, -R¹³-N(R¹²)₂, -R¹³-C(O)R¹², -R¹³-C(O)OR¹², -R¹³-C(O)N(R¹²)₂, -R¹³-C(O)N(R¹²)-R¹⁴-N(R¹²)R¹³, -R¹³-C(O)N(R¹²)-R¹⁴-OR¹², -R¹³-N(R¹²)C(O)OR¹², -R¹³-N(R¹²)C(O)R¹², -R¹³-N(R¹²)S(O)_tR¹² (where t is 1 or 2), -R¹³-S(O)_tOR¹² (where t is 1 or 2), -R¹³-S(O)_pR¹² (where p is 0, 1 or 2), and -R¹³-S(O)_tN(R¹²)₂ (where t is 1 or 2);

R³ is a polycyclic heteroaryl containing more than 14 ring atoms optionally substituted by one or more substituents selected from the group consisting of oxo, thiooxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, -R⁹-OR⁸, -R⁹-O-R¹⁰-OR⁸, -R⁹-O-R¹⁰-O-R¹⁰-OR⁸, -R⁹-O-R¹⁰-CN, -R⁹-O-R¹⁰-C(O)OR⁸, -R⁹-O-R¹⁰-C(O)N(R⁶)R⁷, -R⁹-O-R¹⁰-S(O)_pR⁸ (where p is 0, 1 or 2), -R⁹-O-R¹⁰-N(R⁶)R⁷, -R⁹-O-R¹⁰-C(NR¹¹)N(R¹¹)H, -R⁹-OC(O)-R⁸, -R⁹-N(R⁶)R⁷, -R⁹-C(O)R⁸, -R⁹-C(O)OR⁸, -R⁹-C(O)N(R⁶)R⁷, -R⁹-N(R⁶)C(O)OR¹², -R⁹-N(R⁶)C(O)R⁸, -R⁹-N(R⁶)S(O)_tR⁸ (where t is 1 or 2), -R⁹-S(O)_tOR⁸ (where t is 1 or 2), -R⁹-S(O)_pR⁸ (where p is 0, 1 or 2), and -R⁹-S(O)_tN(R⁶)R⁷ (where t is 1 or 2); and each R⁶, each R⁷, each R⁸, each R⁹, each R¹⁰, each R¹¹, each R¹², each R¹³ and each R¹⁴ are as described above for compounds of formula (Ia); and each R⁶, each R⁷, each R⁸, each R⁹, each R¹⁰, each R¹¹, each R¹², each R¹³ and each R¹⁴ are as described above for compounds of formula (Ia).

In some embodiments in the compound of formula (Ia) as set forth above:

R² is heteroaryl selected from the group consisting of pyridinyl, pyrimidinyl, 4,5-dihydro-1*H*-benzo[*b*]azepin-2(3*H*)-on-8-yl, benzo[*d*]imidazolyl, 6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*d*]azepin-3-yl, 6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*c*]azepin-3-yl, 5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl, 5,6,7,8-tetrahydroquinolin-3-yl,

1,2,3,4-tetrahydroisoquinolin-7-yl, 2,3,4,5-tetrahydrobenzo[*b*]oxepin-7-yl,
 3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepin-7-yl, benzo[*d*]oxazol-5-yl, 3,4-
 dihydro-2*H*-benzo[*b*][1,4]oxazin-7-yl, benzo[*b*]thiophenyl, and
 6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-3-yl, each optionally substituted by one or more
 substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl,
 haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally
 substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl,
 optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally
 substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted
 heterocyclylalkenyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl,
 optionally substituted heteroarylalkenyl, $-R^{13}-OR^{12}$, $-R^{13}-OC(O)-R^{12}$, $-R^{13}-O-R^{14}-N(R^{12})_2$,
 $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)OR^{12}$, $-R^{13}-C(O)N(R^{12})_2$, $-R^{13}-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}$,
 $-R^{13}-C(O)N(R^{12})-R^{14}-OR^{12}$, $-R^{13}-N(R^{12})C(O)OR^{12}$, $-R^{13}-N(R^{12})C(O)R^{12}$, $-R^{13}-N(R^{12})S(O)_tR^{12}$
 (where *t* is 1 or 2), $-R^{13}-S(O)_tOR^{12}$ (where *t* is 1 or 2), $-R^{13}-S(O)_pR^{12}$ (where *p* is 0, 1 or 2),
 and $-R^{13}-S(O)_tN(R^{12})_2$ (where *t* is 1 or 2); and

R^3 is a polycyclic heteroaryl containing more than 14 ring atoms selected from the
 group consisting of 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl, 6,7,8,9-
 tetrahydro-5*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-
 benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[2,3]azepino[4,5-*c*]pyridazin-
 3-yl, (Z)-dibenzo[*b*,*f*][1,4]thiazepin-11-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[4,5-
c]pyridazin-2-yl, 6,7-dihydro-5*H*-benzo[2,3]oxepino[4,5-*c*]pyridazin-3-yl, spiro[chromeno[4,3-
c]pyridazine-5,1'-cyclopentane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-
 [1,3]dioxolane]-3-yl, 5,6,8,9-tetrahydrospiro[benzo[7]annulene-7,2'-[1,3]dioxolane]-3-yl,
 5,7,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-6,2'-[1,3]dioxolane]-3-yl, 6,7-dihydro-5*H*-
 benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-
 2-yl, 5,6,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 6,8,9,10-
 tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxane]-3-yl and 6,7-dihydro-5*H*-
 benzo[6,7]cyclohepta[1,2-*b*]pyridin-2-yl, each optionally substituted by one or more
 substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl,
 alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally
 substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally
 substituted heterocyclyl, $-R^9-OR^8$, $-R^9-OC(O)-R^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)R^8$, $-R^9-C(O)OR^8$,
 $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)OR^{12}$, $-R^9-N(R^6)C(O)R^8$, $-R^9-N(R^6)S(O)_tR^8$ (where *t* is 1 or
 2), $-R^9-S(O)_tOR^8$ (where *t* is 1 or 2), $-R^9-S(O)_pR^8$ (where *p* is 0, 1 or 2), and $-R^9-S(O)_tN(R^6)R^7$
 (where *t* is 1 or 2).

Another embodiment is the use where, in the compound of formula (Ia) as set forth above:

R^2 is selected from the group consisting of pyridinyl and pyrimidinyl, each optionally
 substituted by one or more substituents selected from the group consisting of alkyl, alkenyl,
 alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally
 substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally
 substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted
 cycloalkylalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl,
 optionally substituted heterocyclylalkenyl, optionally substituted heteroaryl, optionally
 substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, $-R^{13}-OR^{12}$,
 $-R^{13}-OC(O)-R^{12}$, $-R^{13}-O-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)OR^{12}$,
 $-R^{13}-C(O)N(R^{12})_2$, $-R^{13}-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}$, $-R^{13}-C(O)N(R^{12})-R^{14}-OR^{12}$,

$-R^{13}-N(R^{12})C(O)OR^{12}$, $-R^{13}-N(R^{12})C(O)R^{12}$, $-R^{13}-N(R^{12})S(O)_tR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_tOR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_pR^{12}$ (where p is 0, 1 or 2), and $-R^{13}-S(O)_tN(R^{12})_2$ (where t is 1 or 2).

In some embodiments the compound of formula (Ia), as set forth above, is selected from the group consisting of:

- 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(6-(4-(bicyclo[2.2.1]heptan-2-yl)piperazin-1-yl)pyridin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(6-(4-cyclopentyl-1,4-diazepan-1-yl)pyridin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(6-(4-(4-methylpiperazin-1-yl)piperidin-1-yl)pyridine-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(pyridin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(6-(6-aminopyridin-3-yl)pyridine-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;;
- 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(6-(3-aminophenyl)pyridine-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(6-(3-cyanophenyl)pyridine-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(6-(benzo[d][1,3]dioxole-6-yl)pyridine-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(6-(3-methylsulfonamidylphenyl)pyridine-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(6-(2-diethylaminomethyl)pyrrolidin-1-ylpyridin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(6-(3-diethylaminopyrrolidin-1-yl)pyridin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(6-(3-(4-(N-methylpiperazin-4-yl)piperidin-1-yl)-(E)-propenyl)pyridin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(6-(4-(pyrrolidin-1-yl)piperidin-1-yl)-5-methylpyridin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(6-(3-piperidin-1-yl)-(E)-propenyl)pyridin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(6-(4-(bicyclo[2.2.1]heptan-2-yl)-1,4-diazepan-1-yl)pyridin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(6-(3-(4-(pyrrolidin-1-yl)piperidin-1-yl)-(E)-propenyl)pyridin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(6-(3-piperidin-1-yl)-propanylpyridin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(6-(3-(4-(piperidin-1-yl)piperidin-1-yl)-(E)-propenyl)pyridin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(6-(3-(4-dimethylaminopiperidin-1-yl)-(E)-propenyl)pyridin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(2-(4-pyrrolidin-1-yl)piperidin-1-yl)pyrimidin-5-yl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(2-(4-(piperidin-1-ylmethyl)piperidin-1-yl)pyrimidin-5-yl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(6-((4-piperidin-1-yl)piperidin-1-yl)carbonyl)pyridin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(2-(4-cyclopropylmethylpiperazin-1-yl)pyridine-5-yl)-1*H*-1,2,4-triazole-3,5-diamine; and
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(2-(3-(*S*)-methyl-4-cyclopropylmethylpiperazin-1-yl)pyridine-5-yl)-1*H*-1,2,4-triazole-3,5-diamine.

In some embodiments in the compound of formula (Ia) as set forth above:

*R*¹, *R*⁴ and *R*⁵ are each independently hydrogen;

*R*² is selected from the group consisting of 4,5-dihydro-1*H*-benzo[*b*]azepin-2(3*H*)-on-8-yl, benzo[*d*]imidazolyl, 6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*d*]azepin-3-yl, 6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*c*]azepin-3-yl, 5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl, 5,6,7,8-tetrahydroquinolin-3-yl, 1,2,3,4-tetrahydroisoquinolin-7-yl, 2,3,4,5-tetrahydrobenzo[*b*]oxepin-7-yl, 3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepin-7-yl, benzo[*d*]oxazol-5-yl, 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-7-yl, benzo[*b*]thiophenyl, and 6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-3-yl, each optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, -*R*¹³-OR¹², -*R*¹³-OC(O)-*R*¹², -*R*¹³-O-*R*¹⁴-N(*R*¹²)₂, -*R*¹³-N(*R*¹²)₂, -*R*¹³-C(O)*R*¹², -*R*¹³-C(O)OR¹², -*R*¹³-C(O)N(*R*¹²)₂, -*R*¹³-C(O)N(*R*¹²)-*R*¹⁴-N(*R*¹²)*R*¹³, -*R*¹³-C(O)N(*R*¹²)-*R*¹⁴-OR¹², -*R*¹³-N(*R*¹²)C(O)OR¹², -*R*¹³-N(*R*¹²)C(O)*R*¹², -*R*¹³-N(*R*¹²)S(O)_{*t*}*R*¹² (where *t* is 1 or 2), -*R*¹³-S(O)_{*t*}OR¹² (where *t* is 1 or 2), -*R*¹³-S(O)_{*p*}*R*¹² (where *p* is 0, 1 or 2), and -*R*¹³-S(O)_{*t*}N(*R*¹²)₂ (where *t* is 1 or 2); and

*R*³ is a polycyclic heteroaryl containing more than 14 ring atoms selected from the group consisting of 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl, 6,7,8,9-tetrahydro-5*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[2,3]azepino[4,5-*c*]pyridazin-3-yl, (Z)-dibenzo[*b*,*f*][1,4]thiazepin-11-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[4,5-*c*]pyridazin-2-yl, 6,7-dihydro-5*H*-benzo[2,3]oxepino[4,5-*c*]pyridazin-3-yl, spiro[chromeno[4,3-*c*]pyridazine-5,1'-cyclopentane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 5,6,8,9-tetrahydrospiro[benzo[7]annulene-7,2'-[1,3]dioxolane]-3-yl, 5,7,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-6,2'-[1,3]dioxolane]-3-yl, 6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-2-yl, 5,6,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxane]-3-yl and 6,7-dihydro-5*H*-

benzo[6,7]cyclohepta[1,2-*b*]pyridin-2-yl, each optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-R^9-OR^8$, $-R^9-OC(O)-R^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)R^8$, $-R^9-C(O)OR^8$, $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)OR^{12}$, $-R^9-N(R^6)C(O)R^8$, $-R^9-N(R^6)S(O)_tR^8$ (where *t* is 1 or 2), $-R^9-S(O)_tOR^8$ (where *t* is 1 or 2), $-R^9-S(O)_pR^8$ (where *p* is 0, 1 or 2), and $-R^9-S(O)_tN(R^6)R^7$ (where *t* is 1 or 2).

In some embodiments the compound of formula (Ia), as set forth above, is selected from the group consisting of:

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(4,5-dihydro-1*H*-benzo[*b*]azepin-2(3*H*)-on-8-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(2-(dimethylaminomethyl)-1*H*-benzo[*d*]imidazol-5-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-cyclopentyl-6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*d*]azepin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(6-(4-(4-methylpiperazin-1-yl)piperidin-1-yl)pyridine-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(6-(4-methylpiperazin-1-yl)carbonyl-5,6,7,8-tetrahydroquinolin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine, compound #31, 1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(2,3,4,5-tetrahydrobenzo[*b*]oxepin-7-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepin-7-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[2,3]oxepino[4,5-*c*]pyridazin-3-yl)-*N*³-(2-(pyrrolidin-1-ylmethyl)benzo[*d*]oxazol-5-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(4-(2-dimethylaminoethyl)-(3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-7-yl))-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[2,3]oxepino[4,5-*c*]pyridazin-3-yl)-*N*³-(4-(2-dimethylaminoethyl)-(3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-7-yl))-1*H*-1,2,4-triazole-3,5-diamine;

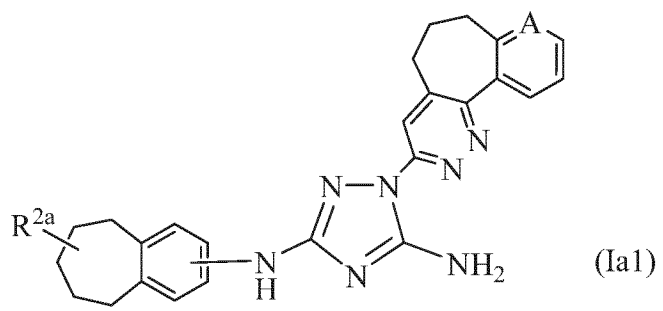
1-(6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl)-*N*³-(2-(1-(4-(2-(dimethylamino)ethyl)piperazin-1-yl)oxomethyl)benzo[*b*]thiophen-5-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(6-cyclopentyl-6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*c*]azepin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7-pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(2-cyclopentyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(6-(pyrrolidin-1-yl)-5,6,7,8-tetrahydroquinolin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(6-cyclopentyl-5,6,7,8-tetrahydro-1,6-naphthyridine-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((*S*)-7-(pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(1,2,3,4-tetrahydroisoquinolin-7-yl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(2-(1-methylpiperidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-1*H*-1,2,4-triazole-3,5-diamine; and
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(2-(cyclopropylmethyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-1*H*-1,2,4-triazole-3,5-diamine.

In some embodiments the compound of formula (Ia), as set forth above, is a compound of formula (Ia1):



wherein:

A is =C(H)- or =N-;

each R^{2a} is independently selected from the group consisting of -N(R^{12a})₂ and -N(R^{12a})C(O)R^{12a},

or R^{2a} is an *N*-heterocyclyl optionally substituted by one or more substituents selected from the group consisting of halo and -R²¹-C(O)OR²⁰,

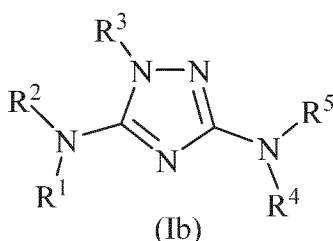
each R^{12a} is independently selected from the group consisting of hydrogen, alkyl, alkenyl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl;

R²⁰ is independently selected from the group consisting of hydrogen, alkyl, alkenyl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl; and

R²¹ is independently selected from the group consisting of a direct bond or an optionally substituted straight or branched alkylene chain;

as an isolated stereoisomer or mixture thereof, or a pharmaceutically acceptable salt thereof.

In some embodiments the compound of formula (I) is a compound of formula (Ib):



wherein R^1 , R^2 , R^3 , R^4 and R^5 are as described above for compounds of formula (I), as an isolated stereoisomer or mixture thereof or as a tautomer or mixture thereof, or a pharmaceutically acceptable salt or *N*-oxide thereof.

In some embodiments in the compound of formula (Ib) as set forth above, R^2 and R^3 are each independently a polycyclic heteroaryl containing more than 14 ring atoms optionally substituted by one or more substituents selected from the group consisting of oxo, thio, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-R^9-OR^8$, $-R^9-O-R^{10}-OR^8$, $-R^9-O-R^{10}-O-R^{10}-OR^8$, $-R^9-O-R^{10}-CN$, $-R^9-O-R^{10}-C(O)OR^8$, $-R^9-O-R^{10}-C(O)N(R^6)R^7$, $-R^9-O-R^{10}-S(O)_pR^8$ (where p is 0, 1 or 2), $-R^9-O-R^{10}-N(R^6)R^7$, $-R^9-O-R^{10}-C(NR^{11})N(R^{11})H$, $-R^9-OC(O)-R^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)R^8$, $-R^9-C(O)OR^8$, $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)OR^{12}$, $-R^9-N(R^6)C(O)R^8$, $-R^9-N(R^6)S(O)_tR^8$ (where t is 1 or 2), $-R^9-S(O)_tOR^8$ (where t is 1 or 2), $-R^9-S(O)_pR^8$ (where p is 0, 1 or 2), and $-R^9-S(O)_tN(R^6)R^7$ (where t is 1 or 2); and R^1 , R^4 , R^5 , each R^6 , each R^7 , each R^8 , each R^9 , each R^{10} , each R^{11} and R^{12} are as described above in relation to formula (I).

In some embodiments in the compound of formula (Ib) as set forth above:

R^1 , R^4 and R^5 are each hydrogen;

each R^6 and R^7 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, hydroxyalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^{10}-OR^8$, $-R^{10}-CN$, $-R^{10}-NO_2$, $-R^{10}-N(R^8)_2$, $-R^{10}-C(O)OR^8$ and $-R^{10}-C(O)N(R^8)_2$, or any R^6 and R^7 , together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heteroaryl or an optionally substituted *N*-heterocyclyl;

each R^8 is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclalkyl, optionally substituted heteroaryl, and optionally substituted heteroarylalkyl;

each R^9 is independently selected from the group consisting of a direct bond and an optionally substituted straight or branched alkylene chain;

each R^{10} is an optionally substituted straight or branched alkylene chain; and

each R^{11} is independently selected from the group consisting of hydrogen, alkyl, cyano, nitro and $-OR^8$.

In some embodiments in the compound of formula (Ib) as set forth above:

R^2 and R^3 are each independently a polycyclic heteroaryl containing more than 14 ring atoms selected from the group consisting of 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl, 6,7,8,9-tetrahydro-5*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[2,3]azepino[4,5-*c*]pyridazin-3-yl, (Z)-dibenzo[*b,f*][1,4]thiazepin-11-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[4,5-*c*]pyridazin-2-yl, 6,7-dihydro-5*H*-benzo[2,3]oxepino[4,5-*c*]pyridazin-3-yl, spiro[chromeno[4,3-*c*]pyridazine-5,1'-cyclopentane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 5,6,8,9-tetrahydrospiro[benzo[7]annulene-7,2'-[1,3]dioxolane]-3-yl, 5,7,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-6,2'-[1,3]dioxolane]-3-yl, 6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-2-yl, 5,6,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxane]-3-yl and 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridin-2-yl, each optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-R^9-OR^8$, $-R^9-OC(O)-R^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)R^8$, $-R^9-C(O)OR^8$, $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)OR^{12}$, $-R^9-N(R^6)C(O)R^8$, $-R^9-N(R^6)S(O)_tR^8$ (where *t* is 1 or 2), $-R^9-S(O)_tOR^8$ (where *t* is 1 or 2), $-R^9-S(O)_pR^8$ (where *p* is 0, 1 or 2), and $-R^9-S(O)_tN(R^6)R^7$ (where *t* is 1 or 2).

In some embodiments the compound of formula (Ib), as set forth above, is 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*⁵-(5,7,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-6,2'-[1,3]dioxolane]-3-yl)-1*H*-1,2,4-triazole-3,5-diamine.

In some embodiments in the compound of formula (Ib) as set forth above:

R^2 is selected from the group consisting of aryl and heteroaryl, where the aryl and the heteroaryl are each independently optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, $-R^{13}-OR^{12}$, $-R^{13}-OC(O)-R^{12}$, $-R^{13}-O-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)OR^{12}$, $-R^{13}-C(O)N(R^{12})_2$, $-R^{13}-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}$, $-R^{13}-C(O)N(R^{12})-R^{14}-OR^{12}$, $-R^{13}-N(R^{12})C(O)OR^{12}$, $-R^{13}-N(R^{12})C(O)R^{12}$, $-R^{13}-N(R^{12})S(O)_tR^{12}$ (where *t* is 1 or 2), $-R^{13}-S(O)_tOR^{12}$ (where *t* is 1 or 2), $-R^{13}-S(O)_pR^{12}$ (where *p* is 0, 1 or 2), and $-R^{13}-S(O)_tN(R^{12})_2$ (where *t* is 1 or 2); and

R^3 is a polycyclic heteroaryl containing more than 14 ring atoms optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted

cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-R^9-OR^8$, $-R^9-O-R^{10}-OR^8$, $-R^9-O-R^{10}-O-R^{10}-OR^8$, $-R^9-O-R^{10}-CN$, $-R^9-O-R^{10}-C(O)OR^8$, $-R^9-O-R^{10}-C(O)N(R^6)R^7$, $-R^9-O-R^{10}-S(O)_pR^8$ (where p is 0, 1 or 2), $-R^9-O-R^{10}-N(R^6)R^7$, $-R^9-O-R^{10}-C(NR^{11})N(R^{11})H$, $-R^9-OC(O)-R^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)R^8$, $-R^9-C(O)OR^8$, $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)OR^{12}$, $-R^9-N(R^6)C(O)R^8$, $-R^9-N(R^6)S(O)_tR^8$ (where t is 1 or 2), $-R^9-S(O)_tOR^8$ (where t is 1 or 2), $-R^9-S(O)_pR^8$ (where p is 0, 1 or 2), and $-R^9-S(O)_tN(R^6)R^7$ (where t is 1 or 2).

In some embodiments in the compound of formula (Ib) as set forth above:

R^1 , R^4 and R^5 are each independently hydrogen;

each R^6 and R^7 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, hydroxyalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^{10}-OR^8$, $-R^{10}-CN$, $-R^{10}-NO_2$, $-R^{10}-N(R^8)_2$, $-R^{10}-C(O)OR^8$ and $-R^{10}-C(O)N(R^8)_2$, or any R^6 and R^7 , together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heteroaryl or an optionally substituted *N*-heterocyclyl;

each R^8 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclalkyl, optionally substituted heteroaryl, and optionally substituted heteroarylalkyl;

each R^9 is independently selected from the group consisting of a direct bond and an optionally substituted straight or branched alkylene chain;

each R^{10} is an optionally substituted straight or branched alkylene chain;

each R^{11} is independently selected from the group consisting of hydrogen, alkyl, cyano, nitro and $-OR^8$;

each R^{12} is independently selected from the group consisting of hydrogen, alkyl, alkenyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl, or two R^{12s} , together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heterocyclyl or an optionally substituted *N*-heteroaryl;

each R^{13} is independently selected from the group consisting of a direct bond and an optionally substituted straight or branched alkylene chain; and

each R^{14} is an optionally substituted straight or branched alkylene chain.

In some embodiments in the compound of formula (Ib) as set forth above:

R^2 is aryl optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted

cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, $-R^{13}-OR^{12}$, $-R^{13}-OC(O)-R^{12}$, $-R^{13}-O-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)OR^{12}$, $-R^{13}-C(O)N(R^{12})_2$, $-R^{13}-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}$, $-R^{13}-C(O)N(R^{12})-R^{14}-OR^{12}$, $-R^{13}-N(R^{12})C(O)OR^{12}$, $-R^{13}-N(R^{12})C(O)R^{12}$, $-R^{13}-N(R^{12})S(O)_tR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_tOR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_pR^{12}$ (where p is 0, 1 or 2), and $-R^{13}-S(O)_tN(R^{12})_2$ (where t is 1 or 2); and

R^3 is a polycyclic heteroaryl containing more than 14 ring atoms optionally substituted by one or more substituents selected from the group consisting of oxo, thio, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-R^9-OR^8$, $-R^9-O-R^{10}-OR^8$, $-R^9-O-R^{10}-O-R^{10}-OR^8$, $-R^9-O-R^{10}-CN$, $-R^9-O-R^{10}-C(O)OR^8$, $-R^9-O-R^{10}-C(O)N(R^6)R^7$, $-R^9-O-R^{10}-S(O)_pR^8$ (where p is 0, 1 or 2), $-R^9-O-R^{10}-N(R^6)R^7$, $-R^9-O-R^{10}-C(NR^{11})N(R^{11})H$, $-R^9-OC(O)-R^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)R^8$, $-R^9-C(O)OR^8$, $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)OR^{12}$, $-R^9-N(R^6)C(O)R^8$, $-R^9-N(R^6)S(O)_tR^8$ (where t is 1 or 2), $-R^9-S(O)_tOR^8$ (where t is 1 or 2), $-R^9-S(O)_pR^8$ (where p is 0, 1 or 2), and $-R^9-S(O)_tN(R^6)R^7$ (where t is 1 or 2).

In some embodiments in the compound of formula (Ib) as set forth above:

R^1 , R^4 and R^5 are each independently hydrogen;

R^2 is aryl selected from the group consisting of phenyl and 6,7,8,9-tetrahydro-5H-benzo[7]annulene-2-yl, each optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thio, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, $-R^{13}-OR^{12}$, $-R^{13}-OC(O)-R^{12}$, $-R^{13}-O-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)OR^{12}$, $-R^{13}-C(O)N(R^{12})_2$, $-R^{13}-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}$, $-R^{13}-C(O)N(R^{12})-R^{14}-OR^{12}$, $-R^{13}-N(R^{12})C(O)OR^{12}$, $-R^{13}-N(R^{12})C(O)R^{12}$, $-R^{13}-N(R^{12})S(O)_tR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_tOR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_pR^{12}$ (where p is 0, 1 or 2), and $-R^{13}-S(O)_tN(R^{12})_2$ (where t is 1 or 2); and

R^3 is a polycyclic heteroaryl containing more than 14 ring atoms selected from the group consisting of 6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazin-3-yl, 6,7,8,9-tetrahydro-5H-cyclohepta[4,5]thieno[2,3-d]pyrimidin-4-yl, 6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-d]pyrimidin-4-yl, 6,7-dihydro-5H-benzo[2,3]azepino[4,5-c]pyridazin-3-yl, (Z)-dibenzo[b,f][1,4]thiazepin-11-yl, 6,7-dihydro-5H-benzo[6,7]cyclohepta[4,5-c]pyridazin-2-yl, 6,7-dihydro-5H-benzo[2,3]oxepino[4,5-c]pyridazin-3-yl, spiro[chromeno[4,3-c]pyridazine-5,1'-cyclopentane]-3-yl, 6,8,9,10-tetrahydro-5H-spiro[cycloocta[b]pyridine-7,2'-[1,3]dioxolane]-3-yl, 5,6,8,9-tetrahydrospiro[benzo[7]annulene-7,2'-[1,3]dioxolane]-3-yl, 5,7,8,9-tetrahydrospiro[cyclohepta[b]pyridine-6,2'-[1,3]dioxolane]-3-yl, 6,7-dihydro-5H-

benzo[2,3]thiopyrino[4,5-*c*]pyridazin-3-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-2-yl, 5,6,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxane]-3-yl and 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridin-2-yl, each optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-R^9-OR^8$, $-R^9-OC(O)-R^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)R^8$, $-R^9-C(O)OR^8$, $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)OR^{12}$, $-R^9-N(R^6)C(O)R^8$, $-R^9-N(R^6)S(O)_tR^8$ (where *t* is 1 or 2), $-R^9-S(O)_tOR^8$ (where *t* is 1 or 2), $-R^9-S(O)_pR^8$ (where *p* is 0, 1 or 2), and $-R^9-S(O)_tN(R^6)R^7$ (where *t* is 1 or 2).

In some embodiments in the compound of formula (Ib) as set forth above:

R^2 is phenyl optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, $-R^{13}-OR^{12}$, $-R^{13}-OC(O)-R^{12}$, $-R^{13}-O-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)OR^{12}$, $-R^{13}-C(O)N(R^{12})_2$, $-R^{13}-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}$, $-R^{13}-C(O)N(R^{12})-R^{14}-OR^{12}$, $-R^{13}-N(R^{12})C(O)OR^{12}$, $-R^{13}-N(R^{12})C(O)R^{12}$, $-R^{13}-N(R^{12})S(O)_tR^{12}$ (where *t* is 1 or 2), $-R^{13}-S(O)_tOR^{12}$ (where *t* is 1 or 2), $-R^{13}-S(O)_pR^{12}$ (where *p* is 0, 1 or 2), and $-R^{13}-S(O)_tN(R^{12})_2$ (where *t* is 1 or 2).

In some embodiments the compound of formula (Ib), as set forth above, is selected from the group consisting of:

- 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*⁵-(3-fluoro-4-(4-(indolin-2-on-1-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*⁵-(3-fluoro-4-(4-(morpholin-4-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*⁵-(4-(3,5-dimethylpiperazin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
- 1-(7-methyl-6,7-dihydro-5*H*-benzo[2,3]azepino[4,5-*c*]pyridazin-3-yl)-*N*⁵-(4-(*N*-methylpiperazin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*⁵-(4-((5-fluoroindolin-2-on-3-yl)methyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*⁵-(4-(4-pyrrolidin-1-yl)piperidinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*⁵-(4-((4-pyrrolidin-1-yl)piperidinyl)methyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*⁵-(4-((4-cyclopentylpiperazinyl)methyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
- 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*⁵-(4-((4-isopropylpiperazinyl)methyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*⁵-(3-fluoro-4-(4-*N*-methylpiperid-4-ylpiperazinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*⁵-(3-fluoro-4-(7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*⁵-(3-fluoro-4-(3-pyrrolidin-1-ylazetidiny)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*⁵-(3-methyl-4-(4-(*N*-methylpiperazin-4-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl)-*N*⁵-(4-(4-pyrrolidin-1-ylpiperidinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*⁵-(3-fluoro-4-(3-pyrrolidin-1-yl)pyrrolidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*⁵-(3-fluoro-4-(4-methylpiperazin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine; and
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*⁵-(3-fluoro-4-(4-cyclopropylmethylpiperazin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine.

In some embodiments in the compound of formula (Ib) as set forth above:

R¹, R⁴ and R⁵ are each independently hydrogen;

R² is 6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, -R¹³-OR¹², -R¹³-OC(O)-R¹², -R¹³-O-R¹⁴-N(R¹²)₂, -R¹³-N(R¹²)₂, -R¹³-C(O)R¹², -R¹³-C(O)OR¹², -R¹³-C(O)N(R¹²)₂, -R¹³-C(O)N(R¹²)-R¹⁴-N(R¹²)R¹³, -R¹³-C(O)N(R¹²)-R¹⁴-OR¹², -R¹³-N(R¹²)C(O)OR¹², -R¹³-N(R¹²)C(O)R¹², -R¹³-N(R¹²)S(O)_tR¹² (where *t* is 1 or 2), -R¹³-S(O)_tOR¹² (where *t* is 1 or 2), -R¹³-S(O)_pR¹² (where *p* is 0, 1 or 2), and -R¹³-S(O)_tN(R¹²)₂ (where *t* is 1 or 2); and

R³ is a polycyclic heteroaryl containing more than 14 ring atoms selected from the group consisting of 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl, 6,7,8,9-tetrahydro-5*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[2,3]azepino[4,5-*c*]pyridazin-3-yl, (Z)-dibenzo[*b*,*f*][1,4]thiazepin-11-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[4,5-*c*]pyridazin-2-yl, 6,7-dihydro-5*H*-benzo[2,3]oxepino[4,5-*c*]pyridazin-3-yl, spiro[chromeno[4,3-*c*]pyridazine-5,1'-cyclopentane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 5,6,8,9-tetrahydrospiro[benzo[7]annulene-7,2'-[1,3]dioxolane]-3-yl, 5,7,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-6,2'-[1,3]dioxolane]-3-yl, 6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-2-yl, 5,6,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxane]-3-yl and 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridin-2-yl, each optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally

substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-R^9-OR^8$, $-R^9-OC(O)-R^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)R^8$, $-R^9-C(O)OR^8$, $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)OR^{12}$, $-R^9-N(R^6)C(O)R^8$, $-R^9-N(R^6)S(O)_tR^8$ (where t is 1 or 2), $-R^9-S(O)_tOR^8$ (where t is 1 or 2), $-R^9-S(O)_pR^8$ (where p is 0, 1 or 2), and $-R^9-S(O)_tN(R^6)R^7$ (where t is 1 or 2).

In some embodiments the compound of formula (Ib), as set forth above, is selected from the group consisting of:

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*⁵-(7-(pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-1-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*⁵-((7*S*)-7-(*t*-butoxycarbonylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*⁵-(7-((bicyclo[2.2.1]heptan-2-yl)(methyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine; and

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*⁵-(7-(*S*)-pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine.

In some embodiments in the compound of formula (Ib) as set forth above:

R^1 , R^4 and R^5 are each independently hydrogen;

R^2 is heteroaryl optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, $-R^{13}-OR^{12}$, $-R^{13}-OC(O)-R^{12}$, $-R^{13}-O-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)OR^{12}$, $-R^{13}-C(O)N(R^{12})_2$, $-R^{13}-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}$, $-R^{13}-C(O)N(R^{12})-R^{14}-OR^{12}$, $-R^{13}-N(R^{12})C(O)OR^{12}$, $-R^{13}-N(R^{12})C(O)R^{12}$, $-R^{13}-N(R^{12})S(O)_tR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_tOR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_pR^{12}$ (where p is 0, 1 or 2), and $-R^{13}-S(O)_tN(R^{12})_2$ (where t is 1 or 2); and

R^3 is a polycyclic heteroaryl containing more than 14 ring atoms optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-R^9-OR^8$, $-R^9-O-R^{10}-OR^8$, $-R^9-O-R^{10}-O-R^{10}-OR^8$, $-R^9-O-R^{10}-CN$, $-R^9-O-R^{10}-C(O)OR^8$, $-R^9-O-R^{10}-C(O)N(R^6)R^7$, $-R^9-O-R^{10}-S(O)_pR^8$ (where p is 0, 1 or 2), $-R^9-O-R^{10}-N(R^6)R^7$, $-R^9-O-R^{10}-C(NR^{11})N(R^{11})H$, $-R^9-OC(O)-R^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)R^8$, $-R^9-C(O)OR^8$, $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)OR^{12}$, $-R^9-N(R^6)C(O)R^8$, $-R^9-N(R^6)S(O)_tR^8$ (where t is 1 or 2), $-R^9-S(O)_tOR^8$

(where t is 1 or 2), $-R^9-S(O)_pR^8$ (where p is 0, 1 or 2), and $-R^9-S(O)_tN(R^6)R^7$ (where t is 1 or 2).

In some embodiments in the compound of formula (Ib) as set forth above:

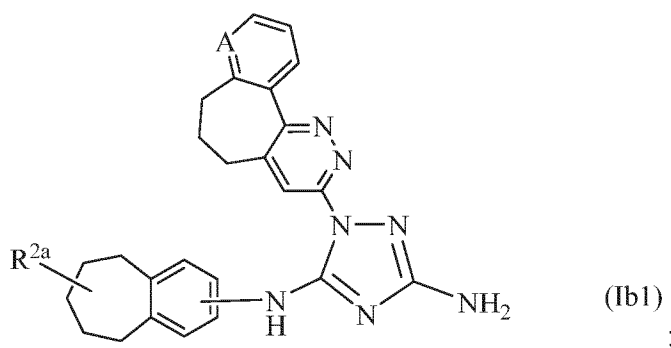
R^2 is heteroaryl selected from the group consisting of pyridinyl, pyrimidinyl, 4,5-dihydro-1*H*-benzo[*b*]azepin-2(3*H*)-on-8-yl, benzo[*d*]imidazolyl, 6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*d*]azepin-3-yl, 6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*c*]azepin-3-yl, 5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl, 5,6,7,8-tetrahydroquinolin-3-yl, 1,2,3,4-tetrahydroisoquinolin-7-yl, 2,3,4,5-tetrahydrobenzo[*b*]oxepin-7-yl, 3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepin-7-yl, benzo[*d*]oxazol-5-yl, 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-7-yl, benzo[*b*]thiophenyl, and 6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-3-yl, each optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, $-R^{13}-OR^{12}$, $-R^{13}-OC(O)-R^{12}$, $-R^{13}-O-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)OR^{12}$, $-R^{13}-C(O)N(R^{12})_2$, $-R^{13}-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}$, $-R^{13}-C(O)N(R^{12})-R^{14}-OR^{12}$, $-R^{13}-N(R^{12})C(O)OR^{12}$, $-R^{13}-N(R^{12})C(O)R^{12}$, $-R^{13}-N(R^{12})S(O)_tR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_tOR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_pR^{12}$ (where p is 0, 1 or 2), and $-R^{13}-S(O)_tN(R^{12})_2$ (where t is 1 or 2); and

R^3 is a polycyclic heteroaryl containing more than 14 ring atoms selected from the group consisting of 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl, 6,7,8,9-tetrahydro-5*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[2,3]azepino[4,5-*c*]pyridazin-3-yl, (Z)-dibenzo[*b,f*][1,4]thiazepin-11-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[4,5-*c*]pyridazin-2-yl, 6,7-dihydro-5*H*-benzo[2,3]oxepino[4,5-*c*]pyridazin-3-yl, spiro[chromeno[4,3-*c*]pyridazine-5,1'-cyclopentane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 5,6,8,9-tetrahydrospiro[benzo[7]annulene-7,2'-[1,3]dioxolane]-3-yl, 5,7,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-6,2'-[1,3]dioxolane]-3-yl, 6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-2-yl, 5,6,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxane]-3-yl and 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridin-2-yl, each optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-R^9-OR^8$, $-R^9-OC(O)-R^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)R^8$, $-R^9-C(O)OR^8$, $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)OR^{12}$, $-R^9-N(R^6)C(O)R^8$, $-R^9-N(R^6)S(O)_tR^8$ (where t is 1 or 2), $-R^9-S(O)_tOR^8$ (where t is 1 or 2), $-R^9-S(O)_pR^8$ (where p is 0, 1 or 2), and $-R^9-S(O)_tN(R^6)R^7$ (where t is 1 or 2).

In some embodiments the compound of formula (Ib), as set forth above, is selected from the group consisting of:

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*⁵-(6-(4-(pyrrolidin-1-yl)piperidin-1-yl)-5-methylpyridin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*⁵-(4-(3,5-dimethylpiperazin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*⁵-(1,2,3,4-tetrahydroisoquinolin-7-yl)-1*H*-1,2,4-triazole-3,5-diamine; and
 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*⁵-(2-(1-methylpiperidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-1*H*-1,2,4-triazole-3,5-diamine.

In some embodiments the compound of formula (Ib), as set forth above, is a compound of formula (Ib1):



wherein:

A is =C(H)- or =N-;

each R^{2a} is independently selected from the group consisting of -N(R^{12a})₂ and -N(R^{12a})C(O)R²⁰,

or R^{2a} is an *N*-heterocyclyl optionally substituted by one or more substituents selected from the group consisting of halo and -R²¹-C(O)OR²⁰,

each R^{12a} is independently selected from the group consisting of hydrogen, alkyl, alkenyl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl;

R²⁰ is independently selected from the group consisting of hydrogen, alkyl, alkenyl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl; and

R²¹ is independently selected from the group consisting of a direct bond or an optionally substituted straight or branched alkylene chain;

as an isolated stereoisomer or mixture thereof, or a pharmaceutically acceptable salt thereof.

Preferred embodiments

Preferably, the AXL inhibitor is 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*⁵-((7-(*S*)-pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine.

The most preferred AXL inhibitor is bemcentinib (CAS No. 1037624-75-1 ; UNII 0ICW2LX8AS)

Other embodiments

In some other embodiments the AXLi is selected from the group consisting of:

- Duberminib (CAS No. 1341200-45-0 ; UNII 14D65TV20J);
- Gilteritinib (CAS No. 1254053-43-4 ; UNII 66D92MGC8M);
- Cabozantinib (CAS No. 849217-68-1 ; UNII 1C39JW444G);
- SGI7079 (CAS No. 1239875-86-5);
- Merestinib (CAS No. 1206799-15-6 ; UNII 5OGS5K699E);
- Amuvatinib (CAS No. 850879-09-3 ; UNII SO9S6QZB4R);
- Bosutinib (CAS No. 380843-75-4 ; UNII 5018V4AEZ0);
- Glesatinib (CAS No. 936694-12-1; UNII 7Q29OXD98N); and
- foretinib (CAS No. 849217-64-7; UNII 81FH7VK1C4).

Definitions

As used herein, unless specified to the contrary, the following terms have the meaning indicated:

"Amino" refers to the $-NH_2$ radical.

"Carboxy" refers to the $-C(O)OH$ radical.

"Cyano" refers to the $-CN$ radical.

"Nitro" refers to the $-NO_2$ radical.

"Oxa" refers to the $-O-$ radical.

"Oxo" refers to the $=O$ radical.

"Thioxo" refers to the $=S$ radical.

"Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to twelve carbon atoms, preferably one to eight carbon atoms or one to six carbon atoms and which is attached to the rest of the molecule by a single bond, for example, methyl, ethyl, *n*-propyl, 1-methylethyl (*iso*-propyl), *n*-butyl, *n*-pentyl, 1,1-dimethylethyl (*t*-butyl), 3-methylhexyl, 2-methylhexyl, and the like. For purposes of this disclosure, the term "lower alkyl" refers to an alkyl radical having one to six carbon atoms.

"Optionally substituted alkyl" refers to an alkyl radical, as defined above, which is optionally substituted by one or more substituents selected from the group consisting of halo, cyano, nitro, oxo, thioxo, trimethylsilanyl, $-OR^{20}$, $-OC(O)-R^{20}$, $-N(R^{20})_2$, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-C(O)N(R^{20})_2$, $-N(R^{20})C(O)OR^{20}$, $-N(R^{20})C(O)R^{20}$, $-N(R^{20})S(O)_2R^{20}$, $-S(O)_tOR^{20}$ (where *t* is 1 or 2), $-S(O)_pR^{20}$ (where *p* is 0, 1 or 2), and $-S(O)_2N(R^{20})_2$ where each R^{20} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl, or two R^{20} 's, together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heterocyclyl or an optionally substituted *N*-heteroaryl.

"Alkenyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing at least one double bond, having from two to twelve carbon atoms, preferably one to eight carbon atoms and which is attached to the rest of the molecule by a single bond, for example, ethenyl, prop-1-enyl, but-1-enyl, pent-1-enyl, and penta-1,4-dienyl.

"Optionally substituted alkenyl" refers to an alkenyl radical, as defined above, which is optionally substituted by one or more substituents selected from the group consisting of halo, cyano, nitro, oxo, thioxo, trimethylsilyl, $-OR^{20}$, $-OC(O)-R^{20}$, $-N(R^{20})_2$, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-C(O)N(R^{20})_2$, $-N(R^{20})C(O)OR^{20}$, $-N(R^{20})C(O)R^{20}$, $-N(R^{20})S(O)_2R^{20}$, $-S(O)_tOR^{20}$ (where t is 1 or 2), $-S(O)_pR^{20}$ (where p is 0, 1 or 2), and $-S(O)_2N(R^{20})_2$ where each R^{20} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl, or two R^{20} 's, together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heterocyclyl or an optionally substituted *N*-heteroaryl.

"Alkynyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing at least one triple bond, optionally containing at least one double bond, having from two to twelve carbon atoms, preferably one to eight carbon atoms and which is attached to the rest of the molecule by a single bond, for example, ethynyl, propynyl, butynyl, pentynyl, and hexynyl.

"Optionally substituted alkynyl" refers to an alkynyl radical, as defined above, which is optionally substituted by one or more substituents selected from the group consisting of halo, cyano, nitro, oxo, thioxo, trimethylsilyl, $-OR^{20}$, $-OC(O)-R^{20}$, $-N(R^{20})_2$, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-C(O)N(R^{20})_2$, $-N(R^{20})C(O)OR^{20}$, $-N(R^{20})C(O)R^{20}$, $-N(R^{20})S(O)_2R^{20}$, $-S(O)_tOR^{20}$ (where t is 1 or 2), $-S(O)_pR^{20}$ (where p is 0, 1 or 2), and $-S(O)_2N(R^{20})_2$ where each R^{20} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl, or two R^{20} 's, together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heterocyclyl or an optionally substituted *N*-heteroaryl.

"Straight or branched alkylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing no unsaturation and having from one to twelve carbon atoms, for example, methylene, ethylene, propylene, and *n*-butylene. The alkylene chain is attached to the rest of the molecule through a single bond and to the radical group through a single bond. The points of attachment of the alkylene chain to the rest of the molecule and to the radical group can be through one carbon in the alkylene chain or through any two carbons within the chain.

"Optionally substituted straight or branched alkylene chain" refers to an alkylene chain, as defined above, which is optionally substituted by one or more substituents selected from the group consisting of halo, cyano, nitro, aryl, cycloalkyl, heterocyclyl, heteroaryl, oxo, thioxo, trimethylsilyl, $-OR^{20}$, $-OC(O)-R^{20}$, $-N(R^{20})_2$, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-C(O)N(R^{20})_2$, $-N(R^{20})C(O)OR^{20}$, $-N(R^{20})C(O)R^{20}$, $-N(R^{20})S(O)_2R^{20}$, $-S(O)_tOR^{20}$ (where t is 1 or 2), $-S(O)_pR^{20}$ (where p is 0, 1 or 2), and $-S(O)_2N(R^{20})_2$ where each R^{20} is independently selected from the

group consisting of hydrogen, alkyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl, or two R^{20} 's, together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heterocyclyl or an optionally substituted *N*-heteroaryl.

"Straight or branched alkenylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing at least one double bond and having from two to twelve carbon atoms, for example, ethenylene, propenylene, and *n*-butenylene. The alkenylene chain is attached to the rest of the molecule through a double bond or a single bond and to the radical group through a double bond or a single bond. The points of attachment of the alkenylene chain to the rest of the molecule and to the radical group can be through one carbon or any two carbons within the chain.

"Optionally substituted straight or branched alkenylene chain" refers to an alkenylene chain, as defined above, which is optionally substituted by one or more substituents selected from the group consisting of halo, cyano, nitro, aryl, cycloalkyl, heterocyclyl, heteroaryl, oxo, thioxo, trimethylsilanyl, $-OR^{20}$, $-OC(O)-R^{20}$, $-N(R^{20})_2$, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-C(O)N(R^{20})_2$, $-N(R^{20})C(O)OR^{20}$, $-N(R^{20})C(O)R^{20}$, $-N(R^{20})S(O)_2R^{20}$, $-S(O)_tOR^{20}$ (where *t* is 1 or 2), $-S(O)_pR^{20}$ (where *p* is 0, 1 or 2), and $-S(O)_2N(R^{20})_2$ where each R^{20} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl, or two R^{20} 's, together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heterocyclyl or an optionally substituted *N*-heteroaryl.

"Straight or branched alkynylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing at least one triple bond and having from two to twelve carbon atoms, for example, propynylene, and *n*-butynylene. The alkynylene chain is attached to the rest of the molecule through a single bond and to the radical group through a double bond or a single bond. The points of attachment of the alkynylene chain to the rest of the molecule and to the radical group can be through one carbon or any two carbons within the chain.

"Optionally substituted straight or branched alkynylene chain" refers to an alkynylene chain, as defined above, which is optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, halo, haloalkenyl, cyano, nitro, aryl, cycloalkyl, heterocyclyl, heteroaryl, oxo, thioxo, trimethylsilanyl, $-OR^{20}$, $-OC(O)-R^{20}$, $-N(R^{20})_2$, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-C(O)N(R^{20})_2$, $-N(R^{20})C(O)OR^{20}$, $-N(R^{20})C(O)R^{20}$, $-N(R^{20})S(O)_2R^{20}$, $-S(O)_tOR^{20}$ (where *t* is 1 or 2), $-S(O)_pR^{20}$ (where *p* is 0, 1 or 2), and $-S(O)_2N(R^{20})_2$ where each R^{20} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl, or two R^{20} 's, together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heterocyclyl or an optionally substituted *N*-heteroaryl.

"Aryl" refers to a hydrocarbon ring system radical comprising hydrogen, 6 to 14 carbon atoms and at least one aromatic ring. For purposes of this disclosure, the aryl radical may be a monocyclic, bicyclic, or tricyclic system and which may include spiro ring systems. An aryl radical is commonly, but not necessarily, attached to the parent molecule via an aromatic ring of the aryl radical. For purposes of this disclosure, an "aryl" radical as defined herein can not contain rings having more than 7 members and cannot contain rings wherein two non-adjacent ring atoms thereof are connected through an atom or a group of atoms (*i.e.*, a bridged ring system). Aryl radicals include, but are not limited to, aryl radicals derived from acenaphthylene, anthracene, azulene, benzene, 6,7,8,9-tetrahydro-5*H*-benzo[7]annulene, fluorene, *as*-indacene, *s*-indacene, indane, indene, naphthalene, phenalene, and phenanthrene.

"Optionally substituted aryl" refers to an aryl radical, as defined above, which is optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, $-R^{21}-OR^{20}$, $-R^{21}-OC(O)-R^{20}$, $-R^{21}-N(R^{20})_2$, $-R^{21}-C(O)R^{20}$, $-R^{21}-C(O)OR^{20}$, $-R^{21}-C(O)N(R^{20})_2$, $-R^{21}-O-R^{22}-C(O)N(R^{20})_2$, $-R^{21}-N(R^{20})C(O)OR^{20}$, $-R^{21}-N(R^{20})C(O)R^{20}$, $-R^{21}-N(R^{20})S(O)_2R^{20}$, $-R^{21}-C(=NR^{20})N(R^{20})_2$, $-R^{21}-S(O)_tOR^{20}$ (where *t* is 1 or 2), $-R^{21}-S(O)_pR^{20}$ (where *p* is 0, 1 or 2), and $-R^{21}-S(O)_2N(R^{20})_2$, where each R^{20} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl, or two R^{20} 's, together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heterocyclyl or an optionally substituted *N*-heteroaryl, each R^{21} is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^{22} is a straight or branched alkylene or alkenylene chain.

"Aralkyl" refers to a radical of the formula $-R_b-R_c$ where R_b is an alkylene chain as defined above and R_c is one or more aryl radicals as defined above, for example, benzyl and diphenylmethyl.

"Optionally substituted aralkyl" refers to an aralkyl radical, as defined above, wherein the alkylene chain of the aralkyl radical is an optionally substituted alkylene chain, as defined above, and each aryl radical of the aralkyl radical is an optionally substituted aryl radical, as defined above.

"Aralkenyl" refers to a radical of the formula $-R_d-R_c$ where R_d is an alkenylene chain as defined above and R_c is one or more aryl radicals as defined above.

"Optionally substituted aralkenyl" refers to an aralkenyl radical, as defined above, wherein the alkenylene chain of the aralkenyl radical is an optionally substituted alkenylene chain, as defined above, and each aryl radical of the aralkenyl radical is an optionally substituted aryl radical, as defined above.

"Aralkynyl" refers to a radical of the formula $-R_eR_c$ where R_e is an alkynylene chain as defined above and R_c is one or more aryl radicals as defined above.

"Optionally substituted aralkynyl" refers to an aralkynyl radical, as defined above, wherein the alkynylene chain of the aralkynyl radical is an optionally substituted alkynylene chain, as defined above, and each aryl radical of the aralkynyl radical is an optionally substituted aryl radical, as defined above.

"Cycloalkyl" refers to a stable non-aromatic monocyclic or polycyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, which includes fused, spiro or bridged ring systems, having from three to fifteen carbon atoms, preferably having from three to ten carbon atoms, more preferably from five to seven carbons and which is saturated or unsaturated and attached to the rest of the molecule by a single bond. For purposes of this disclosure, a bridged ring system is a system wherein two non-adjacent ring atoms thereof are connected through an atom or a group of atoms, wherein the atom or the group of atoms are the bridging element. An example of a bridged cycloalkyl (monovalent) radical is norbornanyl (also called bicyclo[2.2.1]heptanyl). For purposes of this disclosure, a non-bridged ring system is a system which does not contain a bridging element, as described above. For purposes of this disclosure, a fused ring system is a system wherein two adjacent ring atoms thereof are connected through an atom or a group of atoms. An example of a fused cycloalkyl (monovalent) radical is decahydronaphthalenyl (also called decalanyl). For purposes of this disclosure, a spiro ring system is a system wherein two rings are joined via a single carbon (quaternary) atom. An example of a spiro cycloalkyl (monovalent) radical is spiro[5.5]undecanyl. Monocyclic cycloalkyl radicals do not include spiro, fused or bridged cycloalkyl radicals, but do include for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic radicals include fused, spiro or bridged cycloalkyl radicals, for example, C_{10} radicals such as adamantanyl (bridged) and decalanyl (fused), and C_7 radicals such as bicyclo[3.2.0]heptanyl (fused), norbornanyl and norbornenyl (bridged), as well as substituted polycyclic radicals, for example, substituted C_7 radicals such as 7,7-dimethylbicyclo[2.2.1]heptanyl (bridged).

"Optionally substituted cycloalkyl" refers to a cycloalkyl radical, as defined above, which is optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, $-R^{21}-OR^{20}$, $-R^{21}-OC(O)-R^{20}$, $-R^{21}-N(R^{20})_2$, $-R^{21}-C(O)R^{20}$, $-R^{21}-C(O)OR^{20}$, $-R^{21}-C(O)N(R^{20})_2$, $-R^{21}-N(R^{20})C(O)OR^{20}$, $-R^{21}-N(R^{20})C(O)R^{20}$, $-R^{21}-N(R^{20})S(O)_2R^{20}$, $-R^{21}-C(=NR^{20})N(R^{20})_2$, $-R^{21}-S(O)_tOR^{20}$ (where t is 1 or 2), $-R^{21}-S(O)_pR^{20}$ (where p is 0, 1 or 2), and $-R^{21}-S(O)_2N(R^{20})_2$, where each R^{20} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl, or two R^{20} 's, together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heterocyclyl or an

optionally substituted *N*-heteroaryl, and each R²¹ is independently a direct bond or a straight or branched alkylene or alkenylene chain.

"Cycloalkylalkyl" refers to a radical of the formula -R_bR_g where R_b is an alkylene chain as defined above and R_g is a cycloalkyl radical as defined above.

"Optionally substituted cycloalkylalkyl" refers to a cycloalkylalkyl radical, as defined above, wherein the alkylene chain of the cycloalkylalkyl radical is an optionally substituted alkylene chain, as defined above, and the cycloalkyl radical of the cycloalkylalkyl radical is an optionally substituted cycloalkyl radical, as defined above.

"Cycloalkylalkenyl" refers to a radical of the formula -R_dR_g where R_d is an alkenylene chain as defined above and R_g is a cycloalkyl radical as defined above.

"Optionally substituted cycloalkylalkenyl" refers to a cycloalkylalkenyl radical, as defined above, wherein the alkenylene chain of the cycloalkylalkenyl radical is an optionally substituted alkenylene chain, as defined above, and the cycloalkyl radical of the cycloalkylalkenyl radical is an optionally substituted cycloalkyl radical as defined above.

"Cycloalkylalkynyl" refers to a radical of the formula -R_eR_g where R_e is an alkynylene radical as defined above and R_g is a cycloalkyl radical as defined above.

"Optionally substituted cycloalkylalkynyl" refers to a cycloalkylalkynyl radical, as defined above, wherein the alkynylene chain of the cycloalkylalkynyl radical is an optionally substituted alkynylene chain, as defined above, and the cycloalkyl radical of the cycloalkylalkynyl radical is an optionally substituted cycloalkyl radical as defined above.

"Halo" refers to bromo, chloro, fluoro or iodo.

"Haloalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, for example, trifluoromethyl, difluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, 3-bromo-2-fluoropropyl, and 1-bromomethyl-2-bromoethyl.

"Haloalkenyl" refers to an alkenyl radical, as defined above, that is substituted by one or more halo radicals, as defined above.

"Haloalkynyl" refers to an alkynyl radical, as defined above, that is substituted by one or more halo radicals, as defined above.

"Heterocyclyl" refers to a stable 3- to 18-membered non-aromatic ring system radical which comprises one to twelve carbon atoms and from one to six heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. Unless stated otherwise specifically in the specification, the heterocyclyl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include spiro or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heterocyclyl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized; and the heterocyclyl radical may be partially or fully saturated. Examples of a bridged heterocyclyl include, but are not limited to, azabicyclo[2.2.1]heptanyl, diazabicyclo[2.2.1]heptanyl, diazabicyclo[2.2.2]octanyl, diazabicyclo[3.2.1]octanyl, diazabicyclo[3.3.1]nonanyl, diazabicyclo[3.2.2]nonanyl and oxazabicyclo[2.2.1]heptanyl. A "bridged *N*-heterocyclyl" is a bridged heterocyclyl containing at least one nitrogen, but which optionally contains up to four additional heteroatoms selected from O, N and S. For purposes of this disclosure, a non-bridged ring system is a system wherein no two non-adjacent ring atoms thereof are connected through an atom or a group of atoms. Examples of heterocyclyl radicals include, but are not limited to, dioxolanyl, 1,4-diazepanyl, decahydroisoquinolyl, imidazoliny, imidazolidiny, isothiazolidiny, isoxazolidiny, morpholiny, octahydroindolyl, octahydroisoindolyl, octahydro-1*H*-pyrrolo[3,2-*c*]pyridiny, octahydro-1*H*-

pyrrolo[2,3-*c*]pyridinyl, octahydro-1*H*-pyrrolo[2,3-*b*]pyridinyl, octahydro-1*H*-pyrrolo[3,4-*b*]pyridinyl, octahydropyrrolo[3,4-*c*]pyrrolyl, octahydro-1*H*-pyrido[1,2-*a*]pyrazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, 3,7-diazabicyclo[3.3.1]nonan-3-yl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuranyl, thienyl[1,3]dithianyl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, 1,1-dioxo-thiomorpholinyl, azetidiny, octahydropyrrolo[3,4-*c*]pyrrolyl, octahydropyrrolo[3,4-*b*]pyrrolyl, decahydroprazino[1,2-*a*]azepinyl, azepanyl, azabicyclo[3.2.1]octyl, and 2,7-diazaspiro[4.4]nonanyl.

"Optionally substituted heterocyclyl" refers to a heterocyclyl radical, as defined above, which is optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thio, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, $-R^{21}-OR^{20}$, $-R^{21}-OC(O)-R^{20}$, $-R^{21}-N(R^{20})_2$, $-R^{21}-C(O)R^{20}$, $-R^{21}-C(O)OR^{20}$, $-R^{21}-C(O)N(R^{20})_2$, $-R^{21}-N(R^{20})C(O)OR^{20}$, $-R^{21}-N(R^{20})C(O)R^{20}$, $-R^{21}-N(R^{20})S(O)_2R^{20}$, $-R^{21}-C(=NR^{20})N(R^{20})_2$, $-R^{21}-S(O)_tOR^{20}$ (where *t* is 1 or 2), $-R^{21}-S(O)_pR^{20}$ (where *p* is 0, 1 or 2), and $-R^{21}-S(O)_2N(R^{20})_2$, where each R^{20} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl, or two R^{20} 's, together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heterocyclyl or an optionally substituted *N*-heteroaryl, and each R^{21} is independently a direct bond or a straight or branched alkylene or alkenylene chain.

"*N*-heterocyclyl" refers to a heterocyclyl radical as defined above containing at least one nitrogen and where the point of attachment of the *N*-heterocyclyl radical to the rest of the molecule may be through a nitrogen atom in the *N*-heterocyclyl radical or through a carbon in the *N*-heterocyclyl radical.

"Optionally substituted *N*-heterocyclyl" refers to an *N*-heterocyclyl, as defined above, which is optionally substituted by one or more substituents as defined above for optionally substituted heterocyclyl.

"Heterocyclylalkyl" refers to a radical of the formula $-R_bR_h$ where R_b is an alkylene chain as defined above and R_h is a heterocyclyl radical as defined above, and when the heterocyclyl is a nitrogen-containing heterocyclyl, the heterocyclyl may be attached to the alkylene chain at the nitrogen atom.

"Optionally substituted heterocyclylalkyl" refers to a heterocyclylalkyl radical, as defined above, wherein the alkylene chain of the heterocyclylalkyl radical is an optionally substituted alkylene chain, as defined above, and the heterocyclyl radical of the heterocyclylalkyl radical is an optionally substituted heterocyclyl radical, as defined above.

"Heterocyclylalkenyl" refers to a radical of the formula $-R_dR_h$ where R_d is an alkenylene chain as defined above and R_h is a heterocyclyl radical as defined above, and

when the heterocyclyl is a nitrogen-containing heterocyclyl, the heterocyclyl may be attached to the alkenylene chain at the nitrogen atom.

"Optionally substituted heterocyclylalkenyl" refers to a heterocyclylalkenyl radical, as defined above, wherein the alkenylene chain of the heterocyclylalkenyl radical is an optionally substituted alkenylene chain, as defined above, and the heterocyclyl radical of the heterocyclylalkenyl radical is an optionally substituted heterocyclyl radical, as defined above.

"Heterocyclylalkynyl" refers to a radical of the formula $-R_eR_h$ where R_e is an alkynylene chain as defined above and R_h is a heterocyclyl radical as defined above, and when the heterocyclyl is a nitrogen-containing heterocyclyl, the heterocyclyl may be attached to the alkynylene chain at the nitrogen atom.

"Optionally substituted heterocyclylalkynyl" refers to a heterocyclylalkynyl radical, as defined above, wherein the alkynylene chain of the heterocyclylalkynyl radical is an optionally substituted alkynylene chain, as defined above, and the heterocyclyl radical of the heterocyclylalkynyl radical is an optionally substituted heterocyclyl radical, as defined above.

"Heteroaryl" refers to a 5- to 14-membered ring system radical comprising hydrogen atoms, one to thirteen carbon atoms, one to six heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and at least one aromatic ring. A heteroaryl radical is commonly, but not necessarily, attached to the parent molecule via an aromatic ring of the heteroaryl radical. For purposes of this disclosure, the heteroaryl radical may be a monocyclic, bicyclic or tricyclic ring system, which may include spiro or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heteroaryl radical may be optionally oxidized and the nitrogen atom may be optionally quaternized. For purposes of this disclosure, the aromatic ring of the heteroaryl radical need not contain a heteroatom, as long as one ring of the heteroaryl radical contains a heteroatom. For example benzo-fused heterocyclyls such as 1,2,3,4-tetrahydroisoquinolin-7-yl are considered a "heteroaryl" for the purposes of this disclosure. Except for the polycyclic heteroaryls containing more than 14 ring atoms, as defined below, a "heteroaryl" radical as defined herein can not contain rings having more than 7 members and cannot contain rings wherein two non-adjacent members thereof are connected through an atom or a group of atoms (*i.e.*, a bridged ring system). Examples of heteroaryl radicals include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzindolyl, 1,3-benzodioxolyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, benzo[*b*][1,4]dioxepinyl, benzo[*b*][1,4]oxazinyl, benzo[*b*]azepinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzothieno[3,2-*d*]pyrimidinyl, benzotriazolyl, benzo[4,6]imidazo[1,2-*a*]pyridinyl, carbazolyl, cinnolyl, cyclopenta[*d*]pyrimidinyl, 3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepinyl, cyclopenta[4,5]thieno[2,3-*d*]pyrimidinyl such as 6,7-dihydro-5*H*-cyclopenta[4,5]thieno[2,3-*d*]pyrimidinyl, 5,6-dihydrobenzo[*h*]quinazolinyl, 3,4-dihydro-2*H*-benzo[*b*][1,4]thiazinyl, 5,6-dihydrobenzo[*h*]cinnolyl, 7',8'-dihydro-5'*H*-spiro[[1,3]dioxolane-2,6'-quinoline]-3'-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazinyl, 2,3-dihydro-1*H*-pyrido[2,3-*b*][1,4]oxazinyl, 3',4'-dihydrospiro[cyclobutane-1,2'-pyrido[3,2-*b*][1,4]oxazinyl, dihydropyridooxazinyl such as 3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazinyl, dihydropyridothiazinyl such as 3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, furo[3,2-*c*]pyridinyl, furopyrimidinyl, furopyridazinyl, fuopyrazinyl, isothiazolyl, imidazolyl, imidazopyrimidinyl, imidazopyridazinyl,

imidazopyrazinyl, imidazo[1,2-*a*]pyridinyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolinyl (isoquinolyl), indoliziny, isoxazolyl, naphthyridinyl, 1,6-naphthyridinonyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 5,6,6a,7,8,9,10,10a-octahydrobenzo[*h*]quinazoliny, 3'-oxo-3',4'-dihydrospiro[cyclobutane-1,2'-pyrido[3,2-*b*][1,4]oxazine]yl, 7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridinyl, 1-phenyl-1*H*-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, phenanthridinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyrazolo[3,4-*d*]pyrimidinyl, pyridinyl (pyridyl), pyrido[3,2-*d*]pyrimidinyl, pyrido[3,4-*d*]pyrimidinyl, pyrazinyl, pyrimidinyl, pyridazinyl (pyridazyl), pyrrolyl, pyrrolopyrimidinyl, pyrrolopyridazinyl, pyrrolopyrazinyl, 2*H*-pyrido[3,2-*b*][1,4]oxazinonyl, 1*H*-pyrido[2,3-*b*][1,4]oxazinonyl, pyrrolopyridinyl such as 1*H*-pyrrolo[2,3-*b*]pyridinyl, quinazoliny, quinoxalinyl, quinolinyl, quinuclidinyl, tetrahydroquinolinyl, 5,6,7,8-tetrahydroquinazoliny, 2,3,4,5-tetrahydrobenzo[*b*]oxepinyl, 6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridinyl, 6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*c*]azepinyl, 5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidinyl, 6,7,8,9-tetrahydro-5*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidinyl, 5,6,7,8-tetrahydropyrido[4,5-*c*]pyridazinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, 1,2,3,4-tetrahydroisoquinolin-7-yl, triazinyl, thieno[2,3-*d*]pyrimidinyl, thienopyrimidinyl (*e.g.*, thieno[3,2-*d*]pyrimidinyl), thieno[2,3-*c*]pyridinyl, thienopyridazinyl, thienopyrazinyl, and thiophenyl (thienyl).

"Optionally substituted heteroaryl" refers to a heteroaryl radical, as defined above, which is optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, $-R^{21}-OR^{20}$, $-R^{21}-OC(O)-R^{20}$, $-R^{21}-N(R^{20})_2$, $-R^{21}-C(O)R^{20}$, $-R^{21}-C(O)OR^{20}$, $-R^{21}-C(O)N(R^{20})_2$, $-R^{21}-N(R^{20})C(O)OR^{20}$, $-R^{21}-N(R^{20})C(O)R^{20}$, $-R^{21}-N(R^{20})S(O)_2R^{20}$, $-R^{21}-C(=NR^{20})N(R^{20})_2$, $-R^{21}-S(O)_tOR^{20}$ (where *t* is 1 or 2), $-R^{21}-S(O)_pR^{20}$ (where *p* is 0, 1 or 2), and $-R^{21}-S(O)_2N(R^{20})_2$, where each R^{20} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl, or two R^{20} 's, together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heterocyclyl or an optionally substituted *N*-heteroaryl, and each R^{21} is independently a direct bond or a straight or branched alkylene or alkenylene chain.

"*N*-heteroaryl" refers to a heteroaryl radical as defined above containing at least one nitrogen and where the point of attachment of the *N*-heteroaryl radical to the rest of the molecule may be through a nitrogen atom in the *N*-heteroaryl radical or through a carbon atom in the *N*-heteroaryl radical.

"Optionally substituted *N*-heteroaryl" refers to an *N*-heteroaryl, as defined above, which is optionally substituted by one or more substituents as defined above for optionally substituted heteroaryl.

"Polycyclic heteroaryl containing more than 14 ring atoms" refers to a 15- to 20-membered ring system radical comprising hydrogen atoms, one to fourteen carbon atoms, one to eight heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and at least one aromatic ring. A "polycyclic heteroaryl containing more than 14 ring atoms" radical is commonly, but not necessarily, attached to the parent molecule via an aromatic ring of the "polycyclic heteroaryl containing more than 14 ring atoms" radical. For purposes of this disclosure, the "polycyclic heteroaryl containing more than 14 ring atoms" radical may be a bicyclic, tricyclic or tetracyclic ring system, which may include fused or spiro ring systems; and the nitrogen, carbon or sulfur atoms in the "polycyclic heteroaryl containing more than 14 ring atoms" radical may be optionally oxidized and the nitrogen atom may also be optionally quaternized. For purposes of this disclosure, the aromatic ring of the "polycyclic heteroaryl containing more than 14 ring atoms" radical need not contain a heteroatom, as long as one ring of the "polycyclic heteroaryl containing more than 14 ring atoms" radical contains a heteroatom. Examples of "polycyclic heteroaryl containing more than 14 ring atoms" radicals include, but are not limited to, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl, 6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl, 6,7,8,9-tetrahydro-5*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[2,3]azepino[4,5-*c*]pyridazin-3-yl, (Z)-dibenzo[*b*,*f*][1,4]thiazepin-11-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[4,5-*c*]pyridazin-2-yl, 6,7-dihydro-5*H*-benzo[2,3]oxepino[4,5-*c*]pyridazin-3-yl, spiro[chromeno[4,3-*c*]pyridazine-5,1'-cyclopentane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 5,6,8,9-tetrahydrospiro[benzo[7]annulene-7,2'-[1,3]dioxolane]-3-yl, 5,7,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-6,2'-[1,3]dioxolane]-3-yl, 6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-2-yl, 5,6,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxane]-3-yl and 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridin-2-yl.

"Optionally substituted polycyclic heteroaryl containing more than 14 ring atoms" is meant to include "polycyclic heteroaryl containing more than 14 ring atoms" radicals, as defined above, which are optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, -R²¹-OR²⁰, -R²¹-OC(O)-R²⁰, -R²¹-N(R²⁰)₂, -R²¹-C(O)R²⁰, -R²¹-C(O)OR²⁰, -R²¹-C(O)N(R²⁰)₂, -R²¹-N(R²⁰)C(O)OR²⁰, -R²¹-N(R²⁰)C(O)R²⁰, -R²¹-N(R²⁰)S(O)_tR²⁰ (where *t* is 1 or 2), -R²¹-S(O)_tOR²⁰ (where *t* is 1 or 2), -R²¹-S(O)_pR²⁰ (where *p* is 0, 1 or 2), and -R²¹-S(O)_tN(R²⁰)₂ (where *t* is 1 or 2), where each R²⁰ is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl and

optionally substituted heteroarylalkyl, or two R^{20} 's, together with the common nitrogen to which they are both attached, may optionally form an optionally substituted *N*-heterocyclyl or an optionally substituted *N*-heteroaryl, and each R^{21} is independently a direct bond or a straight or branched alkylene or alkenylene chain.

"Heteroarylalkyl" refers to a radical of the formula $-R_bR_i$ where R_b is an alkylene chain as defined above and R_i is a heteroaryl radical as defined above, and when the heteroaryl is a nitrogen-containing heteroaryl, the heteroaryl may be attached to the alkylene chain at the nitrogen atom.

"Optionally substituted heteroarylalkyl" refers to a heteroarylalkyl radical, as defined above, wherein the alkylene chain of the heteroarylalkyl radical is an optionally substituted alkylene chain, as defined above, and the heteroaryl radical of the heteroarylalkyl radical is an optionally substituted heteroaryl radical, as defined above.

"Heteroarylalkenyl" refers to a radical of the formula $-R_dR_i$ where R_d is an alkenylene chain as defined above and R_i is a heteroaryl radical as defined above, and when the heteroaryl is a nitrogen-containing heteroaryl, the heteroaryl may be attached to the alkenylene chain at the nitrogen atom.

"Optionally substituted heteroarylalkenyl" refers to a heteroarylalkenyl radical, as defined above, wherein the alkenylene chain of the heteroarylalkenyl radical is an optionally substituted alkenylene chain, as defined above, and the heteroaryl radical of the heteroarylalkenyl radical is an optionally substituted heteroaryl radical, as defined above.

"Heteroarylalkynyl" refers to a radical of the formula $-R_eR_i$ where R_e is an alkynylene chain as defined above and R_i is a heteroaryl radical as defined above, and when the heteroaryl is a nitrogen-containing heteroaryl, the heteroaryl may be attached to the alkynylene chain at the nitrogen atom.

"Optionally substituted heteroarylalkynyl" refers to a heteroarylalkynyl radical, as defined above, wherein the alkynylene chain of the heteroarylalkynyl radical is an optionally substituted alkynylene chain, as defined above, and the heteroaryl radical of the heteroarylalkynyl radical is an optionally substituted heteroaryl radical, as defined above.

"Hydroxyalkyl" refers to an alkyl radical as defined above which is substituted by one or more hydroxy radicals (-OH).

Certain chemical groups named herein may be preceded by a shorthand notation indicating the total number of carbon atoms that are to be found in the indicated chemical group. For example; C_7-C_{12} alkyl describes an alkyl group, as defined below, having a total of 7 to 12 carbon atoms, and C_4-C_{12} cycloalkylalkyl describes a cycloalkylalkyl group, as defined below, having a total of 4 to 12 carbon atoms. The total number of carbons in the shorthand notation does not include carbons that may exist in substituents of the group described.

The compounds of formula (I), or their pharmaceutically acceptable salts, may contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)- or, as (*D*)- or (*L*)- for amino acids. The present disclosure is meant to include all such possible isomers, as well as their racemic and optically pure forms. Optically active (+) and (-), (*R*)- and (*S*)-, or (*D*)- and (*L*)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, such as HPLC using a chiral column. When the compounds described herein contain olefinic double bonds or other

centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included.

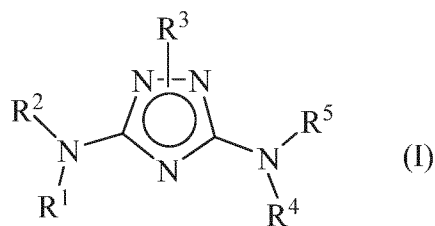
A "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures, which are not interchangeable. The present disclosure contemplates various stereoisomers and mixtures thereof and includes "enantiomers", which refers to two stereoisomers whose molecules are nonsuperimposable mirror images of one another.

A "tautomer" refers to a proton shift from one atom of a molecule to another atom of the same molecule. The present disclosure includes tautomers of any said compounds.

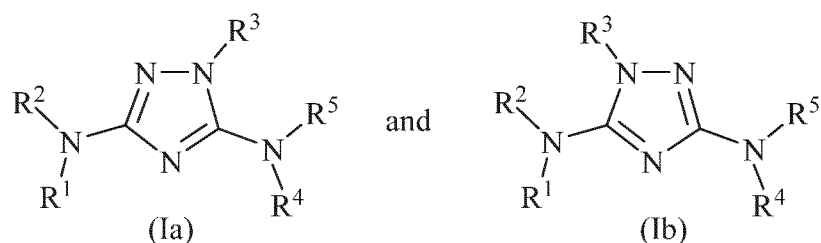
"Atropisomers" are stereoisomers resulting from hindered rotation about single bonds where the barrier to rotation is high enough to allow for the isolation of the conformers (Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley & Sons: New York, 1994; Chapter 14). Atropisomerism is significant because it introduces an element of chirality in the absence of stereogenic atoms. The disclosure is meant to encompass atropisomers, for example in cases of limited rotation around the single bonds emanating from the core triazole structure, atropisomers are also possible and are also specifically included in the compounds of the disclosure.

The chemical naming protocol and structure diagrams used herein are a modified form of the IUPAC nomenclature system wherein the compounds of formula (I) are named herein as derivatives of the central core structure, *i.e.*, the triazole structure. For complex chemical names employed herein, a substituent group is named before the group to which it attaches. For example, cyclopropylethyl comprises an ethyl backbone with cyclopropyl substituent. In chemical structure diagrams, all bonds are identified, except for some carbon atoms, which are assumed to be bonded to sufficient hydrogen atoms to complete the valency.

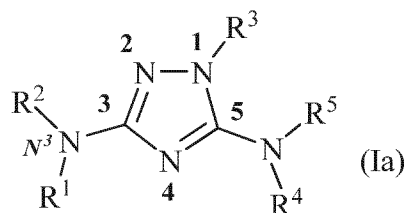
For purposes of this disclosure, the depiction of the bond attaching the R³ substituent to the parent triazole moiety in formula (I), as shown below:



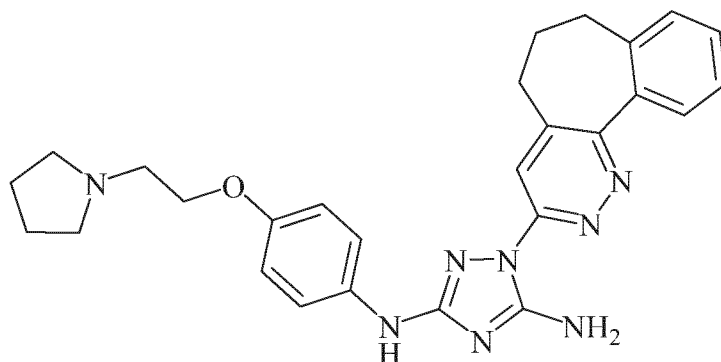
is intended to include only the two regioisomers shown below, *i.e.*, compounds of formula (Ia) and (Ib):



The numbering system of the ring atoms in compounds of formula (Ia) is shown below:

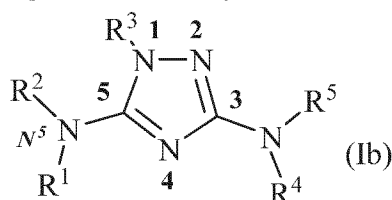


For example, a compound of formula (Ia) wherein R¹, R⁴ and R⁵ are each hydrogen, R² is 4-(2-(pyrrolidin-1-yl)ethoxy)phenyl and R³ is 6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazin-3-yl; *i.e.*, a compound of the following formula:



is named herein as 1-(6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazin-3-yl)-N³-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-1H-1,2,4-triazole-3,5-diamine.

The numbering system of the ring atoms in compounds of formula (Ib) is shown below:



Compounds of formula (Ib) are similarly named herein.

Antibody AXL inhibitors

In some embodiments the AXLi is an antibody. Preferably the antibody AXL inhibitory activity. In some cases the antibody inhibits the binding of AXL to the GAS6 ligand.

In some embodiments, the anti-AXL antibody is an antibody as described in any of the following references: WO/2016/097370, WO/2017/220695, WO/2015/193428, WO/2016/166296, WO/2015/193430, EP2267454, WO/2009/063965, WO/2011/159980, WO/2012/175691, WO/2012/175692, WO/2013/064685, WO/2014/068139,

WO/2009/062690, and WO/2010/130751 (the contents of each of which is hereby incorporated by reference).

In another embodiment, the anti-AXL antibody is an antibody as described in international patent application WO/2015/193428, the contents of which is hereby incorporated by reference, particularly as shown at pages 82-83.

In another embodiment, the anti-AXL antibody is an antibody as described in international patent application WO/2016/166296, the contents of which is hereby incorporated by reference, particularly the humanized 1H12 antibody disclosed therein.

In another embodiment, the anti-AXL antibody is an antibody as described in international patent application WO/2015/193430, the contents of which is hereby incorporated by reference, particularly as shown at pages 72-73.

In another embodiment, the anti-AXL antibody is an antibody as described in European patent publication EP2267454, the contents of which is hereby incorporated by reference.

In another embodiment, the anti-AXL antibody is an antibody as described in European patent publication WO/2009/063965, the contents of which is hereby incorporated by reference, particularly as shown at pages 31-33.

In another embodiment, the anti-AXL antibody is an antibody as described in US patent publication US 2012/0121587 A1, the contents of which is hereby incorporated by reference, particularly as shown at pages 26-61.

In another embodiment, the anti-AXL antibody is an antibody as described in international patent publication WO/2011/159980, the contents of which is hereby incorporated by reference, particularly the YW327.6S2 antibody as shown in Figure 2, Figure page 6 (of 24).

In another embodiment, the anti-AXL antibody is an antibody as described in international patent publication WO/2012/175691, the contents of which is hereby incorporated by reference, particularly as shown at page 5.

In another embodiment, the anti-AXL antibody is an antibody as described in international patent publication WO/2012/175692, the contents of which is hereby incorporated by reference, particularly as shown at pages 4-5.

In another embodiment, the anti-AXL antibody is an antibody as described in international patent publication WO/2009/062690, the contents of which is hereby incorporated by reference.

In another embodiment, the anti-AXL antibody is an antibody as described in international patent publication WO/2010/130751, the contents of which is hereby incorporated by reference, particularly as shown at pages 1-17 (of 78).

In another embodiment, the anti-AXL antibody is an antibody as described in international patent publication WO/2013/064685, the contents of which is hereby incorporated by reference, particularly the 1613F12 antibody described therein as shown at, for example, Examples 6 to 8.

In another embodiment, the anti-AXL antibody is an antibody as described in international patent publication WO/2014/068139, the contents of which is hereby incorporated by reference, particularly the 110D7, 1003A2, and 1024G11 antibodies described therein as shown at, for example, Examples 6 to 8.

In another embodiment, the anti-AXL antibody is an antibody as described in international patent publication WO/2016/097370, the contents of which is hereby incorporated by reference, particularly the murine 10G5 and 10C9 antibodies described therein as shown at, for example, Examples 6 to 8.

In another embodiment, the anti-AXL antibody is an antibody as described in international patent publication WO/2017/220695, the contents of which is hereby incorporated by reference, particularly the humanized 10G5 antibody described therein as shown at, for example, SEQ ID NO. 1 to 10.

Preferred embodiments

Preferably, the anti-AXL antibody is an antibody as described in WO/2016/097370, WO/2017/220695, WO/2015/193428, WO/2016/166296, WO/2015/193430, WO/2011/159980, WO/2013/064685, or WO/2014/068139 (the contents of each of which is hereby incorporated by reference).

More preferably, the anti-AXL antibody is an antibody as described in WO/2016/097370, WO/2017/220695, WO/2011/159980, WO/2013/064685, or WO/2014/068139 (the contents of each of which is hereby incorporated by reference).

Most preferably the anti-AXL antibody is an antibody as described in WO/2017/220695, particularly the humanized 10G5 antibody described therein as shown at, for example, Examples 6 to 8.

In some embodiments, the anti-AXL antibody comprises the 6 CDRs having the sequences set out herein in SEQ ID Nos. 1 to 6.

In some embodiments, the anti-AXL antibody comprises the 6 CDRs having the sequences set out herein in SEQ ID Nos. 7 to 12.

In some embodiments, the anti-AXL antibody comprises a VH domain having the sequence set out herein in either one of SEQ ID Nos. 13 or 14. In some embodiments the antibody further comprises a VL domain having the sequence set out herein in either one of SEQ ID Nos. 15 or 16.

Immune regulators (IRs)

As already described herein, the present authors studies of the drug-tolerant 'persister phenotype' revealed that treatment with AXL inhibitors resulted in a switch to a more antigenic profile, with the release of DAMPs and other molecules having adjuvant activity. Accordingly, the function of the immune regulators described here is to increase the ability of the immune system to sense the neoplastic cells and/ or to increase the amplitude of the resultant immune activation. This may be achieved in a number of ways, such as increasing the activity of stimulatory pathways and decreasing the activity of inhibitory pathways.

In some embodiments the IR is an immune checkpoint inhibitor (ICI). For example, an agent which acts at T cell co-inhibitory receptors, such as CTLA-4, PD-1, PD-L1, BTLA, TIM-3, VISTA, LAG-3, and TIGIT.

In some embodiments the IR is a T-cell co-stimulatory agonist. For example, an agonist of a T-cell co-stimulatory receptor such as CD28, ICOS, 4-1BB, OX40, GITR, CD27, TWEAKR, HVEM, and TIM-1.

In some embodiments the IR acts at dendritic cell co-stimulatory receptors, such as CD40 and 4-1BB.

In some embodiments the IR is selected from the group consisting of: anti-CTLA-4 antibodies, anti-PD-1 antibodies, anti-PD-L1 antibodies, anti-4-1BB antibodies, anti-OX-40 antibodies, anti-GITR antibodies, anti-CD27 antibodies, anti-CD28 antibodies, anti-CD40 antibodies, anti-LAG3 antibodies, anti-ICOS antibodies, anti-TWEAKR antibodies, anti-HVEM antibodies, anti-TIM-1 antibodies, anti-TIM-3 antibodies, anti-VISTA antibodies, and anti-TIGIT antibodies.

In some preferred embodiments the IR is selected from the group consisting of: anti-CTLA-4 antibodies, anti-PD-1 antibodies, anti-PD-L1 antibodies, anti-4-1BB antibodies, anti-OX-40 antibodies, anti-GITR antibodies, anti-CD27 antibodies, anti-CD40 antibodies, and anti-LAG3 antibodies.

Examples of IRs suitable for use in the methods described herein include ipilimumab, tremelimumab, pembrolizumab, nivolumab, and urelumab, and those which can be identified by the drug candidate identifiers AMP-514/MEDI0680 (MedImmune/AstraZeneca), MPDL3280A (Genentech/Roche), MEDI4736 (MedImmune/AstraZeneca), MSB0010718C (EMD Serono), BMS-936559 (Bristol-Myers Squibb), PF-05082566 (Pfizer), MEDI6469 (MedImmune/AstraZeneca), MEDI6383 (rOX40L; MedImmune/AstraZeneca), MOXR0916 (Genentech/Roche), TRX518 (Tolerx), CDX-1127 (Celldex), CP-870,893 (Genentech/Roche), and BMS-986016 (Bristol-Myers Squibb) (preferably ipilimumab, tremelimumab, pembrolizumab, and nivolumab).

In some embodiments, the anti-GITR antibody or GITR agonist is selected from MEDI1873, TRX518, GWN323, MK-1248, MK 4166, BMS-986156 and INCAGN1876.

In some embodiments, the anti-OX40 antibody or OX40 agonist is selected from MEDI0562, MEDI6383, MOXR0916, RG7888, OX40mAb24, INCAGN1949, GSK3174998, and PF-04518600.

In a particularly preferred embodiment of the invention, two or more immune checkpoint (activity) modulators are employed in conjunction with the AXL inhibitor. Results have shown that an improved synergistic effect can be obtained when at least two different immune checkpoint (activity) modulators are employed, especially when such immune checkpoint (activity) modulators act at different cell receptor sub-types. For example, the combination of at least one immune checkpoint inhibitor and at least one T cell co-stimulatory receptor agonist or dendritic cell co-stimulatory receptor agonist.

Preferably, at least one of the two immune checkpoint (activity) modulators is an anti-CTLA-4 antibody or an anti-PD-1 antibody. In particular, the combination of an anti-CTLA-4 antibody and an anti-PD-1 antibody has proven to be particularly effective.

In some preferred embodiments two or more IRs are administered. The two or more IRs may include: (i) an immune checkpoint inhibitor, and (ii) a T cell co-stimulatory receptor agonist or a dendritic cell co-stimulatory receptor agonist. In some embodiments the two or more IRs include: (i) an anti-CTLA-4 antibody; and/or (ii) either an anti-PD-1 antibody or an anti-PD-L1 antibodies.

In some embodiments the anti-CTLA-4 antibody is ipilimumab or tremelimumab.

In some embodiments the anti-PD-1 antibody is pembrolizumab, nivolumab, spartalizumab, Camrelizumab, Pidilizumab, or Cemiplimab. Preferably the anti-PD-1 antibody is pembrolizumab or nivolumab.

In some embodiments the anti-PDL1 antibody is Atezolizumab (CAS number 1380723-44-3), Avelumab (CAS number 1537032-82-8), or Durvalumab (CAS number 1428935-60-7).

In some embodiments the two or more IRs are administered concurrently. In other embodiments the two or more IRs are administered separately and/or sequentially.

Anti-proliferative agents

In some embodiments the anti-proliferative agent is a receptor signalling inhibitor.

In some embodiments the anti-proliferative agent is an EGFR inhibitor. In some cases the EGFR inhibitor is selected from the group consisting of: Gefitinib, Erlotinib, osimertinib, Lapatinib, Brigatinib, rociletinib, olmutinib, nazartinib, naquotinib, and mavelertinib.

Preferably the EGFR inhibitor is erlotinib.

In a second aspect the present disclosure provides a method for identifying a subject having a neoplastic disorder characterized by the presence of cells having a persister-cell phenotype, the method comprising the steps of (i) determining whether the cells, disorder, and/or subject are as defined as described above for the first aspect, and (ii) identifying the subject as having a neoplastic disorder characterized by the presence of cells having a persister-cell phenotype if the cells, disorder, and/or subject are as defined as described above for the first aspect.

The determining step may comprise (i) providing a sample from the subject; and (ii) analysing the sample for the features of cells, disorder, and/or subject described above in the first aspect.

The providing step may comprise obtaining the sample from the subject. In preferred embodiments the sample is a tumour sample.

Additional optional features of the sample are described in the section below entitled "samples".

In a third aspect, the present disclosure provides a method for diagnosing a subject having a neoplastic disorder characterized by the presence of cells having a persister-cell phenotype, the method comprising the step of: (i) identifying a subject as described in the second aspect; and (ii) diagnosing the subject as having a neoplastic disorder characterized by the presence of cells having a persister-cell phenotype are identified.

In a fourth aspect, the present disclosure provides the method as described in the first aspect wherein: (i) the subject has been identified by a method according to second aspect; or (ii) the subject has been diagnosed by a method according to the third aspect.

In a fifth aspect, the present disclosure provides a method as described in the first aspect, wherein the treatment comprises the step of: (i) identifying the subject according to a method for the second aspect; or (ii) diagnosing the subject according to a method of the third aspect.

In a sixth aspect, the disclosure provides an AXLi, or a composition comprising an AXLi, for use in a method of treatment according to the first, fourth, or fifth aspects.

As part of the sixth aspect, the disclosure also provides an IR, or a composition comprising an IR, for use in a method of treatment according to the first, fourth, or fifth aspects.

As part of the sixth aspect, the disclosure also provides a combination of an AXLi and an IR, or a composition comprising a combination of an AXLi and an IR, for use in a method of treatment according to the first, fourth, or fifth aspects.

As part of the sixth aspect, the disclosure also provides an anti-proliferative agent, or a composition comprising an anti-proliferative agent, for use in a method of treatment according to the first, fourth, or fifth aspects.

Also included in the sixth aspect is the use of an AXLi in the manufacture of a medicament for treating a disorder in a subject, wherein the treatment comprises the method of treatment of the first, fourth, or fifth aspects.

Also included in the sixth aspect is the use of an IR in the manufacture of a medicament for treating a disorder in a subject, wherein the treatment comprises the method of treatment of the first, fourth, or fifth aspects.

Also included in the sixth aspect is the use of a combination of an AXLi and an IR in the manufacture of a medicament for treating a disorder in a subject, wherein the treatment comprises the method of treatment of the first, fourth, or fifth aspects.

Also included in the sixth aspect is the use of an anti-proliferative agent in the manufacture of a medicament for treating a disorder in a subject, wherein the treatment comprises the method of treatment of the first, fourth, or fifth aspects.

Treated disorders

The combined therapies described herein include those with utility for anticancer activity. In particular, in certain aspects the therapies include an AXLi combined with an IR.

Thus, in one aspect, the present disclosure provides combined therapies comprising administering an AXLi and an IR to a subject having a neoplastic disorder characterized by the presence of cells having a persister-cell phenotype.

In one aspect, the present disclosure provides a combined therapy with a label that specifies that the therapy is suitable for use with a subject determined to be suitable for such use. The label may specify that the therapy is suitable for use in a subject has expression of the first target protein, such as overexpression of AXL, CD44 or another of the persister-cell phenotype markers described herein. The label may specify that the subject has a neoplastic disorder characterized by the presence of cells having a persister-cell phenotype, defined by one or more of the features described herein.

The disorder may be a proliferative disease, for example a cancer such as breast, lung, gastric, head and neck, colorectal, renal, pancreatic, uterine, hepatic, bladder, endometrial and prostate cancers as well as lymphomas (e.g., non-Hodgkin's lymphoma, NHL) and leukemia (particularly acute myeloid leukemia, AML). The disorder may be an immune disorder, cardiovascular disorder, thrombosis, diabetes, immune checkpoint disorder, or

fibrotic disorder (fibrosis) such as strabismus, scleroderma, keloid, Nephrogenic systemic fibrosis, pulmonary fibrosis, idiopathic pulmonary fibrosis (IPF), cystic fibrosis (CF), systemic sclerosis, cardiac fibrosis, non-alcoholic steatohepatitis (NASH), other types of liver fibrosis, primary biliary cirrhosis, renal fibrosis, cancer, and atherosclerosis.

In a further aspect there is also provided a combined therapy as described herein for use in the treatment of a neoplastic disorder characterized by the presence of cells having a persister-cell phenotype. Another aspect of the present disclosure provides the use of the combination in the manufacture of a medicament for treating a neoplastic disorder characterized by the presence of cells having a persister-cell phenotype.

One of ordinary skill in the art is readily able to determine whether or not a candidate combined therapy treats a proliferative condition for any particular cell type. For example, assays which may conveniently be used to assess the activity offered by a particular compound are described below.

The combined therapies described herein may be used to treat a neoplastic disorder characterized by the presence of cells having a persister-cell phenotype. The term "neoplastic" pertains to an unwanted or uncontrolled cellular proliferation of excessive or abnormal cells which is undesired, and includes hyperplastic growth, whether *in vitro* or *in vivo*.

Examples of neoplastic conditions include, but are not limited to, benign, pre-malignant, and malignant cellular proliferation, including but not limited to, neoplasms and tumours (e.g. histocytoma, glioma, astrocyoma, osteoma), cancers (e.g. lung cancer, small cell lung cancer, gastrointestinal cancer, bowel cancer, colon cancer, breast carcinoma, ovarian carcinoma, prostate cancer, testicular cancer, liver cancer, kidney cancer, bladder cancer, pancreas cancer, brain cancer, sarcoma, osteosarcoma, Kaposi's sarcoma, melanoma), lymphomas, leukemias, psoriasis, bone diseases, fibroproliferative disorders (e.g. of connective tissues), and atherosclerosis. Cancers of particular interest include, but are not limited to, lung cancer, in particular non-small-cell lung cancer (NSCLC).

Any type of cell may be treated, including but not limited to cells derived from tissues such as lung, gastrointestinal (including, e.g. bowel, colon), breast (mammary), ovarian, prostate, liver (hepatic), kidney (renal), bladder, pancreas, brain, and skin.

Disorders of interest include, but are not limited to cancers, including metastatic cancers and metastatic cancer cells, such as circulating tumour cells, which may be found circulating in body fluids such as blood or lymph. Cancers of particular interest include breast, lung, gastric, head and neck, colorectal, renal, pancreatic, uterine, hepatic, bladder, endometrial and prostate cancers as well as lymphomas (e.g., non-Hodgkin's lymphoma, NHL) and leukemia (particularly acute myeloid leukemia, AML).

Other disorders of interest include any condition which is characterized by the presence of cells having a persister-cell phenotype, in particular those defined by one or more of the features described herein. These may include immune disorders, cardiovascular disorders,

thrombosis, diabetes, immune checkpoint disorders, fibrotic disorders (fibrosis), or proliferative diseases such as cancer, particularly metastatic cancer.

Fibrotic disorders of interest include strabmisus, scleroderma, keloid, Nephrogenic systemic fibrosis, pulmonary fibrosis, idiopathic pulmonary fibrosis (IPF), cystic fibrosis (CF), systemic sclerosis, cardiac fibrosis, non-alcoholic steatohepatitis (NASH), other types of liver fibrosis, primary biliary cirrhosis, renal fibrosis, cancer, and atherosclerosis. In these diseases, the chronic development of fibrosis in tissue leads to marked alterations in the architecture of the affected organs and subsequently cause defective organ function. As a result of this process of sustained attrition to organs, many diseases that involve fibrosis are often progressive conditions and have a poor long-term prognosis (see Rockey, D.C., Bell, P.D. and Hill, J.A. (2015), N. Engl. Med., Vol. 372, pp. 1138-1149).

The neoplastic disorder characterized by the presence of cells having a persister-cell phenotype, may be further characterised by the presence of a neoplasm comprising neoplastic cells having a persister cell phenotype. Neoplastic cells not having a persister cell phenotype may also be present in the neoplasm.

The cells having a persister cell phenotype may be all or part of a solid tumour.

“Solid tumor” herein will be understood to include solid haematological cancers such as lymphomas (Hodgkin’s lymphoma or non-Hodgkin’s lymphoma) which are discussed in more detail herein.

Solid tumors may be neoplasms, including non-haematological cancers, comprising or composed of cells having a persister cell phenotype.

It is contemplated that the combined therapies of the present disclosure may be used to treat various diseases or disorders, e.g. characterized by the presence of cells having a persister cell phenotype. Exemplary conditions include benign or malignant tumors; leukemia, haematological, and lymphoid malignancies. Others include neuronal, glial, astrocytal, hypothalamic, glandular, macrophagal, epithelial, stromal, blastocoelic, inflammatory, angiogenic and immunologic, including autoimmune disorders and graft-versus-host disease (GVHD).

The combined therapies may also have utility in disorders such as rheumatologic disorders (such as, for example, rheumatoid arthritis, Sjögren's syndrome, scleroderma, lupus such as SLE and lupus nephritis, polymyositis/dermatomyositis, cryoglobulinemia, anti-phospholipid antibody syndrome, and psoriatic arthritis), osteoarthritis, autoimmune gastrointestinal and liver disorders (such as, for example, inflammatory bowel diseases (e.g. ulcerative colitis and Crohn's disease), autoimmune gastritis and pernicious anemia, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, and celiac disease), vasculitis (such as, for example, ANCA-associated vasculitis, including Churg-Strauss vasculitis, Wegener's granulomatosis, and polyarteriitis), autoimmune neurological disorders (such as, for example, multiple sclerosis, opsoclonus myoclonus syndrome, myasthenia gravis, neuromyelitis optica, Parkinson's disease, Alzheimer's disease, and autoimmune

polyneuropathies), renal disorders (such as, for example, glomerulonephritis, Goodpasture's syndrome, and Berger's disease), autoimmune dermatologic disorders (such as, for example, psoriasis, urticaria, hives, pemphigus vulgaris, bullous pemphigoid, and cutaneous lupus erythematosus), hematologic disorders (such as, for example, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, post-transfusion purpura, and autoimmune hemolytic anemia), atherosclerosis, uveitis, autoimmune hearing diseases (such as, for example, inner ear disease and hearing loss), Behcet's disease, Raynaud's syndrome, organ transplant, graft-versus-host disease (GVHD), and autoimmune endocrine disorders (such as, for example, diabetic-related autoimmune diseases such as insulin-dependent diabetes mellitus (IDDM), Addison's disease, and autoimmune thyroid disease (e.g. Graves' disease and thyroiditis)). More preferred such diseases include, for example, rheumatoid arthritis, ulcerative colitis, ANCA-associated vasculitis, lupus, multiple sclerosis, Sjögren's syndrome, Graves' disease, IDDM, pernicious anemia, thyroiditis, and glomerulonephritis.

In some aspects, the subject has a proliferative disorder selected from a cancer such as breast, lung, gastric, head and neck, colorectal, renal, pancreatic, uterine, hepatic, bladder, endometrial and prostate cancers as well as lymphomas (e.g., non-Hodgkin's lymphoma, NHL) and leukemia (particularly acute myeloid leukemia, AML). In some aspects, the subject has a disorder selected from an immune disorder, cardiovascular disorder, thrombosis, diabetes, immune checkpoint disorder, or fibrotic disorder (fibrosis) such as strabismus, scleroderma, keloid, Nephrogenic systemic fibrosis, pulmonary fibrosis, idiopathic pulmonary fibrosis (IPF), cystic fibrosis (CF), systemic sclerosis, cardiac fibrosis, non-alcoholic steatohepatitis (NASH), other types of liver fibrosis, primary biliary cirrhosis, renal fibrosis, cancer, and atherosclerosis. The label may specify that the subject has a AXL+ cancer. Breast cancer and AML are cancers of particular interest.

Subject Selection

In certain aspects, the subjects are selected as suitable for treatment with the combined treatments before the treatments are administered.

As used herein, subjects who are considered suitable for treatment are those subjects who are expected to benefit from, or respond to, the treatment.

Subjects may have, or be suspected of having, or be at risk of having a neoplastic disorder characterized by the presence of cells having a persister-cell phenotype. Subjects may have received a diagnosis of a neoplastic disorder characterized by the presence of cells having a persister-cell phenotype. In particular, subjects may have, or be suspected of having, or be at risk of having, cancer, such as NSCLC. In some cases, subjects may have, or be suspected of having, or be at risk of having, a solid tumour that is characterized by the presence of cells having a persister-cell phenotype.

In some aspects, subjects are selected on the basis of the amount or pattern of expression of a marker protein such as AXL or CD44. Marker proteins expressed on the cell surface, such as AXL, may be particularly preferred.

In some cases, expression of the marker in a particular tissue of interest is determined. For example, in a sample of lymphoid tissue or, especially, tumor tissue. In some cases, systemic expression of the target is determined. For example, in a sample of circulating fluid such as blood, plasma, serum or lymph.

In some aspects, the subject is selected as suitable for treatment due to the level of marker expression in a sample. Depending on the specific marker(s) tested, subjects with or without marker may be considered suitable for treatment.

In other aspects, the level of marker expression is used to select a subject as suitable for treatment. In some cases, depending on the specific marker(s) tested, where the level of expression of the marker is increased or decreased relative to a control the subject is determined to be suitable for treatment.

In some aspects, the presence of a marker or combination of markers in the sample indicates that the subject is suitable for treatment with the methods described herein. In other aspects, the amount of a marker or combination of markers must be increased or decreased relative to a control to indicate that the subject is suitable for treatment. In some aspects, the observation that a marker's localisation is altered in the sample as compared to a control indicates that the subject is suitable for treatment.

Samples

The sample may comprise or may be derived from: a quantity of blood; a quantity of serum derived from the subject's blood which may comprise the fluid portion of the blood obtained after removal of the fibrin clot and blood cells; a quantity of pancreatic juice; a tissue sample or biopsy; or cells isolated from said subject.

A sample may be taken from any tissue or bodily fluid. In certain aspects, the sample may include or may be derived from a tissue sample, biopsy, resection or isolated cells from said subject.

In certain aspects, the sample is a tissue sample. The sample may be a sample of tumor tissue, such as neoplastic tumor tissue. The sample may have been obtained by a tumor biopsy. In some aspects, the sample is a lymphoid tissue sample, such as a lymphoid lesion sample or lymph node biopsy.

In some aspects the sample is taken from a bodily fluid, more preferably one that circulates through the body. Accordingly, the sample may be a blood sample or lymph sample. In some cases, the sample is a urine sample or a saliva sample.

In some cases, the sample is a blood sample or blood-derived sample. The blood derived sample may be a selected fraction of a subject's blood, e.g. a selected cell-containing fraction or a plasma or serum fraction.

A selected cell-containing fraction may contain cell types of interest which may include white blood cells (WBC), particularly peripheral blood mononuclear cells (PBC) and/or granulocytes, and/or red blood cells (RBC). Accordingly, methods according to the present disclosure may involve detection of a marker polypeptide or nucleic acid in the blood, in white blood cells, peripheral blood mononuclear cells, granulocytes and/or red blood cells.

The sample may be fresh or archival. For example, archival tissue may be from the first diagnosis of a subject, or a biopsy at a relapse. In certain aspects, the sample is a fresh biopsy.

Subject status

The subject may be an animal, mammal, a placental mammal, a marsupial (e.g., kangaroo, wombat), a monotreme (e.g., duckbilled platypus), a rodent (e.g., a guinea pig, a hamster, a rat, a mouse), murine (e.g., a mouse), a lagomorph (e.g., a rabbit), avian (e.g., a bird), canine (e.g., a dog), feline (e.g., a cat), equine (e.g., a horse), porcine (e.g., a pig), ovine (e.g., a sheep), bovine (e.g., a cow), a primate, simian (e.g., a monkey or ape), a monkey (e.g., marmoset, baboon), an ape (e.g., gorilla, chimpanzee, orangutang, gibbon), or a human. In preferred embodiments, the subject is a human.

Furthermore, the subject may be any of its forms of development, for example, a foetus.

The terms "subject", "patient" and "individual" are used interchangeably herein.

In some cases the subject has, is suspected of having, or has received a diagnosis of, a neoplastic disorder characterized by the presence of cells having a persister-cell phenotype. The neoplasm or neoplastic cells may be all or part of a solid tumour. The solid tumour may be a neoplasm, including a non-haematological cancer, comprising or composed of cells having a persister-cell phenotype.

In some aspects disclosed herein, a subject has, or is suspected as having, or has been identified as being at risk of cancer. In some aspects disclosed herein, the subject has already received a diagnosis of cancer. The subject may have received a diagnosis of a cancer such as breast, lung, gastric, head and neck, colorectal, renal, pancreatic, uterine, hepatic, bladder, endometrial and prostate cancers as well as lymphomas (e.g., non-Hodgkin's lymphoma, NHL) and leukemia (particularly acute myeloid leukemia, AML). Lung cancer, in particular NSCLC, is of particular interest.

In some aspects disclosed herein, an subject has, or is suspected as having, or has been identified as being at risk of, or has received a diagnosis of an immune disorder, cardiovascular disorder, thrombosis, diabetes, immune checkpoint disorder, or fibrotic disorder (fibrosis) such as strabmisus, scleroderma, keloid, Nephrogenic systemic fibrosis, pulmonary fibrosis, idiopathic pulmonary fibrosis (IPF), cystic fibrosis (CF), systemic sclerosis, cardiac fibrosis, non-alcoholic steatohepatitis (NASH), other types of liver fibrosis, primary biliary cirrhosis, renal fibrosis, cancer, and atherosclerosis.

The Subject may be undergoing, or have undergone, a therapeutic treatment for that cancer. The subject may, or may not, have previously received an anti-proliferative agent as described herein. In some cases the cancer is NSCLC.

Controls

In some aspects, target expression in the subject is compared to target expression in a control. Controls are useful to support the validity of staining, and to identify experimental artefacts.

Preferably, the control is a sample from a comparable neoplastic disorder that is not characterized by the presence of cells having a persister-cell phenotype, as defined by one or more of the features described herein.

For example, in some cases the control is a sample from a comparable neoplastic disorder that is sensitive to treatment with an anti-proliferative agent. For example, from a neoplastic disorder that is sensitive to an EGFR-inhibitor such as erlotinib, optionally wherein the disorder is characterized by an EGFR activating mutation selected from the group consisting of: an in-frame deletion in exon 19, optionally wherein L747 to E749 are deleted; a L858R substitution; or a G719S/A/C substitution.

In some cases the control is a sample from a comparable neoplastic disorder that is not characterized by cells having a cobblestone-to-spindle morphological switch.

In some cases the control is a sample from a comparable neoplastic disorder wherein levels of AXL-signalling are low or absent. For example, in some cases the control sample has the same levels of AXL-signalling (eg. expression of phospho AXL) as the HCC827 cell line (ATCC accession number CRL-2868) as measured using the method set out in Example 2 or 4, and the materials & methods described herein. In some cases the control sample has the same levels of phosphoAXL expression as the HCC827 cell line.

The control may be a reference sample or reference dataset. The reference may be a sample that has been previously obtained from a subject with a known degree of suitability. The reference may be a dataset obtained from analyzing a reference sample.

Controls may be positive controls in which the marker(s) is known to be present, or expressed at known level, or negative controls in which the target molecule is known to be absent or expressed at low level.

Controls may be samples of tissue that are from subjects who are known to benefit from the treatment. The tissue may be of the same type as the sample being tested. For example, a sample of tumor tissue from a subject may be compared to a control sample of tumor tissue from a subject who is known to be suitable for the treatment, such as a subject who has previously responded to the treatment.

In some cases the control may be a sample obtained from the same subject as the test sample. The test and control samples may be collected at the same time from, for example,

different tissues or locations in the same tissue (ie. the test sample may be a tumour sample and the control sample may be a non-neoplastic sample from the same tissue). Alternatively, the test sample and control sample may be from the same or similar tissue or location, but taken at different times. For example, the test sample may be a tumour sample from anti-proliferative agent resistant tumour (eg. an erlotinib resistant tumour) and the control sample may be a tumour sample taken before the tumour (or another similar tumour in the subject) developed resistance to the anti-proliferative agent.

In some cases, the control is a cell culture sample.

In some cases the control sample is a sample collected from the subject after treatment with an AXLi as disclosed herein. For example, in some cases the test sample may be a tumour sample taken from a subject and the control sample may be tumour sample from the same subject taken after the

In some cases, a test sample is analyzed prior to incubation with an antibody to determine the level of background staining inherent to that sample.

In some cases an isotype control is used. Isotype controls use an antibody of the same class as the target specific antibody, but are not immunoreactive with the sample. Such controls are useful for distinguishing non-specific interactions of the target specific antibody.

The methods may include hematopathologist interpretation of morphology and immunohistochemistry, to ensure accurate interpretation of test results. The method may involve confirmation that the pattern of expression correlates with the expected pattern. For example, where the amount of a first target protein and/or a second target protein expression is analyzed, the method may involve confirmation that in the test sample the expression is observed as membrane staining, with a cytoplasmic component. The method may involve confirmation that the ratio of target signal to noise is above a threshold level, thereby allowing clear discrimination between specific and non-specific background signals.

In some embodiments the control is a comparable neoplastic disorder that is not characterized by the presence of cells having a persister-cell phenotype.

In some embodiments the control is a comparable neoplastic disorder wherein levels of AXL-signalling are low or absent.

In some embodiments the control is sensitive to an anti-proliferative agent. In some embodiments where the neoplastic disorder is resistant to an anti-proliferative agent, the control is the control is sensitive to the same anti-proliferative agent the neoplastic disorder is resistant to.

In some embodiments the control is not characterized by cells having a cobblestone-to-spindle morphological switch.

In some embodiments the control is healthy, non-neoplastic tissue.

In some embodiments the control is the same tissue as the neoplastic disorder.

In some embodiments the control is the same subject as the neoplastic disorder.

In some embodiments the control has the same levels of AXL-signalling as the HCC827 cell line (ATCC accession number CRL-2868).

In some embodiments the control is the HCC827 cell line (ATCC accession number CRL-2868).

Methods of Treatment

The term “treatment,” as used herein in the context of treating a condition, pertains generally to treatment and therapy, whether of a human or an animal (e.g., in veterinary applications), in which some desired therapeutic effect is achieved, for example, the inhibition of the progress of the condition, and includes a reduction in the rate of progress, a halt in the rate of progress, regression of the condition, amelioration of the condition, and cure of the condition. Treatment as a prophylactic measure (i.e., prophylaxis, prevention) is also included.

Typically, in the methods of treatment described herein the agents (eg. AXLi, IR, or anti-proliferative agent) are administered in a therapeutically or prophylactically effective amount.

The term “therapeutically-effective amount” or “effective amount” as used herein, pertains to that amount of an active compound, or a material, composition or dosage from comprising an active compound, which is effective for producing some desired therapeutic effect, commensurate with a reasonable benefit/risk ratio, when administered in accordance with a desired treatment regimen.

Similarly, the term “prophylactically-effective amount,” as used herein, pertains to that amount of an active compound, or a material, composition or dosage from comprising an active compound, which is effective for producing some desired prophylactic effect, commensurate with a reasonable benefit/risk ratio, when administered in accordance with a desired treatment regimen.

Typically, the subjects treated are in need of the described treatment.

Disclosed herein are methods of therapy. Also provided is a method of treatment, comprising administering to a subject in need of treatment a therapeutically-effective amount of an AXLi and an IR. The term “therapeutically effective amount” is an amount sufficient to show benefit to a subject. Such benefit may be at least amelioration of at least one symptom. The actual amount administered, and rate and time-course of administration, will depend on the nature and severity of what is being treated. Prescription of treatment, e.g. decisions on dosage, is within the responsibility of general practitioners and other medical doctors. The subject may have been tested to determine their eligibility to receive the treatment according to the methods disclosed herein. The method of treatment may

comprise a step of determining whether a subject is eligible for treatment, using a method disclosed herein.

The treatment may involve administration of the AXLi / IR combination alone or in further combination with other treatments, either simultaneously or sequentially dependent upon the condition to be treated. Examples of treatments and therapies include, but are not limited to, chemotherapy (the administration of active agents, including, e.g. drugs, such as chemotherapeutics); surgery; and radiation therapy.

A “chemotherapeutic agent” is a chemical compound useful in the treatment of cancer, regardless of mechanism of action. Classes of chemotherapeutic agents include, but are not limited to: alkylating agents, antimetabolites, spindle poison plant alkaloids, cytotoxic/antitumor antibiotics, topoisomerase inhibitors, antibodies, photosensitizers, and kinase inhibitors. Chemotherapeutic agents include compounds used in “targeted therapy” and conventional chemotherapy.

Examples of chemotherapeutic agents include: Lenalidomide (REVLIMID®, Celgene), Vorinostat (ZOLINZA®, Merck), Panobinostat (FARYDAK®, Novartis), Mocetinostat (MGCD0103), Everolimus (ZORTRESS®, CERTICAN®, Novartis), Bendamustine (TREAKISYM®, RIBOMUSTIN®, LEVACT®, TREANDA®, Mundipharma International), erlotinib (TARCEVA®, Genentech/OSI Pharm.), docetaxel (TAXOTERE®, Sanofi-Aventis), 5-FU (fluorouracil, 5-fluorouracil, CAS No. 51-21-8), gemcitabine (GEMZAR®, Lilly), PD-0325901 (CAS No. 391210-10-9, Pfizer), cisplatin (cis-diamine, dichloroplatinum(II), CAS No. 15663-27-1), carboplatin (CAS No. 41575-94-4), paclitaxel (TAXOL®, Bristol-Myers Squibb Oncology, Princeton, N.J.), trastuzumab (HERCEPTIN®, Genentech), temozolomide (4-methyl-5-oxo- 2,3,4,6,8-pentazabicyclo [4.3.0] nona-2,7,9-triene- 9-carboxamide, CAS No. 85622-93-1, TEMODAR®, TEMODAL®, Schering Plough), tamoxifen ((Z)-2-[4-(1,2-diphenylbut-1-enyl)phenoxy]-N,N-dimethylethanamine, NOLVADEX®, ISTUBAL®, VALODEX®), and doxorubicin (ADRIAMYCIN®), Akti-1/2, HPPD, and rapamycin.

More examples of chemotherapeutic agents include: oxaliplatin (ELOXATIN®, Sanofi), bortezomib (VELCADE®, Millennium Pharm.), sunitinib (SUNITINIB®, SU11248, Pfizer), letrozole (FEMARA®, Novartis), imatinib mesylate (GLEEVEC®, Novartis), XL-518 (Mek inhibitor, Exelixis, WO 2007/044515), ARRY-886 (Mek inhibitor, AZD6244, Array BioPharma, Astra Zeneca), SF-1126 (PI3K inhibitor, Semafore Pharmaceuticals), BEZ-235 (PI3K inhibitor, Novartis), XL-147 (PI3K inhibitor, Exelixis), PTK787/ZK 222584 (Novartis), fulvestrant (FASLODEX®, AstraZeneca), leucovorin (folinic acid), rapamycin (sirolimus, RAPAMUNE®, Wyeth), lapatinib (TYKERB®, GSK572016, Glaxo Smith Kline), Ionafernib (SARASAR™, SCH 66336, Schering Plough), sorafenib (NEXAVAR®, BAY43-9006, Bayer Labs), gefitinib (IRESSA®, AstraZeneca), irinotecan (CAMPTOSAR®, CPT-11, Pfizer), tipifarnib (ZARNESTRA™, Johnson & Johnson), ABRAXANE™ (Cremophor-free), albumin-engineered nanoparticle formulations of paclitaxel (American Pharmaceutical Partners, Schaumburg, IL), vandetanib (rINN, ZD6474, ZACTIMA®, AstraZeneca), chlorambucil, AG1478, AG1571 (SU 5271; Sugen), temsirolimus (TORISEL®, Wyeth), pazopanib (GlaxoSmithKline), canfosfamide (TELCYTA®, Telik), thiotepa and cyclophosphamide (CYTOXAN®, NEOSAR®); alkyl sulfonates such as busulfan, improsulfan and piposulfan;

aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramidate, triethylenethiophosphoramidate and trimethylmelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including the synthetic analog topotecan); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogs); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogs, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, chlorophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosoureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimustine; antibiotics such as the enediyne antibiotics (e.g. calicheamicin, calicheamicin gamma11, calicheamicin omegal1 (*Angew Chem. Intl. Ed. Engl.* (1994) 33:183-186); dynemicin, dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabycin, carminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, nemorubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, porfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogs such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitostanol, mepitostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfornithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK® polysaccharide complex (JHS Natural Products, Eugene, OR); razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; vinorelbine (NAVELBINE®); novantrone; teniposide; edatrexate; daunomycin; aminopterin; capecitabine (XELODA®, Roche); ibandronate; CPT-11; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid; and pharmaceutically acceptable salts, acids and derivatives of any of the above. Combinations of agents may be

used, such as CHP (doxorubicin, prednisone, cyclophosphamide), or CHOP (doxorubicin, prednisone, cyclophosphamide, vincristine).

Also included in the definition of “chemotherapeutic agent” are: (i) anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens and selective estrogen receptor modulators (SERMs), including, for example, tamoxifen (including NOLVADEX®; tamoxifen citrate), raloxifene, droloxifene, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, and FARESTON® (toremifine citrate); (ii) aromatase inhibitors that inhibit the enzyme aromatase, which regulates estrogen production in the adrenal glands, such as, for example, 4(5)-imidazoles, aminoglutethimide, MEGASE® (megestrol acetate), AROMASIN® (exemestane; Pfizer), formestane, fadrozole, RIVISOR® (vorozole), FEMARA® (letrozole; Novartis), and ARIMIDEX® (anastrozole; AstraZeneca); (iii) anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; as well as troxacitabine (a 1,3-dioxolane nucleoside cytosine analog); (iv) protein kinase inhibitors such as MEK inhibitors (WO 2007/044515); (v) lipid kinase inhibitors; (vi) antisense oligonucleotides, particularly those which inhibit expression of genes in signaling pathways implicated in aberrant cell proliferation, for example, PKC- α , Raf and H-Ras, such as oblimersen (GENASENSE®, Genta Inc.); (vii) ribozymes such as VEGF expression inhibitors (e.g., ANGIOZYME®) and HER2 expression inhibitors; (viii) vaccines such as gene therapy vaccines, for example, ALLOVECTIN®, LEUVECTIN®, and VAXID®; PROLEUKIN® rIL-2; topoisomerase 1 inhibitors such as LURTOTECAN®, ABARELIX® rmRH; (ix) anti-angiogenic agents such as bevacizumab (AVASTIN®, Genentech); and pharmaceutically acceptable salts, acids and derivatives of any of the above.

Also included in the definition of “chemotherapeutic agent” are therapeutic antibodies such as alemtuzumab (Campath), bevacizumab (AVASTIN®, Genentech); cetuximab (ERBITUX®, Imclone); panitumumab (VECTIBIX®, Amgen), rituximab (RITUXAN®, Genentech/Biogen Idec), ofatumumab (ARZERRA®, GSK), pertuzumab (PERJETA™, OMNITARG™, 2C4, Genentech), trastuzumab (HERCEPTIN®, Genentech), tositumomab (Bexxar, Corixa), MDX-060 (Medarex) and the antibody drug conjugate, gemtuzumab ozogamicin (MYLOTARG®, Wyeth).

Humanized monoclonal antibodies with therapeutic potential as chemotherapeutic agents in combination with the conjugates of the disclosure include: alemtuzumab, apolizumab, aselizumab, atlizumab, bapineuzumab, bevacizumab, bivatumumab mertansine, cantuzumab mertansine, cedelizumab, certolizumab pegol, cidfusituzumab, cidtuzumab, daclizumab, eculizumab, efalizumab, epratuzumab, erlizumab, felvizumab, fontolizumab, gemtuzumab ozogamicin, inotuzumab ozogamicin, ipilimumab, labetuzumab, lintuzumab, matuzumab, mepolizumab, motavizumab, motovizumab, natalizumab, nimotuzumab, nolovizumab, numavizumab, ocrelizumab, omalizumab, palivizumab, pascolizumab, pectusituzumab, pectuzumab, pertuzumab, pexelizumab, ralvizumab, ranibizumab, reslivizumab, reslizumab, resyvizumab, rovelizumab, ruplizumab, sibrotuzumab, sipilizumab, sontuzumab, tacatuzumab tetraxetan, tadocizumab, talizumab, tefibazumab, tocilizumab, toralizumab, trastuzumab, tucotuzumab celmoleukin, tucosituzumab, umavizumab, urtoxazumab, and visilizumab.

Compositions according to the present disclosure are preferably pharmaceutical compositions. Pharmaceutical compositions according to the present disclosure, and for use in accordance with the present disclosure, may comprise, in addition to the active ingredient, i.e. a conjugate compound, a pharmaceutically acceptable excipient, carrier, buffer, stabiliser or other materials well known to those skilled in the art. Such materials should be non-toxic and should not interfere with the efficacy of the active ingredient. The precise nature of the carrier or other material will depend on the route of administration, which may be oral, or by injection, e.g. cutaneous, subcutaneous, or intravenous.

Pharmaceutical compositions for oral administration may be in tablet, capsule, powder or liquid form. A tablet may comprise a solid carrier or an adjuvant. Liquid pharmaceutical compositions generally comprise a liquid carrier such as water, petroleum, animal or vegetable oils, mineral oil or synthetic oil. Physiological saline solution, dextrose or other saccharide solution or glycols such as ethylene glycol, propylene glycol or polyethylene glycol may be included. A capsule may comprise a solid carrier such as a gelatin.

For intravenous, cutaneous or subcutaneous injection, or injection at the site of affliction, the active ingredient will be in the form of a parenterally acceptable aqueous solution which is pyrogen-free and has suitable pH, isotonicity and stability. Those of relevant skill in the art are well able to prepare suitable solutions using, for example, isotonic vehicles such as Sodium Chloride Injection, Ringer's Injection, Lactated Ringer's Injection. Preservatives, stabilisers, buffers, antioxidants and/or other additives may be included, as required.

In some embodiments of the methods of treatment described herein, the AXLi, IR, or AXLi and IR combination is comprised in a pharmaceutical composition, optionally further comprising a pharmaceutically acceptable excipient.

Dosage

It will be appreciated by one of skill in the art that appropriate dosages of the AXLi and/or the IR, and compositions comprising these active elements, can vary from subject to subject. Determining the optimal dosage will generally involve the balancing of the level of therapeutic benefit against any risk or deleterious side effects. The selected dosage level will depend on a variety of factors including, but not limited to, the activity of the particular compound, the route of administration, the time of administration, the rate of excretion of the compound, the duration of the treatment, other drugs, compounds, and/or materials used in combination, the severity of the condition, and the species, sex, age, weight, condition, general health, and prior medical history of the subject. The amount of compound and route of administration will ultimately be at the discretion of the physician, veterinarian, or clinician, although generally the dosage will be selected to achieve local concentrations at the site of action which achieve the desired effect without causing substantial harmful or deleterious side-effects.

In certain aspects, the dosage of AXLi is determined by the expression of a first marker observed in a sample obtained from the subject. Thus, the level or localisation of expression of the first marker in the sample may be indicative that a higher or lower dose of AXLi is required. For example, a high expression level of the first marker may indicate that a higher

dose of AXLi would be suitable. In some cases, a high expression level of the first marker may indicate the need for administration of another agent in addition to the AXLi. For example, administration of the AXLi in conjunction with a chemotherapeutic agent. A high expression level of the first marker may indicate a more aggressive therapy.

In certain aspects, the dosage of the IR is determined by the expression of a second marker observed in a sample obtained from the subject. Thus, the level or localisation of expression of the second marker in the sample may be indicative that a higher or lower dose of IR is required. For example, a high expression level of the second marker may indicate that a higher dose of IR would be suitable. In some cases, a high expression level of the second marker may indicate the need for administration of another agent in addition to the IR. For example, administration of the IR in conjunction with a chemotherapeutic agent. A high expression level of the second marker may indicate a more aggressive therapy.

In certain aspects, the dosage level is determined by the expression of a first target protein, such as AXL, on neoplastic cells in a sample obtained from the subject. For example, when the target neoplasm is composed of, or comprises, neoplastic cells expressing the first target protein.

In certain aspects, the dosage level is determined by the expression of a first target protein, such as AXL, on cells associated with the target neoplasm. For example, the target neoplasm may be a solid tumour composed of, or comprising, neoplastic cells that express the first target protein. For example, the target neoplasm may be a solid tumour composed of, or comprising, neoplastic cells that do not express the first target protein. The cells expressing the first target protein may be neoplastic or non-neoplastic cells associated with the target neoplasm. For example, the cells expressing the first target protein may be cells infiltrating a solid tumour comprising or composed of neoplastic cells which do not express the first target protein.

Administration can be effected in one dose, continuously or intermittently (e.g., in divided doses at appropriate intervals) throughout the course of treatment. Methods of determining the most effective means and dosage of administration are well known to those of skill in the art and will vary with the formulation used for therapy, the purpose of the therapy, the target cell(s) being treated, and the subject being treated. Single or multiple administrations can be carried out with the dose level and pattern being selected by the treating physician, veterinarian, or clinician.

In general, a suitable dose of each active compound is in the range of about 100 ng to about 25 mg (more typically about 1 µg to about 10 mg) per kilogram body weight of the subject per day. Where the active compound is a salt, an ester, an amide, a prodrug, or the like, the amount administered is calculated on the basis of the parent compound and so the actual weight to be used is increased proportionately.

In one embodiment, each active compound is administered to a human subject according to the following dosage regime: about 100 mg, 3 times daily.

In one embodiment, each active compound is administered to a human subject according to the following dosage regime: about 150 mg, 2 times daily.

In one embodiment, each active compound is administered to a human subject according to the following dosage regime: about 200 mg, 2 times daily.

However in one embodiment, each conjugate compound is administered to a human subject according to the following dosage regime: about 50 or about 75 mg, 3 or 4 times daily.

In one embodiment, each conjugate compound is administered to a human subject according to the following dosage regime: about 100 or about 125 mg, 2 times daily.

Antibodies

The term "antibody" herein is used in the broadest sense and specifically covers monoclonal antibodies, polyclonal antibodies, dimers, multimers, multispecific antibodies (*e.g.*, bispecific antibodies), intact antibodies (also described as "full-length" antibodies) and antibody fragments, so long as they exhibit the desired biological activity, for example, the ability to bind a first target protein (Miller *et al* (2003) *Jour. of Immunology* 170:4854-4861). Antibodies may be murine, human, humanized, chimeric, or derived from other species such as rabbit, goat, sheep, horse or camel.

An antibody is a protein generated by the immune system that is capable of recognizing and binding to a specific antigen. (Janeway, C., Travers, P., Walport, M., Shlomchik (2001) *Immuno Biology*, 5th Ed., Garland Publishing, New York). A target antigen generally has numerous binding sites, also called epitopes, recognized by Complementarity Determining Regions (CDRs) on multiple antibodies. Each antibody that specifically binds to a different epitope has a different structure. Thus, one antigen may have more than one corresponding antibody. An antibody may comprise a full-length immunoglobulin molecule or an immunologically active portion of a full-length immunoglobulin molecule, *i.e.*, a molecule that contains an antigen binding site that immunospecifically binds an antigen of a target of interest or part thereof, such targets including but not limited to, cancer cell or cells that produce autoimmune antibodies associated with an autoimmune disease. The immunoglobulin can be of any type (*e.g.* IgG, IgE, IgM, IgD, and IgA), class (*e.g.* IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass, or allotype (*e.g.* human G1m1, G1m2, G1m3, non-G1m1 [that, is any allotype other than G1m1], G1m17, G2m23, G3m21, G3m28, G3m11, G3m5, G3m13, G3m14, G3m10, G3m15, G3m16, G3m6, G3m24, G3m26, G3m27, A2m1, A2m2, Km1, Km2 and Km3) of immunoglobulin molecule. The immunoglobulins can be derived from any species, including human, murine, or rabbit origin.

"Antibody fragments" comprise a portion of a full length antibody, generally the antigen binding or variable region thereof. Examples of antibody fragments include Fab, Fab', F(ab')₂, and scFv fragments; diabodies; linear antibodies; fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies, CDR (complementary determining region), and epitope-binding fragments of any of the above which immunospecifically bind to cancer cell antigens, viral antigens or microbial antigens, single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

The term “monoclonal antibody” as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e. the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to polyclonal antibody preparations which include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to their specificity, the monoclonal antibodies are advantageous in that they may be synthesized uncontaminated by other antibodies. The modifier “monoclonal” indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present disclosure may be made by the hybridoma method first described by Kohler *et al* (1975) *Nature* 256:495, or may be made by recombinant DNA methods (see, US 4816567). The monoclonal antibodies may also be isolated from phage antibody libraries using the techniques described in Clackson *et al* (1991) *Nature*, 352:624-628; Marks *et al* (1991) *J. Mol. Biol.*, 222:581-597 or from transgenic mice carrying a fully human immunoglobulin system (Lonberg (2008) *Curr. Opinion* 20(4):450-459).

The monoclonal antibodies herein specifically include “chimeric” antibodies in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (US 4816567; and Morrison *et al* (1984) *Proc. Natl. Acad. Sci. USA*, 81:6851-6855). Chimeric antibodies include “primatized” antibodies comprising variable domain antigen-binding sequences derived from a non-human primate (e.g. Old World Monkey or Ape) and human constant region sequences.

An “intact antibody” herein is one comprising VL and VH domains, as well as a light chain constant domain (CL) and heavy chain constant domains, CH1, CH2 and CH3. The constant domains may be native sequence constant domains (e.g. human native sequence constant domains) or amino acid sequence variant thereof. The intact antibody may have one or more “effector functions” which refer to those biological activities attributable to the Fc region (a native sequence Fc region or amino acid sequence variant Fc region) of an antibody. Examples of antibody effector functions include C1q binding; complement dependent cytotoxicity; Fc receptor binding; antibody-dependent cell-mediated cytotoxicity (ADCC); phagocytosis; and down regulation of cell surface receptors such as B cell receptor and BCR.

Depending on the amino acid sequence of the constant domain of their heavy chains, intact antibodies can be assigned to different “classes.” There are five major classes of intact antibodies: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into “subclasses” (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA, and IgA2. The heavy-chain

constant domains that correspond to the different classes of antibodies are called α , δ , ϵ , γ , and μ , respectively. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known.

BRIEF DESCRIPTION OF THE FIGURES

Embodiments and experiments illustrating the principles of the disclosure will now be discussed with reference to the accompanying figures in which:

Figure 1.

AXL inhibition delays emergence of acquired resistance to the epidermal growth factor receptor tyrosine kinase inhibitor erlotinib *in vivo*, and AXL signalling is associated with a novel gene signature of post-treatment cancer cell persistence that correlates with decreased patient survival

(A) The growth of human non-small cell lung cancer (NSCLC) HCC827 xenograft tumors in nude mice display the expansive growth of vehicle treated and bemcentinib treated tumors (terminated at day 75). The tumors are initially very sensitive to erlotinib treatment, but eventually regrew. Group mean tumor volumes and standard error of the mean (SEM) are shown.

(B) Zoomed segment from (A) showing mean tumor volumes of groups treated with erlotinib (50 mg/kg, *q.d.*) or erlotinib in combination with bemcentinib (erlotinib 50 mg/kg, *q.d.* and bemcentinib 50 or 100 mg/kg, *b.i.d.*, respectively). The graph displays the final phase of the experiment from day 100 until study termination of experiment at day 138, $n = 14-16$ animals/group.

(C) Representative images of tumor-bearing mice treated with erlotinib (50 mg/kg, *q.d.*) or erlotinib in combination with bemcentinib (50 mg/kg, *q.d.*, and 100 mg/kg, *b.i.d.*, respectively).

(D) Final tumor volumes at termination of study (day 138) of individual HCC827 tumors for different treatment groups are shown. Differences between treatment groups ($n=14-16$ tumors/group) were calculated using one way

ANOVA followed by Tukey's multiple comparisons test ($**P \leq 0.01$).

(E) HCC827 tumors from a separate *in vivo* experiment were harvested after 25 days of treatment with vehicle or erlotinib (50 mg/kg, *q.d.*) in order to perform western blot analysis for the expression of AXL (140 kDa), pAXL (Tyr779, 140 kDa), pAKT (Ser473, 60 kDa), and vimentin (57 kDa). GAPDH (37 kDa) is shown as a loading control.

(F) Volcano plot displaying differentially expressed genes (cutoff: 1.5 fold change and $P < 0.01$) between HCC827 tumors treated for 65 days with erlotinib (50 mg/kg, *q.d.*) or combination of erlotinib and bemcentinib (50 mg/kg, *q.d.*, and 50 mg/kg, *b.i.d.*, respectively), $n = 4$. The x-axis specifies the gene expression $\text{Log}_2(\text{fold-change})$ values and the y-axis specifies significance $-\text{Log}_{10}(P \text{ value})$ for each gene. The position of selected down- and upregulated genes are indicated.

(G) Bemcentinib-induced transcriptional changes in mesenchymal markers involved in negative regulation of MAPK activity (*SPRY1*, *SPRY2*, and *SPRY4*) correlate with overall survival in lung adenocarcinoma patients. Kaplan-Meier survival analysis with survival time (months) on the x-axis and survival probability on the y-axis. Hazard ratio (HR) = 0.38 (0.29 -0.48). Logrank $P = 1.9E-15$.

Figure 2.

The erlotinib resistant subclones have undergone epithelial-to-mesenchymal transition and upregulation of AXL and are characterized by resistance to apoptosis

(A) Erlotinib sensitivity of HCC827 parental cells and the erlotinib resistant subclones (ER3 and ER10) was measured by resazurin assay following 5 days of erlotinib treatment. The mean IC₅₀ value for HCC827 cells was 5.6 nM, and >10 μ M for the two erlotinib resistant subclones ER3 and ER10 (n = 11-13 independent experiments).

(B) Representative confocal images of HCC827, ER3, and ER10 cells immunofluorescently labelled for epithelial cell adhesion molecule CDH1 (green) and mesenchymal intermediate filament VIM (red); DAPI nuclear stain (blue); scale bar: 50 μ m.

(C) Western blotting of lysates from HCC827 parental and ER cells using the indicated antibodies for epithelial marker CDH1 (135 kDa), and mesenchymal markers CDH2(135 kDa), vimentin (54 kDa), and AXL (140 kDa). β -actin (42 kDa) is shown as a loading control.

(D) Relative resistance to apoptosis was measured by induction of caspase activity of the HCC827 parental cells and ER10 cells upon 4 hours treatment with increasing doses of staurosporine by caspase 3/7 Glo luciferase assay. Y-axis represents bioluminescence as photon flux (photons/s). One-way ANOVA was followed by Dunnett's multiple comparisons test comparing every treatment against vehicle (DMSO) control (** $P < 0.001$, **** $P < 0.0001$).

(E) High dimensional analysis of the HCC827 parental cells and the erlotinib resistant clones ER3 and ER10 using a 22 parameter time of flight mass cytometry (CyTOF) panel. Nonlinear dimensionality reduction, t-distributed stochastic neighbor embedding (tSNE) (30) created a 2D projection of the three cell lines based on their CDH1, VIM, CD44, EGFR, AXL and PD-L1 expression. Each point represents a single cell from (equal downsampling at 10,000 cells per sample, 5000 iterations).

(F) The color range represents the intensity of markers included in the CyTOF panel and the distribution is shown for each for the cell lines in separate t-distributed stochastic neighbor embedding (tSNE) plots.

Figure 3.

Bemcentinib treatment reduces clonogenic survival of ER cells

- (A) Representative images of crystal violet-stained colonies from clonogenic survival assay of HCC827, ER3 and ER10 cells treated for 14 days with either vehicle (DMSO), bemcentinib, or erlotinib as monotherapy.
- (B) Survival fraction of HCC827, ER3 and ER10 cells following treatment as indicated in (A). Each experiment was performed in triplicate ($n = 2$ independent experiments). Data represent survival fraction $\pm$ SD. Colony area was quantified using the "ColonyArea" plugin in ImageJ and one-way ANOVA was followed by Dunnett's multiple comparisons test comparing every treatment against vehicle (DMSO) control ($*** P < 0.001$, $****P < 0.0001$).
- (C) Relative resistance to apoptosis was measured by caspase 3/7 Glo luciferase activity assay in HCC827 parental cells, ER3, and ER10 cells upon treatment as indicated for 24 hours. Bioluminescence as photon flux (photons/s) was measured, and fold change relative to vehicle control (DMSO) is given (y-axis). One-way ANOVA was followed by Dunnett's multiple comparisons test comparing every treatment against vehicle (DMSO) control ($****P < 0.0001$).

Figure 4.

AXL expression in lung adenocarcinomas is widely associated with positive regulation of autophagy, and erlotinib resistant non-small cell lung cancer cells are characterized by a cytoprotective autophagic flux that is abrogated by inhibition with the selective AXL inhibitor bemcentinib

- (A) The correlation between AXL mRNA (Fragments Per Kilobase of transcripts per Million mapped reads; FPKM log2) and GO positive regulation of autophagy (enrichment score) from TCGA lung adenocarcinoma cohort (LUAD, $n = 517$. Correlation Rho and p-value were computed by Spearman correlation coefficient rank test).
- (B) Relative protein levels of p62 (SQSTM, 62 kDa) and LC3A/B (LC3-I 17 kDa, LC3-II 19 kDa) were assessed in lysates of HCC827, ER3, and ER10 cells by western blotting. β -actin (42 kDa) is shown as a loading control.
- (C) HCC827 parental cells and ER3 cells grown in complete medium or starved in EBSS with 0.1% BSA in the absence or presence of chloroquine were stained by the Cyto-ID probe and analyzed by flow cytometry. Mean fluorescence intensity (MFI) $\pm$ SD is shown.
- (D) Transmission electron micrographs of HCC827 and ER10 cells $\pm$ the autophagy inhibitor chloroquine; scale bar: 500 nm.
- (E-F) Representative transmission electron microscopy images of erlotinib resistant ER3 cells treated with either erlotinib (D; 1 μ M) alone or in combination with the small-molecule AXL inhibitor bemcentinib (E; 0.8 μ M) for 7 days. Upon combination treatment, massive vacuolization and the presence of autophagosomes (A) and autolysosomes (AL) are shown; scale bar; 5 μ m for 4000x images, 500nm for 40,000x and 60,000x images.
- (G) Western blot analysis of protein levels of p62 (SQSTM, 62 kDa) and the non-lipidated (LC3-I, 17 kDa) and the lipidated (LC3-II, 19 kDa) forms of LC3A/B in the HCC827, ER3, and ER10 cells treated for 24 hours under

various treatment conditions as indicated (1 μ M erlotinib, 0.8 μ M bemcentinib). β -actin (42 kDa) is shown as a vehicle control.

(H) Quantification of LC3 levels shown in (D). Normalization was performed against total protein using Bio-Rad stain-free imaging technology. Data are presented as fold change compared to HCC827 vehicle (DMSO)-treated sample (upper panel) or LC3-II/ LC3-I ratio (lower panel).

(I) Staining of the erlotinib resistant ER3 cells by LysoTracker (red DN-99) in combination with anti-LC3A/B antibody reveals the presence of lysosomes (red puncta), autophagosomes (green puncta), and autolysosomes (yellow puncta) in cells treated with erlotinib (1 μ M) and/or bemcentinib (0.8 μ M) for 7 days. Chloroquine (50 μ M) was added as indicated 16 hours prior to fixation and staining. Scale bar; 10 μ m.

(J) Co-localization intensity profiles from the zoomed images is shown. Marker in (H) indicates the selected area analyzed and the marker used for all experimental conditions is 1 pixel high and 130 pixels wide. Fluorescence intensity (y-axis) along the x-position (x-axis) is presented.

Figure 5.

The specific AXL inhibitor bemcentinib inhibits the high pre-mortem autophagic flux of the erlotinib resistant cells

(A) Dynamics of autophagosome formation and subsequent fusion with lysosomes to form autolysosomes was assessed by RFP-GFP-LC3B sensor experiment. ER10 cells transfected with RFP-GFP-LC3B tandem sensor were treated as indicated for 24 hours with either vehicle (DMSO), rapamycin (200 nM), bemcentinib (0.8 μ M), or chloroquine (50 μ M). Representative confocal images are shown. Scale bar: 10 μ m.

(B) Schematics for the assay described above. The LC3-associated autophagosomes appear yellow due to the simultaneous expression of both RFP and EGFP under neutral pH, whereas upon the fusion of the LC3-associated vesicles with the lysosome, the resultant autolysosomes express RFP only due to the loss of fluorescence from the acid-sensitive EGFP fluorochrome under acidic conditions.

(C) Autophagic flux was assessed in ER3 cells by measuring the balance of autophagosome formation and clearance by pretreating the cells 16 hours with 2,4 μ M bemcentinib in the presence of autophagy induction through starvation in EBSS with 0.1% BSA $\pm$ 50 μ M chloroquine for 3 hours (in the presence of treatment). Relative green fluorescence intensity from the Cyto-ID probe compared to the vehicle-treated cells in complete cell culture medium is given for a representative experiment $\pm$ SD (n=3). Unpaired t-test (**** $P < 0.0001$). (D) Flow cytometry Click-IT AHA chemistry-based long-lived protein degradation assay of ER3 cells pre-treated as indicated for 16 hours, prior to starvation in EBSS + 0.1% BSA for 3 hours (in the presence of treatment). The alkyne-AF488 fluorescence intensity $\pm$ SD (n=3) is given for the starved samples relative to the vehicle treated (DMSO) cells in complete RPMI-1640 cell culture medium. Unpaired t-test (**** $P < 0.0001$).

Figure 6.**Bemcentinib treatment induces a programmed cell death displaying hallmarks of immunogenic cell death with the release of DAMPs**

(A) Release of extracellular ATP following 24 hours treatment as indicated was measured by ATP luciferase assay. Fold change values of extracellular ATP normalized against vehicle control (DMSO) is shown for a representative experiment ($n = 4$). One-way ANOVA was followed by Dunnett's multiple comparisons test comparing every treatment against vehicle (DMSO) control (* $P < 0.05$, *** $P < 0.001$, **** $P < 0.0001$).

(B) Release of high-mobility group box 1 (HMGB1) following 72 hours treatment with erlotinib (1 μM) $\pm$ bemcentinib (0.8 μM) was measured by ELISA. Samples were normalized against the corresponding resazurin measurement for each well, and further normalized against the vehicle control (DMSO) for each cell line. Data are shown for a representative experiment ($n = 4$). One-way ANOVA was followed by Dunnett's multiple comparisons test comparing every treatment against vehicle (DMSO) control (** $P < 0.01$, **** $P < 0.0001$).

(C) Flow cytometric assessment of extracellular CALR. Histograms of ER10 cells treated for 7 days as indicated are shown, and median fluorescence intensity (MFI) for all cell lines from a representative experiment is shown in the corresponding table ($n = 4$). HCC827 cells were treated with 0.8 μM bemcentinib, and ER3 and ER10 cells with 1.2 μM bemcentinib.

(D) Alteration in the expression of major histocompatibility complex 1 (MHC-I) assessed by flow cytometry after 7 days treatment with erlotinib (1 μM) $\pm$ bemcentinib (0.8 μM for HCC827 parental cells, 1.2 μM for ERcells). Histogram shown for ER3 cells. Mean fluorescence intensity (MFI) values for all cell lines are given in the corresponding table.

SEQUENCES

SEQ ID NO.1 [10C9 Heavy CDR1]
DYNFTRYIIH

SEQ ID NO.2 [10C9 Heavy CDR2]
WIYPGTGDSKYNEKFKG

SEQ ID NO.3 [10C9 Heavy CDR3]
NGNYWYFDV

SEQ ID NO.4 [10C9 Light CDR1]
RSSKSLHNSNGNTYLY

SEQ ID NO.5 [10C9 Light CDR2]
RMSNLAS

SEQ ID NO.6 [10C9 Light CDR3]
MQHREYPFT

SEQ ID NO.7 [10G5 Heavy CDR1]
GYSFTDFYIN

SEQ ID NO.8 [10G5 Heavy CDR2]
RIFPGGDNTYYNEKFKG

SEQ ID NO.9 [10G5 Heavy CDR3]
RGLYYAMDY

SEQ ID NO.10 [10G5 Light CDR1]
RSSQSLVHSNGIPYLH

SEQ ID NO.11 [10G5 Light CDR2]
RVSNRFS

SEQ ID NO.12 [10G5 Light CDR3]
SQGTHVPPT

SEQ ID NO.13 [hu10G5 VH(GH1)]

EVQLVQSGAGLVQPGGSVRLSCAASGYSFTDFYINWVRQAPGKGLEWIARIFPGGDNTYY
NEKFKGRFTLSADTSSSTAYLQLNSLRAEDTAVYYCARRGLYYAMDYWGQGTLVTVSS

SEQ ID NO.14 [hu10G5 VH(GH2)]

EVQLVESGGGLVQPGGSLRLSCAASGYSFTDFYINWVRQAPGKGLEWVARIFPGGDNTYY
NEKFKGRFTLSADTSKSTAYLQMNSLRAEDTAVYYCARRGLYYAMDYWGQGTLVTVSS

SEQ ID NO.15 [hu10G5 VL(GL1)]

DIQMTQSPSSLSASVGDRVTITCRSSQSLVHSNGIPYLHWYQQKPGKAPKLLIYRVSNRFS
GVPSRFSGSGSGTDFTLTISLQPEDFATYYCSQGTHVPPTFGQGTKVEIK

SEQ ID NO.16 [hu10G5 VL(GL2)]

DIQMTQSPSSLSASVGDRVTITCRSSQSLVHSNGIPYLHWYQQKPGKAPKLLIYRVSNRFS
GVPSRFSGSRSGTDFTLTISLQPEDFATYYCSQGTHVPPTFGQGTKVEIK

SEQ ID NO.17 [10G5 GH1 Heavy chain]

EVQLVQSGAGLVQPGGSVRLSCAASGYSFTDFYINWVRQAPGKGLEWIARIFPGGDNTYY
NEKFKGRFTLSADTSSSTAYLQLNSLRAEDTAVYYCARRGLYYAMDYWGQGTLVTVSSAS
TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY
SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVF
LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR
VVSFLTTLHQLDNLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ
VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV
FSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO.18 [10G5 GH2 Heavy chain]

EVQLVESGGGLVQPGGSLRLSCAASGYSFTDFYINWVRQAPGKGLEWVARIFPGGDNTYY
NEKFKGRFTLSADTSKSTAYLQMNSLRAEDTAVYYCARRGLYYAMDYWGQGTLVTVSSAS
TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY
SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVF
LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR
VVSFLTTLHQLDNLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ
VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV
FSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO.19 [10G5 GL1 Light chain]

DIQMTQSPSSLSASVGDRVTITCRSSQSLVHSNGIPYLHWYQQKPGKAPKLLIYRVSNRFS
GVPSRFSGSGSGTDFTLTISLQPEDFATYYCSQGTHVPPTFGQGTKVEIKRTVAAPSVFIF
PPSDEQLKSGTASVCLLNNFYPRKAVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST
LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO.20 [10G5 GL2 Light chain]

DIQMTQSPSSLSASVGDRVTITCRSSQSLVHSNGIPYLHWYQQKPGKAPKLLIYRVSNRFS
GVPSRFSGSRSGTDFTLTISLQPEDFATYYCSQGTHVPPTFGQGTKVEIKRTVAAPSVFIF
PPSDEQLKSGTASVCLLNNFYPRKAVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST
LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

STATEMENTS OF INVENTION

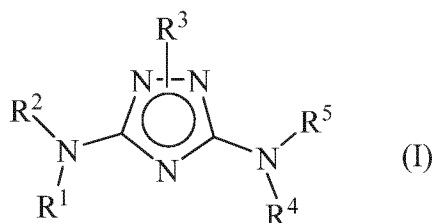
1. A method for treating a neoplastic disorder in a subject with a combination of an AXLi and an IR, the method comprising:
 - (i) administering a combination of the AXLi and the IR to the subject;
 - (ii) administering the AXLi to the subject, wherein the IR has been, is, or will be, administered to the subject; or
 - (iii) administering the IR to the subject, wherein the AXLi has been, is, or will be, administered to the subject;wherein the neoplastic disorder is characterized by the presence of cells having a persister-cell phenotype.
2. The method of paragraph 1, wherein the cells having a persister-cell phenotype have increased AXL-signalling as compared to a control.
3. The method of paragraph 2, wherein the increased AXL-signalling is characterized by increased AXL expression, increased AXL phosphorylation, and/or increased Akt phosphorylation.
4. The method of any one of paragraphs 1 to 3, wherein the cells having a persister-cell phenotype have increased CD44 expression as compared to a control.
5. The method of any one of paragraphs 1 to 4, wherein the cells having a persister-cell phenotype have decreased expression of spry1, spry2, and/or spry4 as compared to a control.
6. The method of any one of paragraphs 1 to 5, wherein the cells having a persister-cell phenotype have decreased expression of pPLCg, pSTAT5, EGFR, and/or pEGFR as compared to a control.
7. The method of any one of paragraphs 1 to 6, wherein the cells having a persister-cell phenotype have increased autophagic flux as compared to a control.
8. The method paragraph 7, wherein the cells having a persister-cell phenotype have increased expression of LC3A/B.
9. The method of either one of paragraphs 7 and 8, wherein the cells having a persister-cell phenotype have increased expression levels of membrane-bound LC3-II.
- 9a. The method of any one of paragraphs 1 to 9, wherein the cells having a persister-cell phenotype have an enrichment of genes associated with established autophagy gene expression signatures downloaded from GSEA Molecular signature database v6.1.
10. The method of any one of paragraphs 1 to 9a, wherein the cells having a persister-cell phenotype exhibit a cobblestone-to-spindle morphological switch.

11. The method of any one of paragraphs 1 to 10, wherein the cells having a persister-cell phenotype have increased resistance to staurosporine induced apoptosis as compared to a control.
12. The method of any one of paragraphs 1 to 11, wherein the cells having a persister-cell phenotype express phospho-AXL.
13. The method of any one of paragraphs 1 to 12, wherein the cells having a persister-cell phenotype express CD44.
14. The method of any one of paragraphs 1 to 13, wherein the cells having a persister-cell phenotype do not express pPLCg, pSTAT5, EGFR, and/or pEGFR.
15. The method of any one of paragraphs 1 to 14, wherein the cells having a persister-cell phenotype comprise a receptor-activating mutation.
16. The method of paragraph 15, wherein the receptor-activating mutation is an EGFR-activating mutation.
17. The method of paragraph 16, wherein the EGFR-activating mutation is a mutation in the EGFR tyrosine-kinase domain.
18. The method of paragraph 17, wherein EGFR-activating mutation is:
 - (viii) an in-frame deletion in exon 19, optionally wherein L747 to E749 are deleted;
 - (ix) a L858R substitution;
 - (x) a G719S/A/C substitution;
 - (xi) a V765A substitution;
 - (xii) a T783A substitution;
 - (xiii) a C797S substitution; or
 - (xiv) an in-frame duplications and/or insertions in exon 20.
19. The method of any one of paragraphs 1 to 18, wherein the cells having a persister-cell phenotype do not comprise an anti-proliferative agent resistance mutation in a receptor.
20. The method of paragraph 19, wherein the receptor is EGFR.
21. The method of paragraph 20, wherein the anti-proliferative agent resistance mutation is:
 - (i) a T790M substitution; and/or
 - (ii) a D761Y substitution
22. The method of any one of paragraphs 1 to 21, wherein the cells having a persister-cell phenotype are neoplastic cells.

23. The method of any one of paragraphs 1 to 22, wherein the cells having a persister-cell phenotype are cancer cells, optionally wherein the cancer cells are EGFR-inhibitor resistant cancer cells, such as erlotinib resistant NSCLC cells.
24. The method of any one of paragraphs 1 to 23, wherein the neoplastic disorder characterized by the presence of cells having a persister-cell phenotype is cancer.
25. The method of paragraph 24, wherein the cancer is selected from the group consisting of: histiocytoma, glioma, astrocytoma, osteoma, lung cancer, small-cell lung cancer, non-small-cell lung cancer, gastrointestinal cancer, bowel cancer, colon cancer, breast carcinoma, ovarian carcinoma, prostate cancer, testicular cancer, liver cancer, kidney cancer, bladder cancer, pancreas cancer, brain cancer, sarcoma, osteosarcoma, Kaposi's sarcoma, melanoma, lymphomas, and leukemias.
26. The method of paragraph 25, wherein the cancer is lung cancer.
27. The method of paragraph 25, wherein the lung cancer is NSCLC.
28. The method of any one of paragraphs 1 to 27, wherein the neoplastic disorder is a solid tumour.
29. The method of paragraph 28, wherein the solid tumour comprises the cells having a persister-cell phenotype.
30. The method of either one of paragraphs 28 and 29, wherein solid tumour comprises cells not having a persister-cell phenotype.
31. The method of any one of paragraphs 1 to 30, wherein the neoplastic disorder is resistant to treatment with an anti-proliferative agent.
32. The method of any one of paragraphs 2 to 31, wherein the control is a comparable neoplastic disorder that is not characterized by the presence of cells having a persister-cell phenotype.
33. The method of any one of paragraphs 2 to 32, wherein the control is a comparable neoplastic disorder wherein levels of AXL-signalling are low or absent.
34. The method of any one of paragraphs 2 to 33, wherein the control is sensitive to the anti-proliferative agent of paragraph 31.
35. The method of any one of paragraphs 2 to 34, wherein the control is not characterized by cells having a cobblestone-to-spindle morphological switch.
36. The method of any one of paragraphs 2 to 31, wherein the control is healthy, non-neoplastic tissue.

37. The method of any one of paragraphs 2 to 36, wherein the control is the same tissue as the neoplastic disorder.
38. The method of any one of paragraphs 2 to 37, wherein the control is the same subject as the neoplastic disorder.
39. The method of any one of paragraphs 2 to 38, wherein the control has the same levels of AXL-signalling as the HCC827 cell line (ATCC accession number CRL-2868).
40. The method of any one of paragraphs 2 to 31, wherein the control is the HCC827 cell line (ATCC accession number CRL-2868).
41. The method of any one of paragraphs 1 to 40, wherein the AXLi and IR are administered concurrently.
42. The method of any one of paragraphs 1 to 40, wherein the AXLi and IR are administered separately and/or sequentially.
43. The method of any one of paragraphs 1 to 42, further comprising administering an anti-proliferative agent in combination with the AXLi and/or IR.
44. The method of paragraph 43, wherein the neoplastic disorder is resistant to treatment with the anti-proliferative agent.
45. The method of either one of paragraphs 42 and 43, wherein the anti-proliferative agent is administered concurrently with the AXLi and/or IR.
46. The method of either one of paragraphs 42 and 43, wherein the anti-proliferative agent is administered separately to and/or sequentially with the AXLi and/or IR.
47. The method of any one of paragraphs 1 to 46, wherein the treatment further comprises administering a chemotherapeutic agent and/or radiation, optionally wherein the radiation is ionizing radiation.
48. The method of any one of paragraphs 1 to 47, wherein the AXLi and IR are administered to the subject no more than 3 weeks apart.
49. The method of any one of paragraphs 1 to 47, wherein the AXLi and IR are administered to the subject no more than 1 week apart.
50. The method of any one of paragraphs 1 to 47, wherein the AXLi and IR are administered to the subject no more than 48 hours apart.
51. The method of any one of paragraphs 1 to 47, wherein the AXLi and IR are administered to the subject no more than 24 hours apart.

52. The method of any one of paragraphs 43 to 51, wherein the anti-proliferative agent is administered no more than 3 weeks before or after the AXLi and/or IR.
53. The method of any one of paragraphs 43 to 51, wherein the anti-proliferative agent is administered no more than 1 week before or after the AXLi and/or IR.
54. The method of any one of paragraphs 43 to 51, wherein the anti-proliferative agent is administered no more than 48 hours before or after the AXLi and/or IR.
55. The method of any one of paragraphs 43 to 51, wherein the anti-proliferative agent is administered no more than 24 hours before or after the AXLi and/or IR.
56. The method of any one of paragraphs 1 to 55, wherein the subject has been, is being, or will be treated with an anti-proliferative agent.
57. The method of paragraph 56, wherein the subject has been treated with an anti-proliferative agent no more than 3 months before treatment with the AXLi and IR combination.
58. The method of paragraph 56, wherein the subject has been treated with an anti-proliferative agent no more than 1 month before treatment with the AXLi and IR combination.
59. The method of any one of paragraphs 1 to 58, wherein the subject is human.
60. The method of any one of paragraphs 1 to 59, wherein the subject responds to the treatment with by reaching an improved clinical outcome as compared to an otherwise comparable subject whose neoplastic disorder is not characterized by the presence of cells having a persister-cell phenotype.
61. The method of paragraph 60, wherein the improved clinical outcome is progression free survival (PFS), overall survival (OS) and/or event free survival (EFS).
62. The method of any one of paragraphs 1 to 61, wherein the AXLi, IR, or AXLi and IR combination is comprised in a pharmaceutical composition, optionally further comprising a pharmaceutically acceptable excipient.
63. The method of any one of paragraphs 1 to 62, wherein the AXLi is a compound of formula (I):



wherein:

R¹, R⁴ and R⁵ are each independently selected from the group consisting of

hydrogen, alkyl, alkenyl, aryl, aralkyl, $-C(O)R^8$, $-C(O)N(R^6)R^7$, and $-C(=NR^6)N(R^6)R^7$;

R^2 and R^3 are each independently a polycyclic heteroaryl containing more than 14 ring atoms optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-R^9-OR^8$, $-R^9-O-R^{10}-OR^8$, $-R^9-O-R^{10}-O-R^{10}-OR^8$, $-R^9-O-R^{10}-CN$, $-R^9-O-R^{10}-C(O)OR^8$, $-R^9-O-R^{10}-C(O)N(R^6)R^7$, $-R^9-O-R^{10}-S(O)_pR^8$ (where p is 0, 1 or 2), $-R^9-O-R^{10}-N(R^6)R^7$, $-R^9-O-R^{10}-C(NR^{11})N(R^{11})H$, $-R^9-OC(O)-R^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)R^8$, $-R^9-C(O)OR^8$, $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)OR^8$, $-R^9-N(R^6)C(O)R^8$, $-R^9-N(R^6)S(O)_tR^8$ (where t is 1 or 2), $-R^9-S(O)_tOR^8$ (where t is 1 or 2), $-R^9-S(O)_pR^8$ (where p is 0, 1 or 2), and $-R^9-S(O)_tN(R^6)R^7$ (where t is 1 or 2);

or R^2 is a polycyclic heteroaryl containing more than 14 ring atoms as described above and R^3 is selected from the group consisting of aryl and heteroaryl, where the aryl and the heteroaryl are each independently optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, $-R^{13}-OR^{12}$, $-R^{13}-OC(O)-R^{12}$, $-R^{13}-O-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)OR^{12}$, $-R^{13}-C(O)N(R^{12})_2$, $-R^{13}-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}$, $-R^{13}-C(O)N(R^{12})-R^{14}-OR^{12}$, $-R^{13}-N(R^{12})C(O)OR^{12}$, $-R^{13}-N(R^{12})C(O)R^{12}$, $-R^{13}-N(R^{12})S(O)_tR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_tOR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_pR^{12}$ (where p is 0, 1 or 2), and $-R^{13}-S(O)_tN(R^{12})_2$ (where t is 1 or 2);

or R^3 is a polycyclic heteroaryl containing more than 14 ring atoms as described above, and R^2 is selected from the group consisting of aryl and heteroaryl, where the aryl and the heteroaryl are each independently optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, $-R^{13}-OR^{12}$, $-R^{13}-OC(O)-R^{12}$, $-R^{13}-O-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)OR^{12}$, $-R^{13}-C(O)N(R^{12})_2$, $-R^{13}-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}$, $-R^{13}-C(O)N(R^{12})-R^{14}-OR^{12}$, $-R^{13}-N(R^{12})C(O)OR^{12}$, $-R^{13}-N(R^{12})C(O)R^{12}$, $-R^{13}-N(R^{12})S(O)_tR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_tOR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_pR^{12}$ (where p is 0, 1 or 2), and $-R^{13}-S(O)_tN(R^{12})_2$ (where t is 1 or 2);

each R^6 and R^7 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, hydroxyalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted

aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, $-R^{10}-OR^8$, $-R^{10}-CN$, $-R^{10}-NO_2$, $-R^{10}-N(R^8)_2$, $-R^{10}-C(O)OR^8$ and $-R^{10}-C(O)N(R^8)_2$, or any R^6 and R^7 , together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heteroaryl or an optionally substituted *N*-heterocyclyl;

each R^8 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, and optionally substituted heteroarylalkynyl;

each R^9 is independently selected from the group consisting of a direct bond, an optionally substituted straight or branched alkylene chain, an optionally substituted straight or branched alkenylene chain and an optionally substituted straight or branched alkynylene chain;

each R^{10} is independently selected from the group consisting of an optionally substituted straight or branched alkylene chain, an optionally substituted straight or branched alkenylene chain and an optionally substituted straight or branched alkynylene chain;

each R^{11} is independently selected from the group consisting of hydrogen, alkyl, cyano, nitro and $-OR^8$;

each R^{12} is independently selected from the group consisting of hydrogen, alkyl, alkenyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^{10}-OR^8$, $-R^{10}-CN$, $-R^{10}-NO_2$, $-R^{10}-N(R^8)_2$, $-R^{10}-C(O)OR^8$ and $-R^{10}-C(O)N(R^8)_2$, or two R^{12s} , together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heterocyclyl or an optionally substituted *N*-heteroaryl;

each R^{13} is independently selected from the group consisting of a direct bond, an optionally substituted straight or branched alkylene chain and an optionally substituted straight or branched alkenylene chain; and

each R^{14} is independently selected from the group consisting of an optionally substituted straight or branched alkylene chain and an optionally substituted straight or branched alkenylene chain;

as an isolated stereoisomer or mixture thereof or as a tautomer or mixture thereof, or a pharmaceutically acceptable salt or N-oxide thereof.

64. The method of any one of paragraphs 1 to 62, wherein the AXLi is selected from the group consisting of:

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-(pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7-(*S*)-pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7-(*R*)-pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(4-(pyrrolidin-1-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*⁵-(7-(pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-1-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*⁵-(7-(*S*)-pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7(*S*)-7-(*t*-butoxycarbonylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-(acetamido)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-((2*R*)-2-(methoxycarbonyl)pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-(4,4-difluoropiperidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-((methoxycarbonylmethyl)(methyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-((2*R*)-2-(carboxy)pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-(4-(ethoxycarbonyl)piperidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-(4-(carboxy)piperidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-((carboxymethyl)(methyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-(4-(ethoxycarbonylmethyl)piperazin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-(4-(carboxymethyl)piperazin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-(pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-1-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-amino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(di(cyclopropylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(2-methylpropyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-((propyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(dipropylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(diethylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(cyclohexylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(cyclopentylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-((1-cyclopentylethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(2-propylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-((3,3-dimethylbut-2-yl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-((cyclohexylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(di(cyclohexylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-((5-chlorothien-2-yl)methyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-((2-carboxyphenyl)methyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-((3-bromophenyl)methyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(dimethylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(cyclobutylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(3-pentylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-((2,2-dimethylpropyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(di(cyclopentylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-((cyclopentylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(di(bicyclo[2.2.1]hept-2-en-5-ylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-((bicyclo[2.2.1]hept-2-en-5-ylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(3-methylbutylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(di(3-methylbutyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(2-ethylbutylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(but-2-enylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(butyl(but-2-enyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*⁵-((7*S*)-7-(*t*-butoxycarbonylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-amino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(dimethylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(diethylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(dipropylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(di(cyclopropylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(di(3-methylbutyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(cyclobutylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(cyclohexylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-((methylethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(cyclopentylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine; and

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(2-butylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

or pharmaceutically acceptable salts thereof.

65. The method of any one of paragraphs 1 to 62, wherein the AXLi is 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7-*S*)-pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, or a pharmaceutically acceptable salt thereof.

66. The method of any one of paragraphs 1 to 62, wherein the AXLi is bemcentinib.

67. The method of any one of paragraphs 1 to 62, wherein the AXLi is selected from the group consisting of:

- Dabrafenib (CAS No. 1341200-45-0 ; UNII 14D65TV20J);
- Gilteritinib (CAS No. 1254053-43-4 ; UNII 66D92MGC8M);
- Cabozantinib (CAS No. 849217-68-1 ; UNII 1C39JW444G);
- SGI7079 (CAS No. 1239875-86-5);
- Merestinib (CAS No. 1206799-15-6 ; UNII 5OGS5K699E);
- Amuvatinib (CAS No. 850879-09-3 ; UNII SO9S6QZB4R);
- Bosutinib (CAS No. 380843-75-4 ; UNII 5018V4AEZ0);
- Glesatinib (CAS No. 936694-12-1; UNII 7Q29OXD98N); and
- foretinib (CAS No. 849217-64-7; UNII 81FH7VK1C4).

68. The method of any one of paragraphs 1 to 62, wherein the AXLi is an antibody.

69. The method of paragraph 68, wherein the antibody is selected from the group consisting of:

- the 1613F12 antibody disclosed in WO/2013/064685;
- the 110D7 antibody disclosed in WO/2014/068139;
- the 1003A2 antibody disclosed in WO/2014/068139;
- the 1024G11 antibody disclosed in WO/2014/068139;
- the hu10G5 antibody disclosed in WO/2017/220695; and
- the YW327.6S2 antibody disclosed in WO/2011/159980.

70. The method of paragraph 68, wherein the antibody comprises the 6 CDRs having the sequences of SEQ ID Nos. 1 to 6.

71. The method of paragraph 68, wherein the antibody comprises the 6 CDRs having the sequences of SEQ ID Nos. 7 to 12.

72. The method of paragraph 68, wherein the antibody comprises:

- a VH domain having the sequence of SEQ ID No. 13 and a VL domain having the sequence of SEQ ID NO.15;
- a VH domain having the sequence of SEQ ID No. 13 and a VL domain having the sequence of SEQ ID NO.16;
- a VH domain having the sequence of SEQ ID No. 14 and a VL domain having the sequence of SEQ ID NO.15; or
- a VH domain having the sequence of SEQ ID No. 14 and a VL domain having the sequence of SEQ ID NO.16.

73. The method of any one of paragraphs 1 to 72, wherein the IR is an immune checkpoint inhibitor (ICI).

74. The method of any one of paragraphs 1 to 72, wherein the IR is a T-cell co-stimulatory agonist.

75. The method of any one of paragraphs 1 to 728, wherein the IR is selected from the group consisting of: anti-CTLA-4 antibodies, anti-PD-1 antibodies, anti-PD-L1 antibodies, anti-4-1BB antibodies, anti-OX-40 antibodies, anti-GITR antibodies, anti-CD27 antibodies, anti-CD28 antibodies, anti-CD40 antibodies, anti-LAG3 antibodies, anti-ICOS antibodies, anti-TWEAKR antibodies, anti-HVEM antibodies, anti-TIM-1 antibodies, anti-TIM-3 antibodies, anti-VISTA antibodies, and anti-TIGIT antibodies.
76. The method of any one of paragraphs 1 to 72, wherein the IR is selected from the group consisting of: anti-CTLA-4 antibodies, anti-PD-1 antibodies, anti-PD-L1 antibodies, anti-4-1BB antibodies, anti-OX-40 antibodies, anti-GITR antibodies, anti-CD27 antibodies, anti-CD40 antibodies, and anti-LAG3 antibodies.
77. The method of any one of paragraphs 1 to 72, wherein the IR is selected from the group consisting of anti-CTLA-4 antibodies, anti-PD-1 antibodies, and anti-PD-L1 antibodies.
78. The method of any one of paragraphs 1 to 72, wherein two or more IRs are administered.
79. The method of paragraph 78, wherein the two or more IRs include: (i) an immune checkpoint inhibitor, and (ii) a T cell co-stimulatory receptor agonist or a dendritic cell co-stimulatory receptor agonist.
80. The method of paragraph 78, wherein the two or more IRs include:
(i) an anti-CTLA-4 antibody; and/or
(ii) either an anti-PD-1 antibody or an anti-PD-L1 antibodies.
81. The method of any one of paragraphs 75 to 80, wherein the anti-CTLA-4 antibody is ipilimumab or tremelimumab.
82. The method of any one of paragraphs 75 to 80, wherein the anti-PD-1 antibody is pembrolizumab or nivolumab.
83. The method of any one of paragraphs 75 to 80, wherein the anti-PD-L1 antibody is Atezolizumab (CAS number 1380723-44-3), Avelumab (CAS number 1537032-82-8), or Durvalumab (CAS number 1428935-60-7).
84. The method of any one of paragraphs 78 to 83, wherein the two or more IRs are administered concurrently.
85. The method of any one of paragraphs 78 to 83, wherein the two or more IRs are administered separately and/or sequentially.
86. The method of any one of paragraphs 1 to 85, wherein the anti-proliferative agent is a receptor signalling inhibitor.

87. The method of any one of paragraphs 1 to 86, wherein the anti-proliferative agent is an EGFR inhibitor.
88. The method of paragraph 87, wherein the EGFR inhibitor is selected from the group consisting of: Gefitinib, Erlotinib, osimertinib, Lapatinib, Brigatinib, rociletinib, olmutinib, nazartinib, naquotinib, and mavelertinib.
89. The method of paragraph 88, wherein the EGFR inhibitor is erlotinib.
90. A method for identifying a subject having a neoplastic disorder characterized by the presence of cells having a persister-cell phenotype, the method comprising the step of:
- (i) determining whether the cells, disorder, and/or subject are as defined in any of paragraphs 1 to 89; and
 - (ii) identifying the subject as having a neoplastic disorder characterized by the presence of cells having a persister-cell phenotype if the cells, disorder, and/or subject are as defined as defined in any of paragraphs 1 to 89.
91. The method of paragraph 90, wherein the determining step comprises:
- (i) providing a sample from the subject;
 - (ii) analysing the sample for the features defined in any of paragraphs 1 to 89.
92. The method of paragraph 91, wherein the providing step comprises obtaining the sample from the subject.
93. The method of either one of paragraphs 91 or 92, wherein the sample is a tumour sample.
94. A method for diagnosing a subject having a neoplastic disorder characterized by the presence of cells having a persister-cell phenotype, the method comprising the step of:
- (i) identifying a subject according to any one of paragraphs 1 to 89;
 - (ii) diagnosing having a neoplastic disorder characterized by the presence of cells having a persister-cell phenotype if the subject or cells are as defined in any of paragraphs 1 to 89.
95. The method of any one of paragraphs 1 to 89 wherein:
- (i) the subject has been identified by a method according to any one of paragraphs 90 to 93; or
 - (ii) the subject has been diagnosed by a method according to the method of paragraph 94.
96. The method of any one of paragraphs 1 to 89, wherein the treatment comprises the step of:
- (i) identifying the subject according to the method according to any one of paragraphs 90 to 93; or
 - (ii) diagnosing the subject according to the method of paragraph 94.

97. An AXLi, or a composition comprising an AXLi, for use in a method of treatment according to any one of paragraphs 1 to 89, 95, or 96.

98. An IR, or a composition comprising an IR, for use in a method of treatment according to any one of paragraphs 1 to 89, 95, or 96.

99. A combination of an AXLi and an IR, or a composition comprising a combination of an AXLi and an IR, for use in a method of treatment according to any one of paragraphs 1 to 89, 95, or 96.

100. An anti-proliferative agent according to any one of paragraphs 43 to 89, 95, or 96, or a composition comprising an anti-proliferative agent according to any one of paragraphs 43 to 89, 95, or 96, for use in a method of treatment according to any one of paragraphs 43 to 89, 95, or 96.

101. Use of an AXLi in the manufacture of a medicament for treating a disorder in a subject, wherein the treatment comprises the method of any one of paragraphs 1 to 89, 95, or 96.

102. Use of an IR in the manufacture of a medicament for treating a disorder in a subject, wherein the treatment comprises the method of any one of paragraphs 1 to 89, 95, or 96.

103. Use of a combination of an AXLi and an IR in the manufacture of a medicament for treating a disorder in an subject, wherein the treatment comprises the method of any one of paragraphs 1 to 89, 95, or 96.

104. Use of an anti-proliferative agent according to any one of paragraphs 43 to 89, 95, or 96 in the manufacture of a medicament for treating a disorder in a subject, wherein the treatment comprises the method of any one of paragraphs 43 to 89, 95, or 96.

EXAMPLES

Materials & Methods

Drugs

Erlotinib hydrochloride salt (E-4007, LC Laboratories, Woburn, MA), bemcentinib (BGB324/R428, BerGenBio ASA, Bergen, Norway), rociletinib (CO-1686, Clovis oncology), staurosporine (ab120056, Abcam), Bafilomycin A (B1793, Sigma-Aldrich, St. Louis, MO) and rapamycin (R8781, Sigma-Aldrich) were prepared in DMSO for *in vitro* studies. Erlotinib and bemcentinib were prepared in 0.5% (w/w) hydroxypropyl methylcellulose/0.1% (w/w) Tween-80 for *in vivo* administration. Chloroquine diphosphate (ab142116, Abcam, Cambridge, UK) was dissolved in water.

Cell culture

The human NSCLC epithelial cell line HCC827 (CRL-2868, ATCC, Manassas, VA) has an activating EGFR mutation (E746–A750 deletion) that engenders sensitivity to erlotinib. HCC827 cells were maintained in RPMI-1640 medium (R8758, Sigma-Aldrich) containing 5% heatinactivated fetal bovine serum (FBS, Gibco), 20 units/ml penicillin, 20 µg/ml streptomycin (penicillin-streptomycin, P-0781, Sigma-Aldrich) and 2 mM L-glutamine (G-0781, Sigma-Aldrich) at 37°C, 5% CO₂, 5% O₂, and 95% relative humidity in a multigas incubator (MCO-5M-PE, Panasonic, Osaka Prefecture, Japan). Erlotinib resistant clones (ER3 and ER10) of HCC827 cells were established *in vitro* by culture in increasing concentrations of erlotinib, as described previously (Zhang Z et al., Nat Genet 2012;44:852-6). The ER3 cells were established in Professor Trevor G. Bivona's laboratory (UCSF, CA), while the ER10 cells were established in Professor Henrik J. Ditzel's laboratory (University of Southern Denmark, Odense, Denmark). Erlotinib resistant cells were maintained in culture in the presence of 1 µM erlotinib. The human NSCLC cell line H1975 and two rociletinib (CO-1686)-resistant (COR) cell clones (COR1-1 and COR10-1) were provided by Clovis oncology (Walter et al., Cancer Discov. 2013;3:1404---15.). H1975 cells were cultured in the same way as HCC827 cells and rociletinib resistant clones were maintained in culture with 1 µM rociletinib. Cell lines were routinely tested for mycoplasma contamination using the MycoAlert Mycoplasma Detection Kit (LT07-218, Lonza, Basel, Switzerland). Cell line authentication was performed using the LGC service of STR-profiling Promega's PowerPlex® 18D System with reference profiling against the AACR STR database (135-XV-5, ATCC).

Animal studies

Animal experiments were approved by the Institutional Animal Care Research Authority and in accordance with The European Convention for the Protection of Vertebrates Used for Scientific Purposes. Animals were housed in a germ-free environment in filter top cages. Environmental parameters were monitored by the Laboratory Animal Facility of UIB and followed the institutional SOP. Animals were provided certified laboratory feed and sterile drinking water *ad libitum*. Athymic Nude-*Foxn1nu* mice 6-8 weeks old were obtained from

Harlan Laboratories (Horst, The Netherlands). Briefly, for xenograft studies, 8×10^6 HCC827 viable cells in 1:1 non-supplemented RPMI1640 medium and Matrigel (Matrigel Basement Membrane Matrix Growth Factor Reduced, BD Biosciences, San Jose, CA) were implanted subcutaneously into the right and left flank of female nude mice. Randomization was conducted using the Latin square method based on total tumor volume of each animal. Randomization of animals was performed so that the average tumor volume for all treatment groups ($n=8$ animals/ group) was approximately 110 mm³. Bemcentinib was administered twice a day (*b.i.d.*) at a concentration of 50 mg/kg or 100 mg/kg by oral gavage. Erlotinib was administered once a day (*q.d.*) at 50 mg/kg by oral gavage. Tumor growth was measured two to three times weekly with digital hand held calipers and tumor volumes were calculated using the formula $(L \times W \times W)/2$. For the 50mg/kg BGB324 + 50mg/kg erlotinib group, one tumor was identified by the Grubbs test (description in Methods/ Statistics) as a statistically significant outlier ($p < 0.01$). Therefore, this tumor was eliminated from further analysis. Clinical observation of animal appearance were recorded daily and examination including tumor and body weight measurements were performed two to three times weekly. In general, a drop in body weight $>20\%$ would indicate toxicity and should lead to euthanization of mice. None of the treatment groups had a reduction in body weight, which would be indicative of toxicity. At study termination the animals were anesthetized by Sevoflurane and euthanized by cervical dislocation euthanized following Institutional SOP.

Gene expression analysis

On the day of study termination, animals were euthanized and harvested tumors were snap-frozen in liquid nitrogen and stored in the nitrogen tank. Total RNA from HCC827 tumors was isolated with RNeasy Mini column (Qiagen) and RNA integrity was evaluated using a Bioanalyzer instrument (Agilent Technologies). Gene expression arrays were performed at the genomics core facility (GCF) at UIB. Briefly, gene expression levels were measured by hybridization to Illumina Human HT-12 v4 Expression BeadChip arrays and analyzed in GeneStudio and J-Express Pro (<http://jexpress.bioinfo.no>). Four samples were excluded based on poor quality control data (one vehicle, two erlotinib treated, one combination treated). SAM (significance analysis of microarray data, J-Express Pro) was used to generate a list of up- and down-regulated genes in erlotinib treated vs combination-treated tumors with associated fold-change and significance calculations. SAM whole-ranked lists were used for gene ontology analyses by employing Gorilla software (<http://cblgorilla.cs.technion.ac.il>). A volcano plot was generated changes in gene expression versus significance ($\text{Log}_2[\text{fold change}]$ versus $-\text{Log}_{10}[P \text{ value}]$) between HCC827 tumors treated for 65 days with erlotinib (50 mg/kg, *q.d.*) or a combination of erlotinib and bemcentinib (50 mg/kg, *q.d.*, and 50 mg/kg, *b.i.d.*, respectively), $n = 4$. KM-plotter was used to assess the effect of sprouty genes (*SPRY1*, *SPRY2* and *SPRY4*) on NSCLC survival (<http://kmplot.com/analysis/>).

Cell viability assays

For a viability assay 1000 cells per well were seeded in a 96-well plate and allowed to attach overnight. The next day, treatment was added in fresh cell medium containing varying concentrations of erlotinib (5083S, Cell Signaling Technology), rociletinib (Clovis Oncology)

and/or bemcentinib (BerGenBio). Following 5 days' treatment, the cell viability was measured by incubating with resazurin (25 µg/ml, R-7017, Sigma-Aldrich) for 3h at 37°C, 5% O₂, 5% CO₂, and fluorescence was measured for 1 second at 560Ex/590Em in a 1420 Multilabel Counter VICTOR3 (Perkin Elmer, Waltham, MA) using the Wallac 1420 software. Background fluorescent signal was removed by subtracting the mean value of fluorescence from blank wells containing only cell culture medium and resazurin, and the cell viability was normalized against vehicle (DMSO) control.

Cell viability for the assessment of drug synergism was calculated using the Bliss independence model (Bliss CI., *Annals of Applied Biology* 1939;26:585-615). Delta Bliss values were calculated as expected cell death (fold change) from the combined therapy minus observed cell death (fold change) at the same concentrations. The Bliss sum is then calculated as the sum of all delta Bliss values for all the different drug combinations in one experiment. Negative delta Bliss values indicate synergy, positive delta Bliss values indicate that the drugs are working as antagonists, while delta Bliss values close to zero indicate that the drugs are acting independently. Cell death was calculated as [1 - cell viability (fold change)], and a mean value of 6 parallels was used for further analysis. Assuming that the drug response from erlotinib and bemcentinib are mutually independent, the expected cell death from treatment with a combination of erlotinib and bemcentinib at concentration *i* and *j* ($E_{\text{Erl}i\text{BGB}j}$) was calculated using the formula: $E_{\text{Erl}i\text{BGB}j} = E_{\text{Erl}i} + E_{\text{BGB}j} - E_{\text{Erl}i} \times E_{\text{BGB}j}$ where $E_{\text{Erl}i}$ is the observed cell death for erlotinib treatment at concentration *i* and $E_{\text{BGB}j}$ is the observed cell death at bemcentinib concentration *j*, and *i* and *j* are all drug concentrations used in the experiment (Bliss CI., *Annals of Applied Biology* 1939;26:585-615).

Clonogenic assay

Clonogenic assays were performed according to a protocol adapted from Franken and colleagues (Franken NA et al., *Nat Protoc* 2006;1:2315-9). Briefly, cells were detached and counted by Nucleocounter NC-100 (Chemometec, Allerød, Denmark) and the number of viable cells/ml was calculated. Subsequently, 1000 viable single cells were plated per well in 6-well cell culture plates. Cells were allowed to attach for 16 hours prior to treatment and three replicate wells were treated per condition. The cells were treated as indicated for 14 days prior to fixation and staining by incubation in a mixture of 25% MeOH and 0.01% crystal violet for 30 minutes at room temperature. Crystal violet binds to DNA in the nuclei of mammalian cells, staining them a deep purple and helping to visualize colonies. Upon removal of the fix/stain solution, the cells were rinsed carefully and immersed in running tap water. The colonies were allowed to dry in normal air at room temperature overnight prior to imaging by an EPSON Perfection V850 Pro scanner (Epson, Suwa, Japan). Clonogenic assays were quantified using the "ColonyArea" plugin (Guzman C et al., *PLoS One* 2014;9:e92444) for ImageJ (Schneider CA, *Nat Methods* 2012;9:671-5). Each experiment was independently repeated three times and the results show the mean colony area (%) +/- SD from a representative experiment.

Caspase 3/7 assay

For determination of induced apoptosis in treated cells, Caspase-Glo 3/7 luminescence-based assay (G8092, Promega, Madison, WI) was used according to the manufacturer's instructions. Briefly, 5000 cells/well were seeded in a 96-well plate and incubated overnight prior to treatment as indicated in 100 μ l culture medium. For the assay, 50 μ l cell medium was removed and 50 μ l Caspase-Glo reagent was added per replicate. The content was mixed by gently shaking the plate for 30 seconds, and the plate was incubated at room temperature for 1 hour prior to measuring luminescence for 0.1s using a Perkin Elmer 1420 Multilabel Counter VICTOR3 (Perkin Elmer) using the Wallac1420 software. Two-way ANOVA was followed by Dunnett's *t*-test comparing the treated cells against the vehicle control for each cell line.

Western blotting

Tumor material was lysed in RIPA buffer (PBS with 1% [vol/vol] NP-40, 0.5% [wt/vol] sodium deoxycholate, and 0.1% [wt/vol] SDS) supplemented with protease and phosphatase inhibitor tablets (Roche, Basel, Switzerland) and 0.2 mM PMSF. *In vitro* cell cultures were treated as indicated and washed with ice-cold PBS, scraped in PBS on ice, collected by centrifugation and lysed in RIPA buffer (sc-24948A, Santa Cruz Biotechnology, Dallas, TX). Protein concentration was measured using a Pierce BCA Protein Assay Kit following manufacturer's instructions (23225/23227, Thermo Fisher Scientific, Waltham, MA). Lysates were dissolved in water with BIO-RADxT sample buffer (1610791, Bio-Rad, Hercules, CA) and incubated for 5 minutes at 90°C. The samples were then centrifuged and 10-20 μ g protein loaded per well on 4%-20% Mini-PROTEAN TGX Stain-Free Gels (4561096, Bio-Rad). The proteins were separated by electrophoresis at 90 V for 10 minutes, followed by 130 V for 1 hour. The stain-free gels were then activated by 2.5 minutes' exposure to UV light (ChemiDoc XRS+, Bio-Rad) to allow total protein quantification. Semi-dry blotting to a Trans-blot turbo mini-size LF PVDF membrane (1704156, Bio-Rad) was performed using the Bio-Rad Trans-Blot system (2.5 A, 25 V, 7 minutes). TGS buffer (1610772, Bio-Rad) was used for the transfer. Images of the total protein amount of the membrane were obtained directly after the transfer and these images were later used for normalization against total protein for further quantifications of western blots as described for stain free gels by the manufacturer (ChemiDoc XRS+, Bio-Rad). Membranes were blocked with 5% BSA (A2058, Sigma-Aldrich) or 5% non-fat milk in TBS-T 0.1% and incubated with primary antibody overnight at 4°C. Membranes were washed 3x for 5 minutes with TBS-T and incubated for 1 hour at room temperature with 1:10,000 of goat anti-mouse HRP (170-6516, Bio-Rad) or goat-anti-rabbit HRP (170-6515, Bio-Rad) secondary antibodies. Chemiluminescent substrate was added (Super Signal West Femto Maximum Sensitivity Substrate, 34095, Thermo Fisher Scientific) and chemiluminescence was measured by a Molecular Imager ChemiDoc XRS+ (Bio-Rad). ImageLab v5.0 (Bio-Rad) software was used for analysis and quantification of the results. Quantification of Western blot results are presented as chemiluminescent signal normalized against total protein as described by Gürtler et al. (Gurtler A et al., Anal Biochem 2013;433:105-11.). Although not used for quantification *per se*, actin, β -actin, or GAPDH are shown as loading controls in all figures to improve instant interpretability for readers.

Mass cytometry

Antibody panel

An antibody panel was designed to include antibodies against some of the major signaling proteins downstream of the AXL/EGFR pathways. Available data on signal overlap was used to minimize spillover using the Fluidigm MaxPar Panel Designer. All antibodies are previously verified and described by Pelissier Vatter and colleagues (Pelissier Vatter FA et al., Cell Rep 2018;23:1205-19.) or commercially available and verified by Fluidigm. Phospho-antibodies were titrated using lambda-phosphatase treated cells as a negative control (data not shown).

Sample preparation and data acquisition

Cells were detached using 2 ml TrypLE Express Enzyme (12604021, ThermoFisher Scientific) per T75 flask. Cells were exposed to TrypLE at 37°C until the cells had completely detached after approximately 5 minutes, and then TrypLE was inactivated by adding 8 ml cell medium. Approximately 2 million cells per sample were resuspended in 1 ml Cell-ID Cisplatin 194-Pt (1:2000 dilution in PBS, stock concentration; 1mM, 201194, Fluidigm), and incubated for 1 minute at room temperature before 9 ml serum-free cell medium was added and the cells were spun down. Cells were resuspended in 1 ml 1.6% PFA (15710, ElectronMicroscopySciences) in serum-free medium, and incubated 10 minutes at room temperature. The cells were then spun down, and the supernatant was stored at -80°C until use (less than 2 months). Each sample was washed with 200 µl Maxpar Barcode Perm buffer (201057, Fluidigm), and resuspended in 195 µl Maxpar Barcode Perm Buffer. Then, 5 µl barcoding solution (Cell-ID 20-Plex Pd Barcoding kit, 201060, Fluidigm) was added, and the cells were incubated in barcoding solution for 30 minutes at room temperature. The samples were then washed two times with 200 µl Maxpar Barcode Perm buffer followed by one wash with 1 ml cell staining buffer (CSB, 201068, Fluidigm) and one wash with 1 ml 1% BSA (A9647, Sigma-Aldrich) with 1x DNase (DN25, Sigma-Aldrich) in DPBS (14040-153, ThermoFisher Scientific). Samples were pooled into one sample tube and permeabilized with 1 ml ice cold MeOH for 20 minutes at -20°C. The cells were then washed two times with 1 ml CSB and stained with antibody mixture (Table S2B) dissolved in 300 µl CSB for 1 hour at room temperature. The sample was then washed three times in 1 ml CSB, one time in 1 ml PBS (201058, Fluidigm) and then incubated with 1 ml 1.6% PFA in PBS with 0.3 µl Cell-ID Intercalator Iridium (201192B, Fluidigm) overnight at 4°C. Next day, the sample was washed once with PBS, incubated 10 minutes at room temperature in 1 ml 1% BSA, 1x DNase in DPBS, washed twice with 1 ml PBS, twice with 1 ml MilliQ water and dissolved in MilliQ water with EQ Four Element Calibration Beads (201078, Fluidigm) at a concentration of approximately 106 cells/ml and analyzed by a Helios mass cytometer (Fluidigm).

Data analysis

Data was normalized and de-barcoded using the CyTOF software (Fluidigm). For the de-barcoding, the minimum barcode separation was set to 0.14 and the maximum Mahalanobis distance was set to 3, the rest of the settings were kept as default. Cells were gated as iridium positive events, and cisplatin staining was used to discriminate dead cells. Iridium plotted against event length was used to gate single cells. After gating, approximately

100,000 cells per sample remained and these viable and single cells were included in the analysis. viSNE, a visualization tool for highdimensional single cell data based on the tSNE (t-Distributed Stochastic Neighbor Embedding) algorithm (Amir el AD et al., Nat Biotechnol 2013;31:545-52), was then applied using the Cytobank software with the following settings: downsampling; equal sampling; 10,000 cells per sample, 5000 iterations, perplexity: 30, theta: 0.5, seed: random (1730472643), channels used in tSNE: CDH1, VIM, CD44, EGFR, AXL and PD-L1.

Immunofluorescence and confocal imaging

Immunocytochemistry for the characterization of EMT markers

For ICC, 20,000 cells/well were plated on crystal clear German glass coverslips with Poly-D-lysine coating (GG-12-PDL, Neuvito Corporation, Vancouver, WA) in a 24-well plate, and allowed to attach overnight. Cells were washed in PBS, and fixed with 3.7% formalin for 15 minutes at room temperature. The cells were then washed again with PBS-T 0.1%, permeabilized with 0.3% Triton X-100 for 20 minutes, and blocked with 5% goat serum (G9023, Sigma-Aldrich) for 1 hour at room temperature. Incubation with primary antibody against CDH1(14472S, Cell Signaling Technology, 1:100) and vimentin (ab92547, Abcam, 1:100) overnight at 4°C was followed by washing and 1 hour of incubation with secondary antibodies (goat anti-mouse AF488, 1:200, A11029, Invitrogen and goat anti-rabbit AF546, 1:200, A11035, Invitrogen, Carlsbad, CA) at room temperature. Cells were washed again and mounted with ProLong™ Diamond Antifade Mountant with DAPI (P36962, Molecular Probes, Eugene, OR). Images were obtained on a Leica TCS SP5 confocal microscope (Leica, Wetzlar, Germany) using 63x objective (HCX PL Apo Cs, oil, NA = 1.4, WD = 0.1 mm).

Immunocytochemistry for the co-localization of LC3 puncta and LysoTracker

Cells were treated with various drug combinations as indicated for 7 days, while 50 µM chloroquine was added for the final 16 hours. Live cells were stained with 50 nM LysoTracker Red DND-99 (LY528, Invitrogen) in pre-warmed medium for 15 minutes at 37°C. Cells were plated, fixed, permeabilized and blocked the same way as for the CDH1 and VIM staining. Cells were then incubated in primary Ab LC3 A/B (DU4C) (12741, Cell Signaling Technology) 1:100 overnight at 4°C, carefully rinsed 3x with PBS-T, and incubated with 2°Ab, goat anti-rabbit 488 (A11008, Invitrogen, 1:200) 1 hour at room temperature, and subsequently washed 4x PBS-T before mounting with ProLong™ Diamond Antifade Mountant with DAPI (P36962, Molecular Probes). This protocol is adapted from Kang et al (Kang M et al., Int J Mol Sci 2014;15:8106-21). Images were obtained on a Leica TCS SP8 confocal microscope using 100x objective (HC PL Apo STED white, oil, NA = 1.4, WD = 0.13 mm). The co-localization intensity spatial profile was obtained by drawing a one pixel-wide square across the images, and the same area was selected for the green and red channels for each image. The “plot profile” function in ImageJ was then used to find the intensity values that were plotted in GraphPad Prism.

Autophagic flux experiments by tandem sensor LC3 constructs and confocal imaging

The Premo™ Autophagy Tandem Sensor RFP-GFP-LC3B Kit (P36239, Thermo Fisher Scientific) was used following manufacturer's instructions. Briefly, 10,000 cells were seeded on Poly-Dlysine coated coverslips (12 mm, 1.5 thickness, crystal clear German glass coverslips with Poly-D-lysine coating, GG-12-PDL, Neuvito Corporation) in 24-well plates for 48 hours prior to incubation with 10 µL of BacMam reagent (insect baculovirus with a mammalian promoter containing tandem RFP-GFP- LC3B DNA) for 24 hours. Cells were then treated with DMSO (vehicle control), bemcentinib (0.8 µM), chloroquine (50 µM) or a combination of bemcentinib and chloroquine for 24 hours. Rapamycin (27 nM) was applied as an additional positive controls in this assay. Cells were rinsed once with PBS and fixed with 4% PFA in PBS for 15 minutes at room temperature before mounting with ProLong™ Diamond Antifade Mountant with DAPI (P36962, Thermo Fisher Scientific). Images were obtained on a Leica TCS SP8 confocal microscope using 100x objective (HC PL Apo STED white, oil, NA = 1.4, WD = 0.13 mm).

Lentiviral expression plasmids

Lentiviral expression plasmids encoding mCherry-EGFP-LC3B were produced in the pLVX-Tight-Puro backbone (Clontech Laboratories, Mountain View, CA) using a Gibson Assembly of the individual PCR products. Triple transfection of HEK293 packaging cells was performed with either the p-LVX-Tight-Puro-mCherry-EGFP-LC3B expression plasmid or with pLVX-Tet-On Advanced trans-activator expression plasmid, both accompanied by the pMD2.G packaging plasmid and pVSV-G envelope plasmid (Tronolab) as described previously (Wang J et al., PLoS One 2011;6:e23062). Target cells were subsequently simultaneously transduced with trans-activator and mCherry-EGFP-LC3B encoding viral particles in the presence of 4 µg/mL protamine sulphate (P4020, Sigma-Aldrich). Transgene expression was induced by doxycycline (1 µg/ml, 631311, Clontech), and cell populations were sorted twice by FACS (Sony SH800) to obtain a cell population containing a high percentage of stably transduced cells with medium-to-high transgene expression. Stably transduced cells were subsequently used for the live cell imaging described below.

Live cell imaging

We seeded 10,000 cells/well in 4-well plates (1µ-Slide 4-well IbidiTreat, Ibidi GmbH, Martinsried, Germany) and allowed them to attach overnight prior to treatment with DMSO (vehicle control), bemcentinib (0.8 µM) or chloroquine (50 µM). All treatments were done in the presence of doxycycline (1 µg/ml, 631311, Clontech) in order to induce transgene expression. Following 24 hours' treatment, cell culture medium was exchanged with phenol-red free cell culture medium (D5030, Sigma-Aldrich) supplemented with 5% FBS, 1 µg/ml doxycycline and Draq5 (62254, Thermo Fisher Scientific 1:1000), as well as the indicated concentrations of vehicle (DMSO), bemcentinib or chloroquine. Live cell imaging was performed with a Leica TCS SP8 confocal microscope equipped with TokaiHit incubator and CO2 control using 40x objective (HC PL Apo motCORR CS2, water, NA = 1.1, WD = 0.65mm). Images were obtained every 10 minutes with the following settings: sequence 1: 488 nm laser, PMT detector (495-556 nm), gain 833 and 640 laser, HyD detector (650-750

nm); sequence 2: 561 laser, HyD detector (570-625nm). Autofocus control was used to hold current position, and a line averaging of 2 was applied for all images.

Long-lived protein degradation assay by flow cytometry

For quantification of autophagic long-lived protein degradation, we performed a flow cytometry-based protocol developed by Zhang and colleagues (Zhang J et al., Autophagy 2014;10:901-12) with minor modifications. In principle, azide AHA (L-azidohomoalanine) is a surrogate for the essential amino acid L-methionine. A Click reaction between incorporated azide and fluorescently labeled alkyne renders long-lived proteins fluorescently labeled for FACS quantification. Cells were seeded in 6-well plates at a density of 2.5×10^5 cells/well. The following day, the cells were washed with pre-warmed PBS and cultured in L-methionine-free RPMI1640 (R7513, Sigma Aldrich) for 30 minutes to deplete the methionine reserves. The cells were then pulsed with the Click-IT AHA (C10102, Sigma Aldrich) for 24 hours at a final concentration of 25 μ M in L-methionine-free medium supplemented with 5% FBS and 2 mM L-glutamine (Sigma Aldrich). After the pulse, the AHA-containing medium was removed and the cells were washed with 2 ml PBS/2.5% FBS to remove unincorporated AHA, and cultured in regular complete RPMI1640 with 5% FBS and L-glutamine containing 10x L-methionine (final concentration 2 mM) to prevent reincorporation of AHA surrogate for 2 hours to chase out the short-lived proteins. Then, cells were pretreated as indicated in the figure legends for 16 hours in complete RPMI1640 with 5% FBS and L-glutamine (Sigma Aldrich) containing 10x L-methionine (Sigma Aldrich). Then, cells were washed with either 2 ml complete RPMI1640/5% FBS or EBSS/0.1% BSA two times, both media were supplemented with 10x L-methionine, and cells were incubated with the complete media or starvation media with various treatments for 3 hours. After treatment, cells were harvested with trypsin and fixed in 4% formaldehyde in PBS for 15 minutes at room temperature. After fixation, cells were washed twice with PBS/3% BSA and permeabilized with 0.5% Triton X-100 in PBS for 20 minutes at room temperature. Finally, the cells were washed in PBS and incubated in the Click reaction mixture for 2 hours at room temperature. A final concentration of 5 μ M AF-488 labeled alkyne (A10267, Invitrogen) in the copper-containing Click-IT reaction buffer (C10269, Invitrogen) was used. After tagging and wash, single-cell signal intensities were detected in the FL-1 channel and the ratio of fluorescence intensity in treated cells to unlabeled control cells was calculated. Relative fluorescence intensity was calculated as follows: (%) = ((treated group MFI - unstained control MFI) / (vehicle control group MFI - unstained control MFI)) x 100. This represents the rate of degradation of long-lived proteins at given time points.

Detection of autophagic flux by CYTO-ID flow cytometry assay

A quantitative assay for monitoring the autophagic activity at the single-cell level (CYTO-ID® Autophagy detection kit, ENZ-51031, Enzo Life Sciences, Farmingdale, NY) was performed according to the manufacturer's instructions in combination with autophagy induction and inhibition, to measure the autophagosome generation and clearance by live cell flow cytometry by BD Accuri C6 flow cytometer (BD Biosciences). In this assay, starvation for 3 hours in EBSS supplemented with 0.1% BSA was used for autophagy induction, and chloroquine at a final concentration of 300 μ M for 3 hours was used to inhibit the successful

fusion between autophagosomes and lysosomes. Induction and inhibition of autophagy were performed in combination with the treatments as indicated in the figure legends.

Gene expression analysis of human lung adenocarcinoma (LUAD) samples

We investigated the association between AXL expression and Epithelial-Mesenchymal Transition (EMT) score in the TCGA lung adenocarcinoma (LUAD) cohort (Nature 2014;511:543---50) (n=517). The gene expression in fragments per kilobase of transcripts per million mapped reads (FPKM) were downloaded from Broad firehose, version 2016_01_28 (Firehose stddata__2016_01_28 run. In: Harvard BioMa, editor.: Broad Institute TCGA Genome Data Analysis Center 2016). Autophagy signatures were downloaded from GSEA Molecular signature database v6.1 (Subramanian A. et al., PNAS USA 2005;102:15545---50; Kumar D et al., Cell 2010;140:731---43), the Autophagy database (Homma K et al., Nucleic Acids Res 2011;39:D986---90), and HADb (last accessed: 2019 Apr 22; <http://autophagy.lu/index.html>). Enrichment scores were subsequently estimated using R v3.5.1, Bioconductor v3.8 GSVA v1.28.0 (Hanzelmann S et al., BMC Bioinformatics 2013;14:7). The EMT score estimates the degree of a cell or tumor exhibiting a mesenchymal phenotype based on expression of 315 signature genes, and was computed using two-sample Kolmogorov-Smirnov based method and EMT signature (Tan TZ et al., EMBO Mol Med 2014;6:1279---93).

Transmission electron microscopy

For preparation of treated cells for transmission electron microscopy, cells were seeded in 6-well plates and treated with drugs as indicated (7 days' treatment with erlotinib and bemcentinib, chloroquine added for the final 16 hours), washed twice with PBS and then fixed for 1 hour at room temperature in 2.5% ultrapure glutaraldehyde in PBS. Post-fixation was done by 1% OsO₄ for 1h on ice, prior to washing and dehydrating with ascending concentrations of alcohol. Infiltration was carried out using ethanol/propylene oxide (1:1) for 1 hour. Three individual specimens per sample were collected and placed in fresh resin and polymerized at 60°C for 48 hours. Thick sections were cut at 1 µm and stained with 0.6% toluidine blue in 0.3% sodium bicarbonate; 70 nm sections were cut and stained with saturated uranyl acetate in 50% ethanol followed by Reynolds lead citrate. Electron microscopy images were obtained using a Jeol JEM-1230 transmission electron microscope (Jeol, Tokyo, Japan).

ATP release assay

Release of extracellular ATP was measured by the luciferin-based ENLITEN ATP Assay System Bioluminescence Detection Kit for ATP Measurement in excess of luciferin and luciferase, as indicated by the manufacturer (FF2000, Promega). Briefly, 100,000 cells/well were seeded in 12-well plates in serum-free RPMI1640 medium containing 1% BSA. Cells were allowed to attach overnight and then treated with the drugs as indicated for 24 hours in the presence of 50 µM ecto-ATPase inhibitor (ARL67156, A265, Sigma-Aldrich). Harvested samples were transferred to icecold Eppendorf tubes, spun down at 3200g, 5 minutes, 4°C, and supernatant transferred to a new ice-cold Eppendorf tube and stored at -80°C until

assayed. Cell medium was used for background subtraction. ATP-driven chemoluminescence was recorded at 0.1s with a 1420 Multilabel Counter VICTOR3 (Perkin Elmer) with the Wallac1420 software. Three biological replicates are given per condition, and the biological replicate is represented by the mean value of two technical duplicates.

HMGB1 immunoassay

To evaluate HMGB1 release from treated cells in culture, 100,000 cells were allowed to adhere to 12-well culture dishes overnight and then treated with the indicated drugs for 72 hours. Serum-free cell culture media containing 1% BSA was used for this experiment to avoid detecting HMGB1 from serum. Supernatants were collected post-treatment and cleared from dying cancer cells by centrifugation (800g, 5 minutes), and frozen at -80°C or immediately analyzed for HMGB1 abundance. HMGB1 quantification was performed using a HMGB1 enzyme immunoassay kit (ST51011, IBL International GmbH, Hamburg, Germany) according to the manufacturer's instructions for high-sensitivity range detection.

Flow cytometry

For detection of AXL by flow cytometry, cells were harvested by trypsin, washed with PBS/1% BSA and blocked in 5% goat serum in 1% BSA/PBS for 20 minutes. The cells were then stained with mouse monoclonal anti-AXL antibody (MAB154, R&D Systems, Minneapolis, MN) for 30 minutes at room temperature, washed as above and incubated with AF488-conjugated secondary goat anti-mouse antibody (Invitrogen) for 30 minutes at room temperature. The cells were washed and analyzed using a FACS Accuri C6 flow cytometer (BD Biosciences). For the detection of surface-exposed CALR, trypsinized cells were fixed with 0.25% paraformaldehyde in PBS for 5 minutes on ice, washed in PBS, and subjected to indirect immunofluorescence with a rabbit anti-CALR antibody (mouse monoclonal anti-CALR antibody, PE-conjugated, ab83220, Abcam). Ab91357 (Mouse IgG1, PE-conjugated, Abcam) was used as an isotype control for these experiments. Samples were run on an Accuri Flow Cytometer (BD Biosciences), and data were analyzed by Cytobank (Santa Clara, CA).

Statistics

Data are presented as mean values $\pm$ standard deviations (SD) or as fold changes from a representative experiment if not otherwise indicated in the figure legends. In general, all statistical analyses were performed using the GraphPad Prism 7 software (San Diego, CA). For *in vivo* experiments, comparison of tumor volumes between treatment groups were performed by one-way ANOVA with Bonferroni's Multiple Comparison Test using software GraphPad Prism 7 software. Survival was analyzed by Kaplan-Meier estimation. Outliers were determined using Grubbs' test, also called the ESD (extreme studentized deviate) with a significance level 0.01 (two-sided). The Spearman correlation coefficient rank test was performed using Matlab R2016b version 9.1.0.441655 (MathWorks; Natick, MA). The following symbols are given to report statistical significance: NS = $P > 0.05$, * $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.001$, **** $P \leq 0.0001$.

Example 1: AXL signalling is required for acquired resistance to erlotinib *in vivo*

Acquired resistance to BRAF targeting agents in melanoma is shown to proceed via a two-step process where rare, transient, AXL-expressing drug resistant (“AXL jackpot”) cells persist upon drug treatment and lead to stable drug resistance without new mutations (Shaffer SM et al., Nature 2017;546:431-5). The prevalence of AXL expression in EGFRi resistant NSCLC indicates that this mechanism may be an important step in acquired resistance to targeted therapies in lung cancer (Byers LA et al., Clin Cancer Res 2013;19:279-90; Zhang Z et al., Nat Genet 2012;44:852-60; Wu F et al., Int J Clin Exp Pathol 2014;7:6653-61). It was therefore evaluated whether AXL kinase activity was required to achieve erlotinib resistance in HCC827 (EGFRDeIE746-A750) NSCLC tumors *in vivo* treated with erlotinib for 5 months (138 days). To selectively target AXL signalling, the oral small molecule AXL tyrosine kinase inhibitor bemcentinib (BGB324) was used (Holland SJ et al., Cancer Res 2010;70:1544-54; Kimani SG et al., Cell Commun Signal 2016;14:19). As expected, established HCC827 tumors responded to erlotinib treatment, showing a 68% decrease in tumor burden within 10 days of treatment and maintained the maximal antitumor response for 3 months (Figure 1A). However, after 100 days on erlotinib therapy, tumor relapse was observed in 70% of mice belonging to the erlotinib treatment group, as is typical for NSCLC patients treated with erlotinib (50 mg/kg, *q.d.*). By the termination of experiment (138 days), average recurrent tumor volumes had exceeded those at the start of therapy (Figure 1A-B). While bemcentinib treatment alone showed no effect on HCC827 tumor growth, statistically significant tumor growth delay ($P < 0.05$) was observed in the bemcentinib/erlotinib combination treatment groups (erlotinib 50 mg/kg, *q.d.* and 50 mg/kg, *q.d.* or 100 mg/kg, bemcentinib *b.i.d.*, respectively). Importantly, at the time of termination of the experiment, maximal antitumor response comprising non-palpable residual nodules was maintained (Figure 1B-D). These results show that AXL signalling is required for acquired erlotinib resistance *in vivo* in the HCC827 model.

Example 2: AXL signalling is associated with a novel gene signature of post-treatment NSCLC cell persistence that correlates with decreased patient survival

To decipher the molecular basis for the role of AXL in acquired resistance to erlotinib, Western blots and human transcriptome analyses were performed on residual erlotinib treated HCC827 tumor tissues collected at time of progression. Residual erlotinib treated tumors showed AXL expression, as well as increased phosphorylation of AXL and AKT indicating that persistent HCC827 cells upregulated AXL (Figure 1E). To better understand the early changes in erlotinib and bemcentinib/erlotinib-treated tumors, residual tumor tissues were isolated at day 25 and transcription analyses conducted. Analysis of differentially expressed genes in bemcentinib/erlotinib-treated tumors versus erlotinib-treated tumors identified gene ontology (GO) biological processes including neutrophil chemotaxis, negative regulation of the mitogen-activated protein kinase (MAPK) activity and positive regulation of inflammatory response and apoptotic processes (Table 1; Figure 1F). Bemcentinib treatment induced transcriptional changes in negative regulators of RAS/MAPK activity, including the sprouty family (Casci T et al., Cell 1999;96:655-65). Three sprouty family members (*SPRY1*, *SPRY2*, *SPRY4*) were upregulated upon treatment with bemcentinib in combination with erlotinib versus erlotinib alone. A higher expression of *SPRY1*, *SPRY2* and *SPRY4* as observed upon bemcentinib treatment correlated with better

overall survival in lung adenocarcinoma patients (Figure 1G). *SPRY2* expression has been shown to be consistently lower in NSCLC tissue when compared to the corresponding normal lung epithelium (Sutterluty H et al., Mol Cancer Res 2007;5:509-20), while *SPRY4* was recently reported to correlate with AXL-mediated osimertinib resistance (Taniguchi H et al., Nat Commun 2019;10:259). Bemcentinib co-treatment also resulted in downregulation of several autophagy-associated genes, including *KLH24*, *PDK4*, *FBXO32*, and *CDKN1B* (Figure 1F).

Gene ontology (GO) biological process complete	Expected	Fold Enrichment	Significance (P)
neutrophil chemotaxis	.28	21.71	3.49E-03
negative regulation of MAP kinase activity	.32	21.56	3.81E-04
response to gamma radiation	.24	21.11	3.83E-02
regulation of ERK1 and ERK2 cascade	1.13	9.72	1.74E-04
regulation of angiogenesis	.99	9.12	6.09E-03
regulation of cysteine-type endopeptidase activity involved in apoptotic process	.89	8.98	2.89E-02
aging	1.32	8.33	8.16E-04
response to lipopolysaccharide	1.43	7.67	1.85E-03
positive regulation of response to external stimulus	1.18	7.60	2.68E-02
inflammatory response	2.11	7.57	3.03E-06
response to hypoxia	1.40	7.17	1.24E-02
cellular response to growth factor stimulus	2.07	6.76	1.72E-04
regulation of sequence-specific DNA binding transcription factor activity	1.65	6.67	7.22E-03
blood vessel morphogenesis	1.67	6.58	8.20E-03
morphogenesis of an epithelium	1.84	6.51	2.84E-03
MAPK cascade	1.63	6.14	4.79E-02
positive regulation of cell migration	1.80	6.12	1.66E-02
reproductive structure development	1.86	5.91	2.28E-02
positive regulation of apoptotic process	2.59	5.80	3.83E-04

Table1

Example 3: Erlotinib resistant NSCLC cells display epithelial plasticity and broad resistance to apoptosis

To better understand the basis for AXL-mediated drug resistance and survival, the pro-survival effects of AXL signalling were examined in independent erlotinib resistant HCC827 cell clones (ER3, ER10) that lack secondary mutations in EGFR associated with erlotinib resistance (e.g., T790M) (Byers LA et al., Clin Cancer Res 2013;19:279-90; Zhang Z et al., Nat Genet 2012;44:852-60; Bae SY et al., Oncotarget 2015;6:10146-60; Jacobsen K et al., Nat Commun 2017;8:410). As expected, HCC827 cells were sensitive to erlotinib (IC₅₀ ≈ 6 nM), while ER3 and ER10 were unaffected by erlotinib at concentrations up to 10 μM (Figure 2A). Unlike the epithelial HCC827 cells that displayed a cobblestone morphology, ER cells displayed hallmarks of EMT, including a cobblestone-to-spindle morphological switch, downregulation of CDH1 (Ecadherin), and upregulation of CDH2 (N-cadherin) and VIM (vimentin) and profound upregulation of AXL (Figure 2B-C) (Byers LA et al., Clin Cancer Res 2013;19:279-90; Zhang Z et al., Nat Genet 2012;44:852-60; Bae SY et al., Oncotarget 2015;6:10146-60; Jacobsen K et al., Nat Commun 2017;8:410). ER3 and ER10 were more resistant to apoptotic cell death induced by the multikinase inhibitor staurosporine compared to the parental cells, as revealed by a luminescence-based caspase 3/7 assay (Figure 2D) and Western blot for cleaved caspase 3, cleaved caspase 8, and cleaved PARP.

Example 4: AXL is a unifying marker for drug resistance and plasticity in the resistant NSCLC clones

To better understand the phenotypic and signalling heterogeneity within the HCC827 and ER cell populations, single cell mass cytometry profiling was performed with a 22-marker

antibody panel. Non-linear dimensionality reduction by the t-distributed stochastic neighbour embedding (tSNE) algorithm was performed and 2D projection of the three cell lines based on their CDH1 (Ecadherin), VIM (vimentin), CD44, EGFR, AXL and PD-L1 expression were created (Figure 2E). The viSNE distribution revealed that the epithelial HCC827 cells form a distinct cluster from the mesenchymal ER3 cells, while ER10 cells comprised both “mesenchymal-like” (CDH1 low, VIM high) and more “epithelial-like” (CDH1 high, VIM low) subpopulations, indicative of plasticity or a more heterogeneous intermediate state (Figure 2E). Cell signalling differed dramatically between the parental HCC827 and ER populations (Figure 2F). Importantly, ER cells showed loss of pPLCy, pSTAT5, and EGFR/pEGFR expression and strong AXL expression consistent with erlotinib resistance. Surprisingly, for the heterogeneous ER10 clone, AXL expression was independent of CDH1 and VIM status in ER cells, and instead correlated with the stem cell marker CD44. This indicates that AXL is a unifying marker for drug resistance and stem cell-like plasticity.

Example 5: AXL signalling supports a unique pro-survival mode in drug resistant cells

A dose response of erlotinib and bemcentinib on cell viability and Bliss independence analysis was conducted to determine potential synergy in HCC827 and ER cells (Bliss CI., *Annals of Applied Biology* 1939;26:585-615). Interestingly, this analysis showed that erlotinib and bemcentinib action is independent and exert an additive effect on ER cell viability. Clonogenic assays revealed that bemcentinib treatment was sufficient to block ER cell colony formation, revealing AXL-dependence under these conditions (Figure 3A-B). Surprisingly, bemcentinib treatment did not induce caspase 3/7 activity (Figure 3C). Western blot analysis of HCC827 parental cells and ER cells treated for 24 hours with combinations of erlotinib and bemcentinib, verified that the treatment combination did not induce apoptosis. These data suggest that AXL signalling supports a unique pro-survival mode in drug resistant cells.

Example 5: AXL expression is widely associated with autophagy in lung adenocarcinomas

As the ER cells were more resistant to apoptosis than their parental cells, it was investigate whether AXL expression is more broadly associated with autophagy in lung adenocarcinomas. RNAseq data from TCGA wa analysed (*Nature* 2014;511:543---50) and AXL expression found to be significantly associated with positive regulation of autophagy gene expression signature ($Rho=0.3765$, $P<1E-200$, Figure 4A). The significant correlation between AXL expression and autophagy was further validated by three independent autophagy signatures. Interestingly, a positive correlation between an EMT and autophagy signature was also detected.

Example 6: Erlotinib resistant NSCLC cells display an increased autophagic flux

In order to evaluate the correlation between AXL expression and positive regulation of autophagy in human adenocarcinomas, the TCGA lung adenocarcinoma cohort (LUAD, n=517) was mined. A strong positive correlation between AXL and positive regulation of autophagy were detected ($Rho=0.3765$, $P<1E-200$, Figure 4A). Based in this strong positive association between AXL and autophagy in the human TCGA lung adenocarcinoma cohort (Figure 4A), it was next assessed whether the apoptosis-resistant AXL-expressing ER cells were also characterized by an increased autophagic flux. Upon induction of autophagy,

the cytosolic form of the ubiquitin-like protein LC3 (LC3-I) is conjugated to phosphatidylethanolamine in the autophagic membrane (LC3-II), which remains bound to autophagic vesicles throughout the pathway and therefore can be used to quantify the level of autophagy (Kabeya Y et al., EMBO J 2000;19:5720-8.). It was found that compared to HCC827 cells, both ER3 and ER10 cells showed increased expression of LC3A/B, and in particular an increase in the membrane-bound form LC3-II (Figure 4B). A shift in LC3A/B from the cytosolic form LC3-I to the lipid-bound form LC3-II is usually associated with increased autophagosome formation, but could also indicate a block in fusion of autophagosomes with lysosomes. The formation of autophagic compartments in HCC827 cells and the erlotinib resistant ER3 cells was further quantified by a flow cytometry-based selective detection of autolysosomes and earlier autophagic compartments using the Cyto-ID detection probe to measure autophagic activity. The Cyto-ID assay allowed efficient measurement of the dynamic balance between autophagosome generation and clearance. Chloroquine inhibits autophagy by preventing lysosomal acidification, blocking lysosome fusion with autophagosomes and reducing lysosomal protein degradation. Interestingly, the starvation induced autophagic flux was significantly increased in ER versus HCC827 cells (Figure 4C). Morphometric transmission electron microscopy confirmed increased vacuolization in ER cells upon chloroquine treatment (Figure 4D). Moreover, a massive vacuolization and accumulation of autophagic vesicles (autophagosomes and autolysosomes) in ER cells after 7 days treatment with erlotinib and bemcentinib was observed, compared to erlotinib alone (Figure 4 E-F). Next, the expression of autophagy markers was evaluated in erlotinib-sensitive versus erlotinib resistant cells in response to AXL inhibition. A shift from cytosolic LC3-I to lipidated LC3-II in both HCC827 parental cells and ER cells was observed after bemcentinib treatment, suggesting that AXL inhibition interferes with autophagy independently of erlotinib (Figure 4G-H).

Furthermore, co-localization of lysosomes and LC3-positive vesicles confirmed the massive accumulation of LC3-positive autophagosomes, lysosomes, and corresponding fused autolysosomes in the erlotinib and bemcentinib treated cells (Figure 4I). While inhibition of autophagic flux with chloroquine 16 hours prior to fixation and staining caused a substantial accumulation of LC3 and LysoTracker-positive vesicles in the erlotinib-treated cells, no further accumulation of LC3 and LysoTracker double-positive vesicles was observed upon addition of chloroquine to cells co-treated with erlotinib and bemcentinib, indicating that bemcentinib treatment abrogated the autophagic degradation. Co-localization intensity spatial profiles support these observations (Figure 4I-J).

Example 7: AXL inhibition abrogates the elevated pre-mortem autophagic cell flux in erlotinib resistant cell

To dynamically monitor the formation of autophagosomes versus autolysosomes over time in the absence or presence of chloroquine, the Autophagy Tandem Sensor RFP-GFP-LC3B probe was utilized (Figure 5A-B). When autophagic flux is normal, the fusion of autophagosomes with acidic lysosomes results in the formation and acidification of the fused autolysosomes. Due to the nature of the fluorescent probes of the tandem sensor, autophagosomes will appear yellow (GFP +RFP) while autolysosomes appear red (RFP) due to quenching of the pH-sensitive GFP fluorochrome in the acidic autolysosome (Figure 5B). As shown in Figure 5A, bemcentinib treatment of ER cells increased the numbers of

both yellow and red RFP-GFP-LC3B puncta in contrast to chloroquine treatment, which completely inhibited the formation of red puncta (Figure 5A). The mTOR inhibitor Rapamycin induces autophagic flux and was included as a control. To further elucidate how bemcentinib affects autophagic flux, ER10 cells stably expressing a lentiviral doxycycline-inducible mCherry-EGFP-LC3B construct were generated. This enabled live cell imaging and time-lapse studies visualizing real-time dynamics of autophagic vesicles upon pre-treatment. The vehicle (DMSO) treated ER10-mCherry-EGFP-LC3B cells displayed a moderate/low level of LC3B-positive vesicles, and during the 120-minute course of the time-lapse, the colour of individual puncta did not change from yellow to red at a constant rate. Furthermore, newly formed yellow puncta were seen, indicating that the autophagic flux was retained. ER10-mCherry-EGFP-LC3B cells treated with bemcentinib did, however, appear similar to cells treated with chloroquine, showing increased frequency of yellow autophagosomes and a prominent decrease in the movement and transition from yellow to red LC3-associated puncta, indicating that fusion between autophagosomes and lysosomes is compromised upon bemcentinib or chloroquine treatment.

The Cyto-ID assay allowed efficient measurement of the dynamic balance between autophagosome generation and clearance in ER3 cells treated with bemcentinib in the presence or absence of autophagy inducers or inhibitors (starvation and chloroquine, respectively). As expected, no significant alteration was detected in ER3 cells cultured in starvation medium (EBSS with 0.1% BSA) for 3 hours relative to when cultured in complete medium, consistent with uninterrupted flux in both conditions. A significant increase in the relative fluorescence intensity was detected in the starved cells when autophagic degradation was inhibited by chloroquine, indicating that the autophagic flux is intact in the ER3 cells (Figure 5C). The relative fluorescence intensity was also significantly increased upon Bemcentinib treatment of the starved ER3 cells compared to the vehicle treated controls (Figure 5C), confirming that bemcentinib abrogates the balance between autophagosome generation and clearance.

To further corroborate these findings, a flow cytometry-based assay was used to quantify the degradation of long-lived protein, known to occur predominantly through autophagy. The methionine analogue AHA was incorporated into newly synthesized proteins during a long pulse, followed by a chase to degrade short-lived proteins. The long-lived protein degradation was then evaluated at the single-cell level upon autophagy stimulation by starvation through specific labelling of the incorporated AHA with a fluorescently labelled alkyne, followed by flow cytometry analysis. Using this assay, it was demonstrated that bemcentinib treatment significantly reduced the starvation induced degradation of long-lived proteins in ER3 cells when compared to the vehicle-treated starvation controls (Figure 5D). Bafilomycin A, an inhibitor of the lysosomal proton pump, inhibits fusion between autophagosomes and lysosomes and was included as a control in these experiments.

The H1975 cell line harbours the T790M gatekeeper mutation predictive of erlotinib resistance. NSCLC cells harbouring the T790M mutation can be targeted by third generation EGFR TKIs, e.g. rociletinib (CO-1686). AXL has recently been shown to confer intrinsic resistance to osimertinib and promote the emergence of osimertinib tolerant cells (Taniguchi H et al., Nat Commun 2019;10:259). Thus, the question of whether autophagy was

deregulated in the rociletinib-resistant (COR) clones (COR1-1 and COR10-1) versus the H1975 parental cells was assessed. We observed an increased expression of LC3 in the drug resistant COR1-1 and COR10-1 clones compared to the parental H1975 cells. When these cells were treated with the AXL TKI bemcentinib, prominent vacuolization in the H1975 cells was observed, consistent with an abrogation of the autophagic flux by bemcentinib treatment. These studies indicate that an increased flux is a mechanism broadly associated with AXL upregulation in NSCLC, and shows that bemcentinib treatment abrogates the autophagic flux in NSCLC cells resistant to first and third generation EGFR TKIs.

Example 8: Bemcentinib induces immunogenic cell death (ICD) in erlotinib resistant cells

ICD is characterized by active secretion of ATP, exposure of CALR on the outer leaflet of the plasma membrane, and the release of the high mobility group box 1 (HMGB1) protein. Pre-mortem autophagy is an essential determinant of the immunogenicity of drug-induced cancer cell death by affecting the secretion of ATP. Based on the findings above, whether bemcentinib treatment resulted in ICD in the ER cells was assessed by measuring the release of ATP in addition to the two other DAMPs, HMGB1 and surface-exposed CALR (Figure 6). Using a luciferase-based assay, the release of ATP from ER cells treated with erlotinib and bemcentinib for 24 hours was evaluated, either as single agents or in combination. We found that ATP secretion was significantly increased in the erlotinib resistant clones treated with the combination of erlotinib and bemcentinib (Figure 6A). The release of the ATP damage signal into the extracellular space increased in a dose dependent manner (Figure 6A).

HMGB1 secreted from dying cancer cells functions as a potent DAMP, with the potential to attract antigen-presenting cells to the tumor bed. ELISA was used to assess the release of HMGB1 from cancer cells upon treatment with erlotinib and bemcentinib administered as single agents or in combination for 72 hours. A significant increase in extracellular HMGB1 after bemcentinib treatment alone or in combination with erlotinib was observed in the ER3 cells. The HMGB1 increase was only significant upon erlotinib/bemcentinib combination treatment in ER10 cells (Figure 6B).

CALR is externalized at the cell surface on cells during ICD, and this potent “eat-me” signal promotes efficient phagocytosis by dendritic cells, thereby facilitating tumor antigen presentation and incitement of tumor-associated antigen-specific cytotoxic T-cells. Externalized CALR was monitored at the single-cell level by flow cytometry, which showed an increase in the extracellular exposure of CALR after bemcentinib treatment in erlotinib resistant ER10 cells (Figure 6C). Additionally, bemcentinib treatment resulted in a moderate increase in major histocompatibility complex-1 (MHC-I, Figure 6D). Antigen presentation by MHC-I is essential for adaptive immunity. Thus, three potent regulators of immunogenicity were upregulated in the erlotinib resistant tumor cells upon treatment with bemcentinib, indicating an alteration of the tumor immune microenvironment beneficial for tumor cell recognition and eradication by the immune system.

CLAIMS

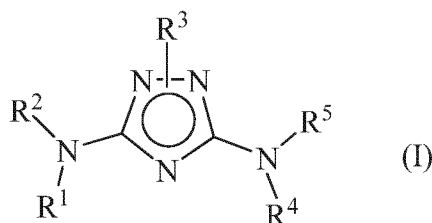
1. A method for treating a neoplastic disorder in a subject with a combination of an AXLi and an IR, the method comprising:
 - (i) administering a combination of the AXLi and the IR to the subject;
 - (ii) administering the AXLi to the subject, wherein the IR has been, is, or will be, administered to the subject; or
 - (iii) administering the IR to the subject, wherein the AXLi has been, is, or will be, administered to the subject;wherein the neoplastic disorder is characterized by the presence of cells having a persister-cell phenotype.
2. The method of claim 1, wherein the cells having a persister-cell phenotype have increased AXL-signalling as compared to a control.
3. The method of claim 2, wherein the increased AXL-signalling is characterized by increased AXL expression, increased AXL phosphorylation, and/or increased Akt phosphorylation.
4. The method of any one of claims 1 to 3, wherein the cells having a persister-cell phenotype have increased CD44 expression as compared to a control.
5. The method of any one of claims 1 to 4, wherein the cells having a persister-cell phenotype have decreased expression of spry1, spry2, and/or spry4 as compared to a control.
6. The method of any one of claims 1 to 5, wherein the cells having a persister-cell phenotype have decreased expression of pPLCg, pSTAT5, EGFR, and/or pEGFR as compared to a control.
7. The method of any one of claims 1 to 6, wherein the cells having a persister-cell phenotype have increased autophagic flux as compared to a control.
8. The method claim 7, wherein the cells having a persister-cell phenotype have increased expression of LC3A/B.
9. The method of either one of claims 7 and 8, wherein the cells having a persister-cell phenotype have increased expression levels of membrane-bound LC3-II.
- 9a. The method of any one of claims 1 to 9, wherein the cells having a persister-cell phenotype have an enrichment of genes associated with established autophagy gene expression signatures downloaded from GSEA Molecular signature database v6.1.
10. The method of any one of claims 1 to 9a, wherein the cells having a persister-cell phenotype exhibit a cobblestone-to-spindle morphological switch.

11. The method of any one of claims 1 to 10, wherein the cells having a persister-cell phenotype have increased resistance to staurosporine induced apoptosis as compared to a control.
12. The method of any one of claims 1 to 11, wherein the cells having a persister-cell phenotype express phospho-AXL.
13. The method of any one of claims 1 to 12, wherein the cells having a persister-cell phenotype express CD44.
14. The method of any one of claims 1 to 13, wherein the cells having a persister-cell phenotype do not express pPLCg, pSTAT5, EGFR, and/or pEGFR.
15. The method of any one of claims 1 to 14, wherein the cells having a persister-cell phenotype comprise a receptor-activating mutation.
16. The method of claim 15, wherein the receptor-activating mutation is an EGFR-activating mutation.
17. The method of claim 16, wherein the EGFR-activating mutation is a mutation in the EGFR tyrosine-kinase domain.
18. The method of claim 17, wherein EGFR-activating mutation is:
 - (xv) an in-frame deletion in exon 19, optionally wherein L747 to E749 are deleted;
 - (xvi) a L858R substitution;
 - (xvii) a G719S/A/C substitution;
 - (xviii) a V765A substitution;
 - (xix) a T783A substitution;
 - (xx) a C797S substitution; or
 - (xxi) an in-frame duplications and/or insertions in exon 20.
19. The method of any one of claims 1 to 18, wherein the cells having a persister-cell phenotype do not comprise an anti-proliferative agent resistance mutation in a receptor.
20. The method of claim 19, wherein the receptor is EGFR.
21. The method of claim 20, wherein the anti-proliferative agent resistance mutation is:
 - (iii) a T790M substitution; and/or
 - (iv) a D761Y substitution
22. The method of any one of claims 1 to 21, wherein the cells having a persister-cell phenotype are neoplastic cells.

23. The method of any one of claims 1 to 22, wherein the cells having a persister-cell phenotype are cancer cells, optionally wherein the cancer cells are EGFR-inhibitor resistant cancer cells, such as erlotinib resistant NSCLC cells.
24. The method of any one of claims 1 to 23, wherein the neoplastic disorder characterized by the presence of cells having a persister-cell phenotype is cancer.
25. The method of claim 24, wherein the cancer is selected from the group consisting of: histiocytoma, glioma, astrocytoma, osteoma, lung cancer, small-cell lung cancer, non-small-cell lung cancer, gastrointestinal cancer, bowel cancer, colon cancer, breast carcinoma, ovarian carcinoma, prostate cancer, testicular cancer, liver cancer, kidney cancer, bladder cancer, pancreas cancer, brain cancer, sarcoma, osteosarcoma, Kaposi's sarcoma, melanoma, lymphomas, and leukemias.
26. The method of claim 25, wherein the cancer is lung cancer.
27. The method of claim 25, wherein the lung cancer is NSCLC.
28. The method of any one of claims 1 to 27, wherein the neoplastic disorder is a solid tumour.
29. The method of claim 28, wherein the solid tumour comprises the cells having a persister-cell phenotype.
30. The method of either one of claims 28 and 29, wherein solid tumour comprises cells not having a persister-cell phenotype.
31. The method of any one of claims 1 to 30, wherein the neoplastic disorder is resistant to treatment with an anti-proliferative agent.
32. The method of any one of claims 2 to 31, wherein the control is a comparable neoplastic disorder that is not characterized by the presence of cells having a persister-cell phenotype.
33. The method of any one of claims 2 to 32, wherein the control is a comparable neoplastic disorder wherein levels of AXL-signalling are low or absent.
34. The method of any one of claims 2 to 33, wherein the control is sensitive to the anti-proliferative agent of claim 31.
35. The method of any one of claims 2 to 34, wherein the control is not characterized by cells having a cobblestone-to-spindle morphological switch.
36. The method of any one of claims 2 to 31, wherein the control is healthy, non-neoplastic tissue.

37. The method of any one of claims 2 to 36, wherein the control is the same tissue as the neoplastic disorder.
38. The method of any one of claims 2 to 37, wherein the control is the same subject as the neoplastic disorder.
39. The method of any one of claims 2 to 38, wherein the control has the same levels of AXL-signalling as the HCC827 cell line (ATCC accession number CRL-2868).
40. The method of any one of claims 2 to 31, wherein the control is the HCC827 cell line (ATCC accession number CRL-2868).
41. The method of any one of claims 1 to 40, wherein the AXLi and IR are administered concurrently.
42. The method of any one of claims 1 to 40, wherein the AXLi and IR are administered separately and/or sequentially.
43. The method of any one of claims 1 to 42, further comprising administering an anti-proliferative agent in combination with the AXLi and/or IR.
44. The method of claim 43, wherein the neoplastic disorder is resistant to treatment with the anti-proliferative agent.
45. The method of either one of claims 42 and 43, wherein the anti-proliferative agent is administered concurrently with the AXLi and/or IR.
46. The method of either one of claims 42 and 43, wherein the anti-proliferative agent is administered separately to and/or sequentially with the AXLi and/or IR.
47. The method of any one of claims 1 to 46, wherein the treatment further comprises administering a chemotherapeutic agent and/or radiation, optionally wherein the radiation is ionizing radiation.
48. The method of any one of claims 1 to 47, wherein the AXLi and IR are administered to the subject no more than 3 weeks apart.
49. The method of any one of claims 1 to 47, wherein the AXLi and IR are administered to the subject no more than 1 week apart.
50. The method of any one of claims 1 to 47, wherein the AXLi and IR are administered to the subject no more than 48 hours apart.
51. The method of any one of claims 1 to 47, wherein the AXLi and IR are administered to the subject no more than 24 hours apart.

52. The method of any one of claims 43 to 51, wherein the anti-proliferative agent is administered no more than 3 weeks before or after the AXLi and/or IR.
53. The method of any one of claims 43 to 51, wherein the anti-proliferative agent is administered no more than 1 week before or after the AXLi and/or IR.
54. The method of any one of claims 43 to 51, wherein the anti-proliferative agent is administered no more than 48 hours before or after the AXLi and/or IR.
55. The method of any one of claims 43 to 51, wherein the anti-proliferative agent is administered no more than 24 hours before or after the AXLi and/or IR.
56. The method of any one of claims 1 to 55, wherein the subject has been, is being, or will be treated with an anti-proliferative agent.
57. The method of claim 56, wherein the subject has been treated with an anti-proliferative agent no more than 3 months before treatment with the AXLi and IR combination.
58. The method of claim 56, wherein the subject has been treated with an anti-proliferative agent no more than 1 month before treatment with the AXLi and IR combination.
59. The method of any one of claims 1 to 58, wherein the subject is human.
60. The method of any one of claims 1 to 59, wherein the subject responds to the treatment with by reaching an improved clinical outcome as compared to an otherwise comparable subject whose neoplastic disorder is not characterized by the presence of cells having a persister-cell phenotype.
61. The method of claim 60, wherein the improved clinical outcome is progression free survival (PFS), overall survival (OS) and/or event free survival (EFS).
62. The method of any one of claims 1 to 61, wherein the AXLi, IR, or AXLi and IR combination is comprised in a pharmaceutical composition, optionally further comprising a pharmaceutically acceptable excipient.
63. The method of any one of claims 1 to 62, wherein the AXLi is a compound of formula (I):



wherein:

R¹, R⁴ and R⁵ are each independently selected from the group consisting of

hydrogen, alkyl, alkenyl, aryl, aralkyl, $-C(O)R^8$, $-C(O)N(R^6)R^7$, and $-C(=NR^6)N(R^6)R^7$;

R^2 and R^3 are each independently a polycyclic heteroaryl containing more than 14 ring atoms optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-R^9-OR^8$, $-R^9-O-R^{10}-OR^8$, $-R^9-O-R^{10}-O-R^{10}-OR^8$, $-R^9-O-R^{10}-CN$, $-R^9-O-R^{10}-C(O)OR^8$, $-R^9-O-R^{10}-C(O)N(R^6)R^7$, $-R^9-O-R^{10}-S(O)_pR^8$ (where p is 0, 1 or 2), $-R^9-O-R^{10}-N(R^6)R^7$, $-R^9-O-R^{10}-C(NR^{11})N(R^{11})H$, $-R^9-OC(O)-R^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)R^8$, $-R^9-C(O)OR^8$, $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)OR^8$, $-R^9-N(R^6)C(O)R^8$, $-R^9-N(R^6)S(O)_tR^8$ (where t is 1 or 2), $-R^9-S(O)_tOR^8$ (where t is 1 or 2), $-R^9-S(O)_pR^8$ (where p is 0, 1 or 2), and $-R^9-S(O)_tN(R^6)R^7$ (where t is 1 or 2);

or R^2 is a polycyclic heteroaryl containing more than 14 ring atoms as described above and R^3 is selected from the group consisting of aryl and heteroaryl, where the aryl and the heteroaryl are each independently optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, $-R^{13}-OR^{12}$, $-R^{13}-OC(O)-R^{12}$, $-R^{13}-O-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)OR^{12}$, $-R^{13}-C(O)N(R^{12})_2$, $-R^{13}-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}$, $-R^{13}-C(O)N(R^{12})-R^{14}-OR^{12}$, $-R^{13}-N(R^{12})C(O)OR^{12}$, $-R^{13}-N(R^{12})C(O)R^{12}$, $-R^{13}-N(R^{12})S(O)_tR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_tOR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_pR^{12}$ (where p is 0, 1 or 2), and $-R^{13}-S(O)_tN(R^{12})_2$ (where t is 1 or 2);

or R^3 is a polycyclic heteroaryl containing more than 14 ring atoms as described above, and R^2 is selected from the group consisting of aryl and heteroaryl, where the aryl and the heteroaryl are each independently optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, $-R^{13}-OR^{12}$, $-R^{13}-OC(O)-R^{12}$, $-R^{13}-O-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)OR^{12}$, $-R^{13}-C(O)N(R^{12})_2$, $-R^{13}-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}$, $-R^{13}-C(O)N(R^{12})-R^{14}-OR^{12}$, $-R^{13}-N(R^{12})C(O)OR^{12}$, $-R^{13}-N(R^{12})C(O)R^{12}$, $-R^{13}-N(R^{12})S(O)_tR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_tOR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_pR^{12}$ (where p is 0, 1 or 2), and $-R^{13}-S(O)_tN(R^{12})_2$ (where t is 1 or 2);

each R^6 and R^7 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, hydroxyalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted

aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, $-R^{10}-OR^8$, $-R^{10}-CN$, $-R^{10}-NO_2$, $-R^{10}-N(R^8)_2$, $-R^{10}-C(O)OR^8$ and $-R^{10}-C(O)N(R^8)_2$, or any R^6 and R^7 , together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heteroaryl or an optionally substituted *N*-heterocyclyl;

each R^8 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, and optionally substituted heteroarylalkynyl;

each R^9 is independently selected from the group consisting of a direct bond, an optionally substituted straight or branched alkylene chain, an optionally substituted straight or branched alkenylene chain and an optionally substituted straight or branched alkynylene chain;

each R^{10} is independently selected from the group consisting of an optionally substituted straight or branched alkylene chain, an optionally substituted straight or branched alkenylene chain and an optionally substituted straight or branched alkynylene chain;

each R^{11} is independently selected from the group consisting of hydrogen, alkyl, cyano, nitro and $-OR^8$;

each R^{12} is independently selected from the group consisting of hydrogen, alkyl, alkenyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^{10}-OR^8$, $-R^{10}-CN$, $-R^{10}-NO_2$, $-R^{10}-N(R^8)_2$, $-R^{10}-C(O)OR^8$ and $-R^{10}-C(O)N(R^8)_2$, or two R^{12s} , together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heterocyclyl or an optionally substituted *N*-heteroaryl;

each R^{13} is independently selected from the group consisting of a direct bond, an optionally substituted straight or branched alkylene chain and an optionally substituted straight or branched alkenylene chain; and

each R^{14} is independently selected from the group consisting of an optionally substituted straight or branched alkylene chain and an optionally substituted straight or branched alkenylene chain;

as an isolated stereoisomer or mixture thereof or as a tautomer or mixture thereof, or a pharmaceutically acceptable salt or N-oxide thereof.

64. The method of any one of claims 1 to 62, wherein the AXLi is selected from the group consisting of:

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-(pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7-(*S*)-pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7-(*R*)-pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(3-fluoro-4-(4-(pyrrolidin-1-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*⁵-(7-(pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-1-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*⁵-(7-(*S*)-pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7(*S*)-7-(*t*-butoxycarbonylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-(acetamido)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-((2*R*)-2-(methoxycarbonyl)pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-(4,4-difluoropiperidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-((methoxycarbonylmethyl)(methyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-((2*R*)-2-(carboxy)pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-(4-(ethoxycarbonyl)piperidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-(4-(carboxy)piperidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-((carboxymethyl)(methyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-(4-(ethoxycarbonylmethyl)piperazin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-(4-(carboxymethyl)piperazin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-(7-(pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-1-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-amino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(di(cyclopropylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(2-methylpropyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-((propyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(dipropylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(diethylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(cyclohexylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(cyclopentylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-((1-cyclopentylethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(2-propylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-((3,3-dimethylbut-2-yl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-((cyclohexylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(di(cyclohexylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-((5-chlorothien-2-yl)methyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-((2-carboxyphenyl)methyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-((3-bromophenyl)methyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(dimethylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(cyclobutylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(3-pentylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-((2,2-dimethylpropyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(di(cyclopentylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-((cyclopentylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(di(bicyclo[2.2.1]hept-2-en-5-ylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-((bicyclo[2.2.1]hept-2-en-5-ylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(3-methylbutylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(di(3-methylbutyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(2-ethylbutylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(but-2-enylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(butyl(but-2-enyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*⁵-((7*S*)-7-(*t*-butoxycarbonylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-amino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(dimethylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(diethylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(dipropylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(di(cyclopropylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(di(3-methylbutyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(cyclobutylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(cyclohexylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-((methylethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(cyclopentylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine; and

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-7-(2-butylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

or pharmaceutically acceptable salts thereof.

65. The method of any one of claims 1 to 62, wherein the AXLi is 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-*N*³-((7*S*)-pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, or a pharmaceutically acceptable salt thereof.

66. The method of any one of claims 1 to 62, wherein the AXLi is bemcentinib.

67. The method of any one of claims 1 to 62, wherein the AXLi is selected from the group consisting of:

- Dabrafenib (CAS No. 1341200-45-0 ; UNII 14D65TV20J);
- Gilteritinib (CAS No. 1254053-43-4 ; UNII 66D92MGC8M);
- Cabozantinib (CAS No. 849217-68-1 ; UNII 1C39JW444G);
- SGI7079 (CAS No. 1239875-86-5);
- Merestinib (CAS No. 1206799-15-6 ; UNII 5OGS5K699E);
- Amuvatinib (CAS No. 850879-09-3 ; UNII SO9S6QZB4R);
- Bosutinib (CAS No. 380843-75-4 ; UNII 5018V4AEZ0);
- Glesatinib (CAS No. 936694-12-1; UNII 7Q29OXD98N); and
- foretinib (CAS No. 849217-64-7; UNII 81FH7VK1C4).

68. The method of any one of claims 1 to 62, wherein the AXLi is an antibody.

69. The method of claim 68, wherein the antibody is selected from the group consisting of:

- the 1613F12 antibody disclosed in WO/2013/064685;
- the 110D7 antibody disclosed in WO/2014/068139;
- the 1003A2 antibody disclosed in WO/2014/068139;
- the 1024G11 antibody disclosed in WO/2014/068139;
- the hu10G5 antibody disclosed in WO/2017/220695; and
- the YW327.6S2 antibody disclosed in WO/2011/159980.

70. The method of claim 68, wherein the antibody comprises the 6 CDRs having the sequences of SEQ ID Nos. 1 to 6.

71. The method of claim 68, wherein the antibody comprises the 6 CDRs having the sequences of SEQ ID Nos. 7 to 12.

72. The method of claim 68, wherein the antibody comprises:

- a VH domain having the sequence of SEQ ID No. 13 and a VL domain having the sequence of SEQ ID NO.15;
- a VH domain having the sequence of SEQ ID No. 13 and a VL domain having the sequence of SEQ ID NO.16;
- a VH domain having the sequence of SEQ ID No. 14 and a VL domain having the sequence of SEQ ID NO.15; or
- a VH domain having the sequence of SEQ ID No. 14 and a VL domain having the sequence of SEQ ID NO.16.

73. The method of any one of claims 1 to 72, wherein the IR is an immune checkpoint inhibitor (ICI).

74. The method of any one of claims 1 to 72, wherein the IR is a T-cell co-stimulatory agonist.

75. The method of any one of claims 1 to 728, wherein the IR is selected from the group consisting of: anti-CTLA-4 antibodies, anti-PD-1 antibodies, anti-PD-L1 antibodies, anti-4-1BB antibodies, anti-OX-40 antibodies, anti-GITR antibodies, anti-CD27 antibodies, anti-CD28 antibodies, anti-CD40 antibodies, anti-LAG3 antibodies, anti-ICOS antibodies, anti-TWEAKR antibodies, anti-HVEM antibodies, anti-TIM-1 antibodies, anti-TIM-3 antibodies, anti-VISTA antibodies, and anti-TIGIT antibodies.
76. The method of any one of claims 1 to 72, wherein the IR is selected from the group consisting of: anti-CTLA-4 antibodies, anti-PD-1 antibodies, anti-PD-L1 antibodies, anti-4-1BB antibodies, anti-OX-40 antibodies, anti-GITR antibodies, anti-CD27 antibodies, anti-CD40 antibodies, and anti-LAG3 antibodies.
77. The method of any one of claims 1 to 72, wherein the IR is selected from the group consisting of anti-CTLA-4 antibodies, anti-PD-1 antibodies, and anti-PD-L1 antibodies.
78. The method of any one of claims 1 to 72, wherein two or more IRs are administered.
79. The method of claim 78, wherein the two or more IRs include: (i) an immune checkpoint inhibitor, and (ii) a T cell co-stimulatory receptor agonist or a dendritic cell co-stimulatory receptor agonist.
80. The method of claim 78, wherein the two or more IRs include:
(iii) an anti-CTLA-4 antibody; and/or
(iv) either an anti-PD-1 antibody or an anti-PD-L1 antibodies.
81. The method of any one of claims 75 to 80, wherein the anti-CTLA-4 antibody is ipilimumab or tremelimumab.
82. The method of any one of claims 75 to 80, wherein the anti-PD-1 antibody is pembrolizumab or nivolumab.
83. The method of any one of claims 75 to 80, wherein the anti-PD-L1 antibody is Atezolizumab (CAS number 1380723-44-3), Avelumab (CAS number 1537032-82-8), or Durvalumab (CAS number 1428935-60-7).
84. The method of any one of claims 78 to 83, wherein the two or more IRs are administered concurrently.
85. The method of any one of claims 78 to 83, wherein the two or more IRs are administered separately and/or sequentially.
86. The method of any one of claims 1 to 85, wherein the anti-proliferative agent is a receptor signalling inhibitor.
87. The method of any one of claims 1 to 86, wherein the anti-proliferative agent is an EGFR inhibitor.

88. The method of claim 87, wherein the EGFR inhibitor is selected from the group consisting of: Gefitinib, Erlotinib, osimertinib, Lapatinib, Brigatinib, rociletinib, olmutinib, nazartinib, naquotinib, and mavelertinib.

89. The method of claim 88, wherein the EGFR inhibitor is erlotinib.

90. A method for identifying a subject having a neoplastic disorder characterized by the presence of cells having a persister-cell phenotype, the method comprising the step of:

(i) determining whether the cells, disorder, and/or subject are as defined in any of claims 1 to 89; and

(ii) identifying the subject as having a neoplastic disorder characterized by the presence of cells having a persister-cell phenotype if the cells, disorder, and/or subject are as defined as defined in any of claims 1 to 89.

91. The method of claim 90, wherein the determining step comprises:

(iii) providing a sample from the subject;

(iv) analysing the sample for the features defined in any of claims 1 to 89.

92. The method of claim 91, wherein the providing step comprises obtaining the sample from the subject.

93. The method of either one of claims 91 or 92, wherein the sample is a tumour sample.

94. A method for diagnosing a subject having a neoplastic disorder characterized by the presence of cells having a persister-cell phenotype, the method comprising the step of:

(i) identifying a subject according to any one of claims 1 to 89;

(ii) diagnosing having a neoplastic disorder characterized by the presence of cells having a persister-cell phenotype if the subject or cells are as defined in any of claims 1 to 89.

95. The method of any one of claims 1 to 89 wherein:

(i) the subject has been identified by a method according to any one of claims 90 to 93; or

(ii) the subject has been diagnosed by a method according to the method of claim 94.

96. The method of any one of claims 1 to 89, wherein the treatment comprises the step of:

(i) identifying the subject according to the method according to any one of claims 90 to 93; or

(ii) diagnosing the subject according to the method of claim 94.

97. An AXLi, or a composition comprising an AXLi, for use in a method of treatment according to any one of claims 1 to 89, 95, or 96.

98. An IR, or a composition comprising an IR, for use in a method of treatment according to any one of claims 1 to 89, 95, or 96.
99. A combination of an AXLi and an IR, or a composition comprising a combination of an AXLi and an IR, for use in a method of treatment according to any one of claims 1 to 89, 95, or 96.
100. An anti-proliferative agent according to any one of claims 43 to 89, 95, or 96, or a composition comprising an anti-proliferative agent according to any one of claims 43 to 89, 95, or 96, for use in a method of treatment according to any one of claims 43 to 89, 95, or 96.
101. Use of an AXLi in the manufacture of a medicament for treating a disorder in a subject, wherein the treatment comprises the method of any one of claims 1 to 89, 95, or 96.
102. Use of an IR in the manufacture of a medicament for treating a disorder in a subject, wherein the treatment comprises the method of any one of claims 1 to 89, 95, or 96.
103. Use of a combination of an AXLi and an IR in the manufacture of a medicament for treating a disorder in an subject, wherein the treatment comprises the method of any one of claims 1 to 89, 95, or 96.
104. Use of an anti-proliferative agent according to any one of claims 43 to 89, 95, or 96 in the manufacture of a medicament for treating a disorder in a subject, wherein the treatment comprises the method of any one of claims 43 to 89, 95, or 96.

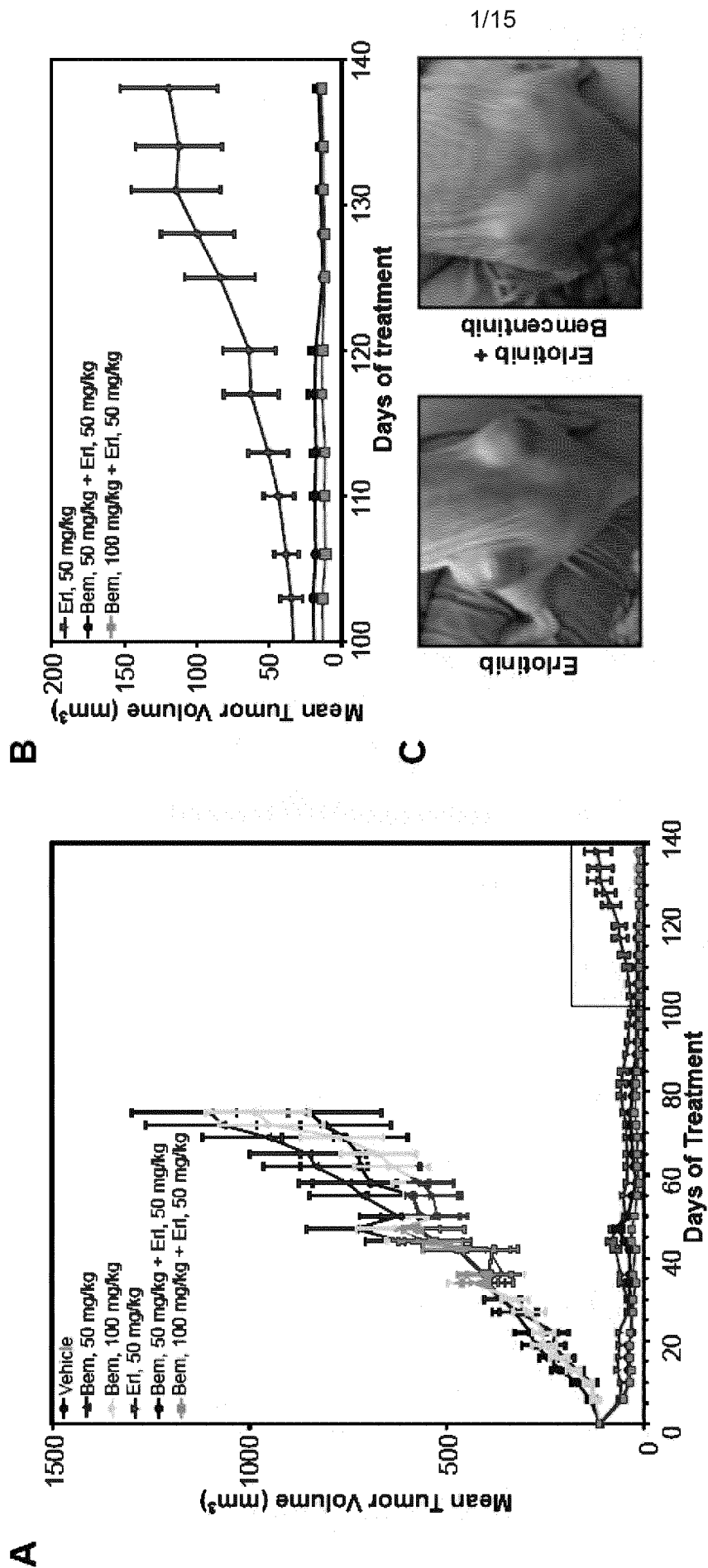


Figure 1

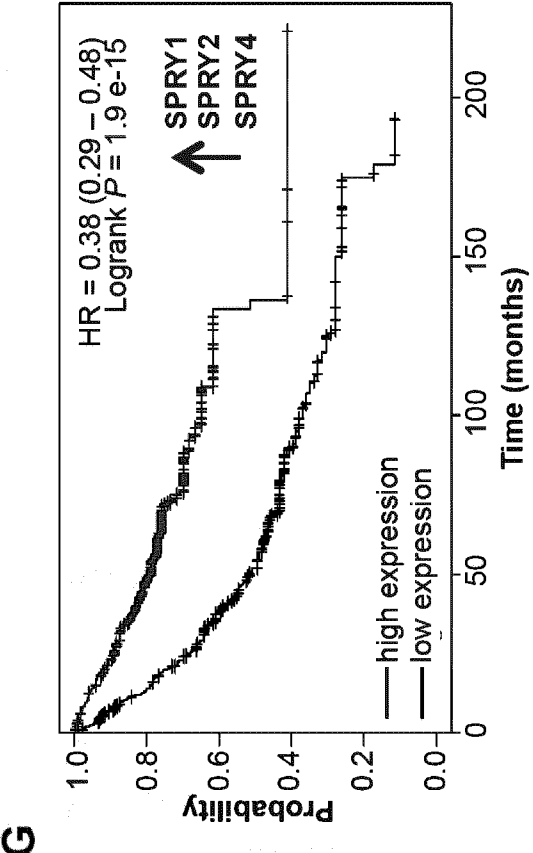
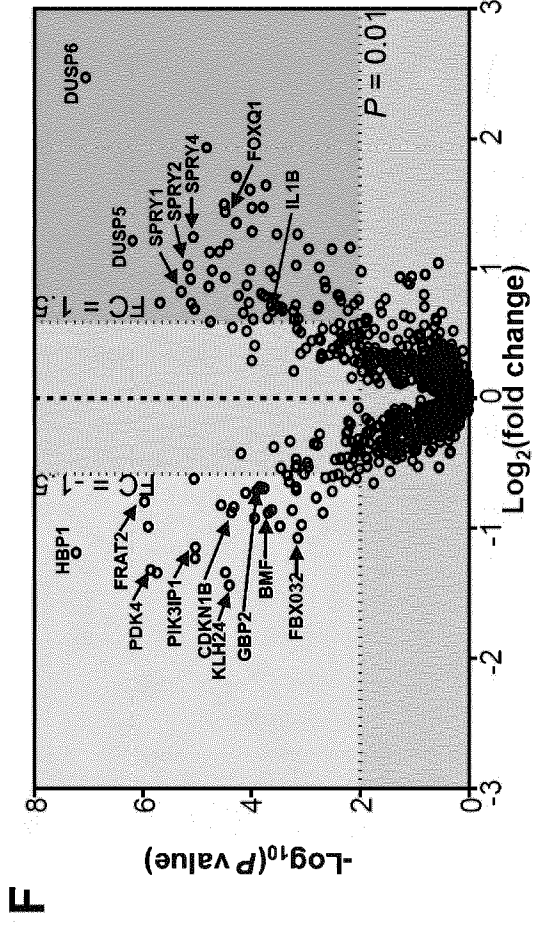
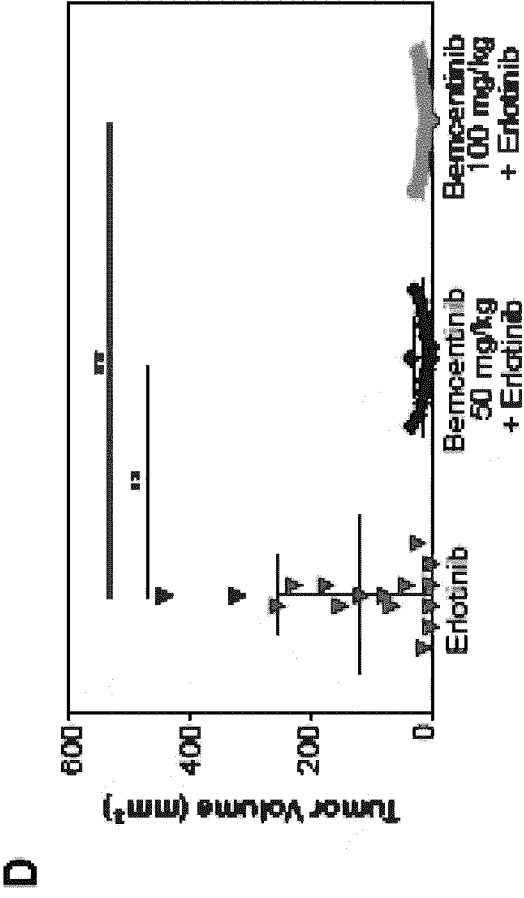
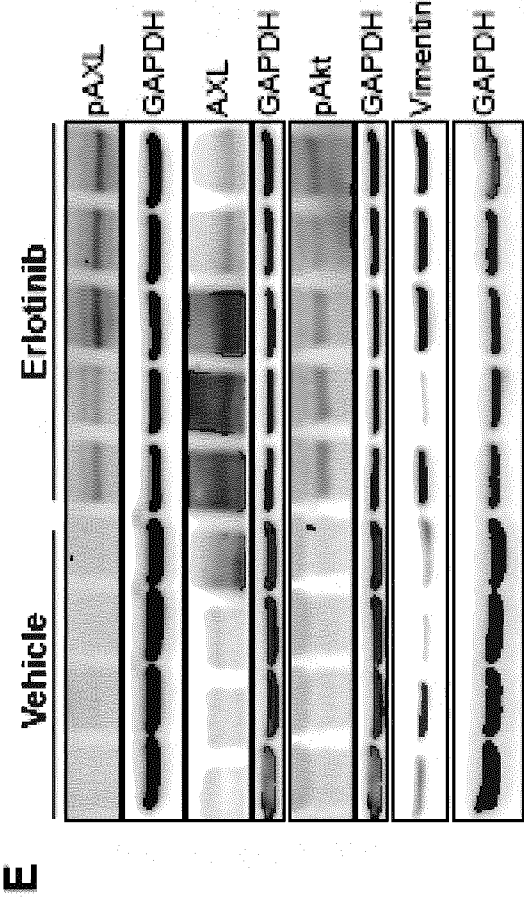


Figure 1

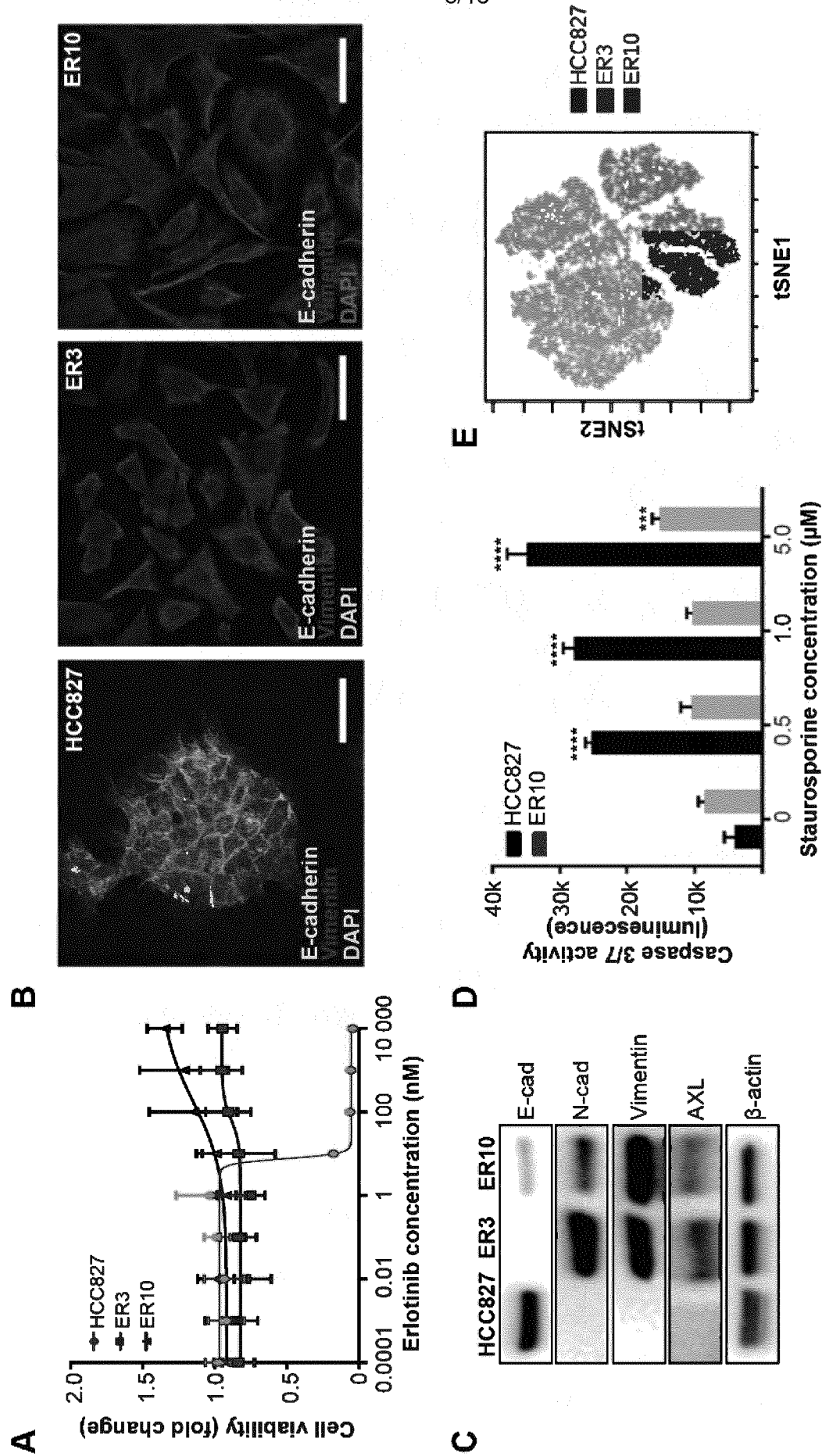


Figure 2

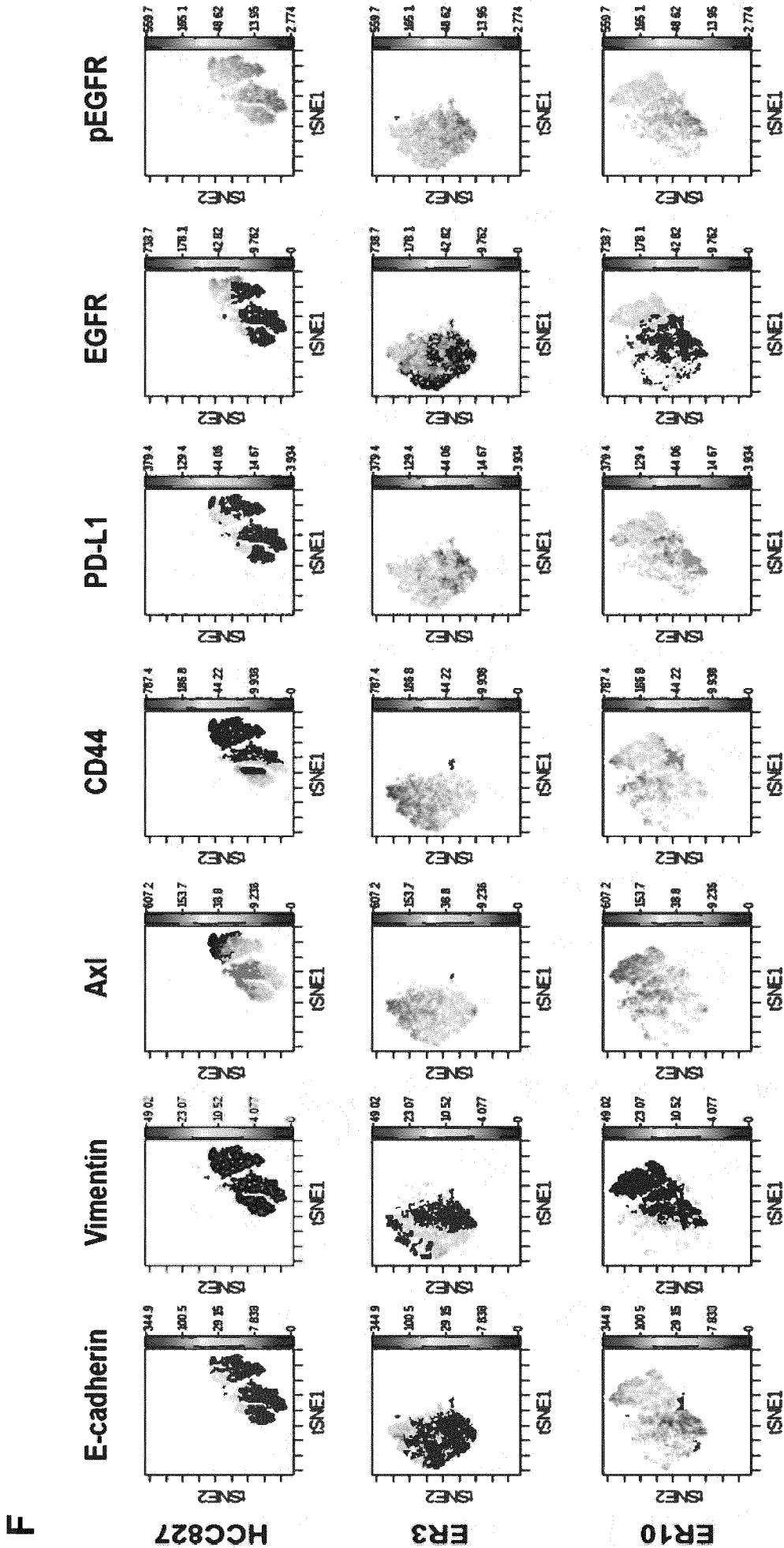


Figure 2

5/15

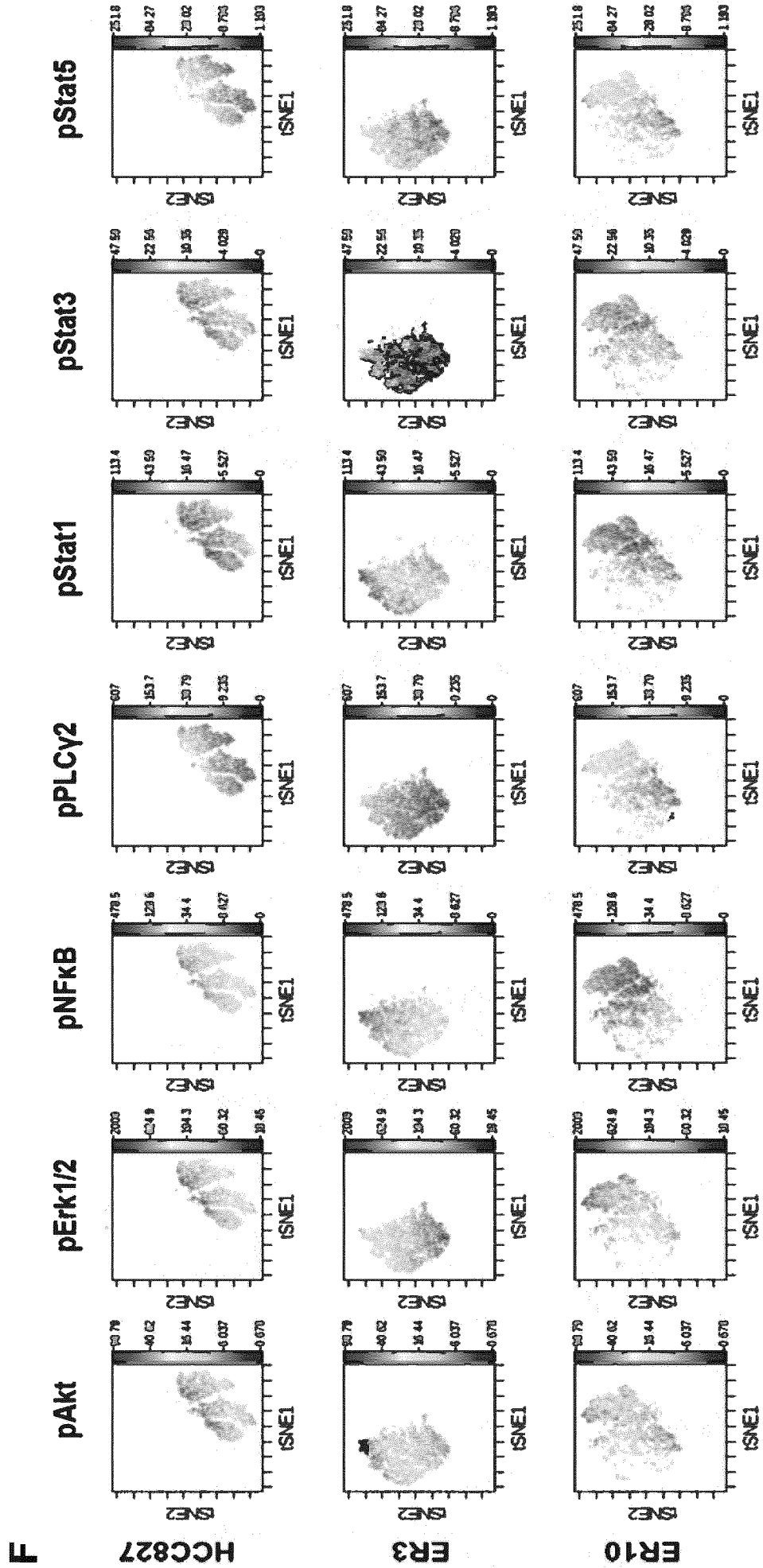


Figure 2

A

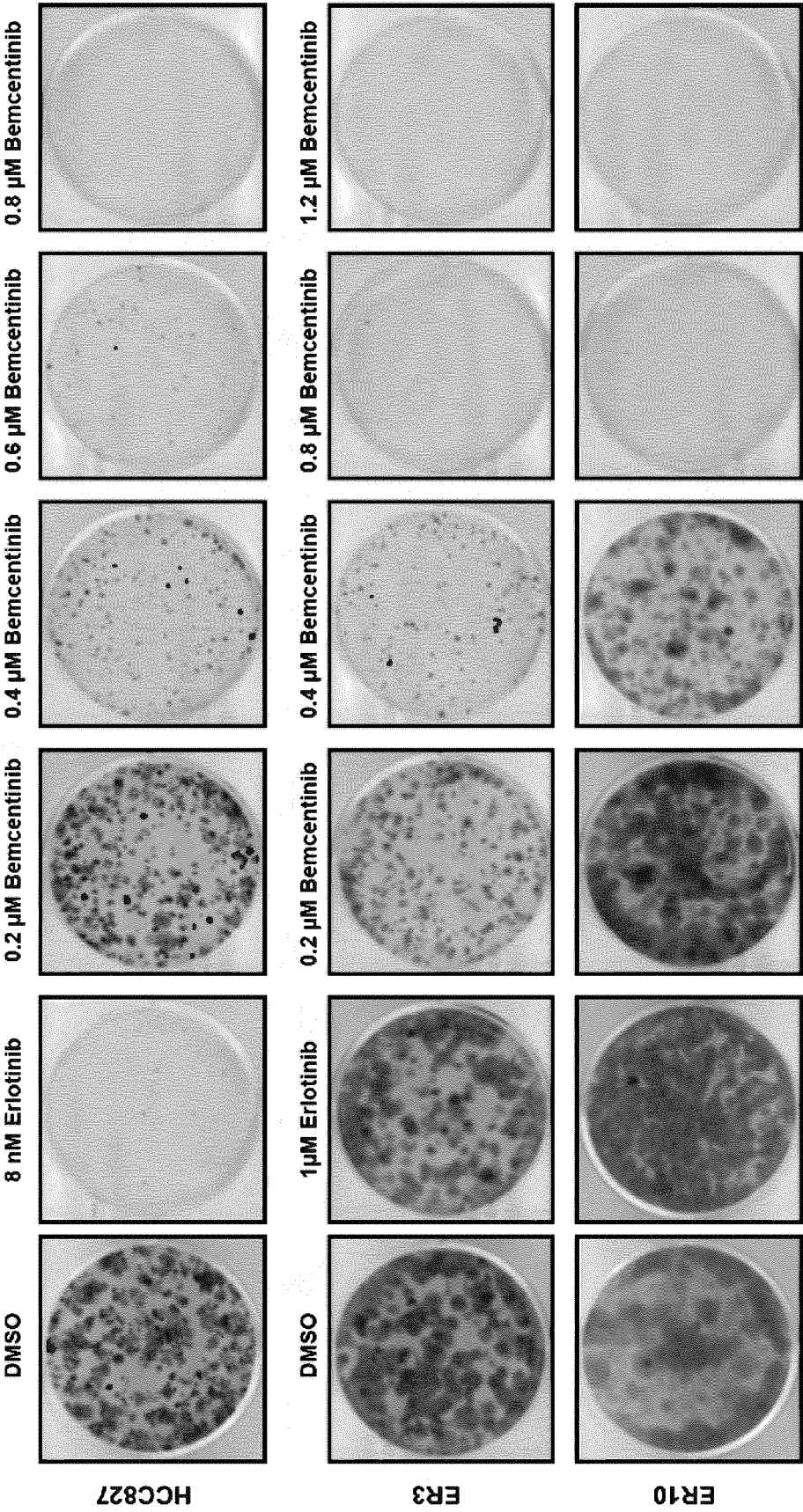


Figure 3

7/15

B

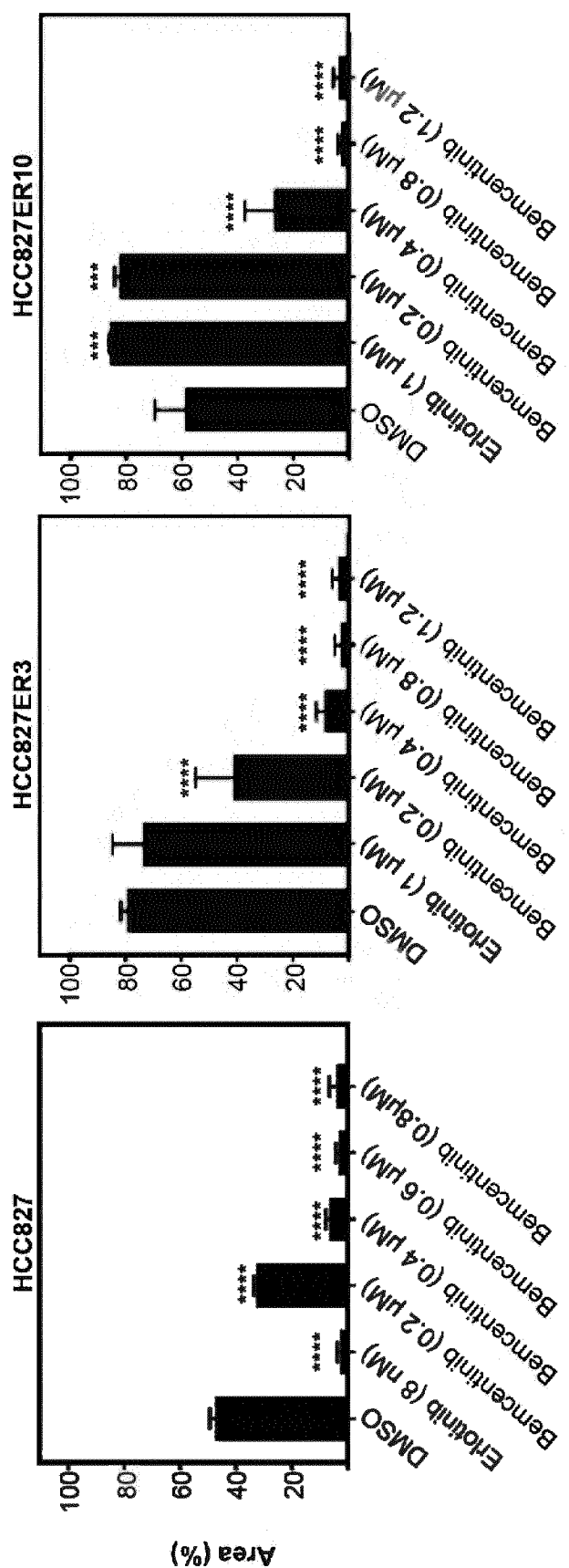
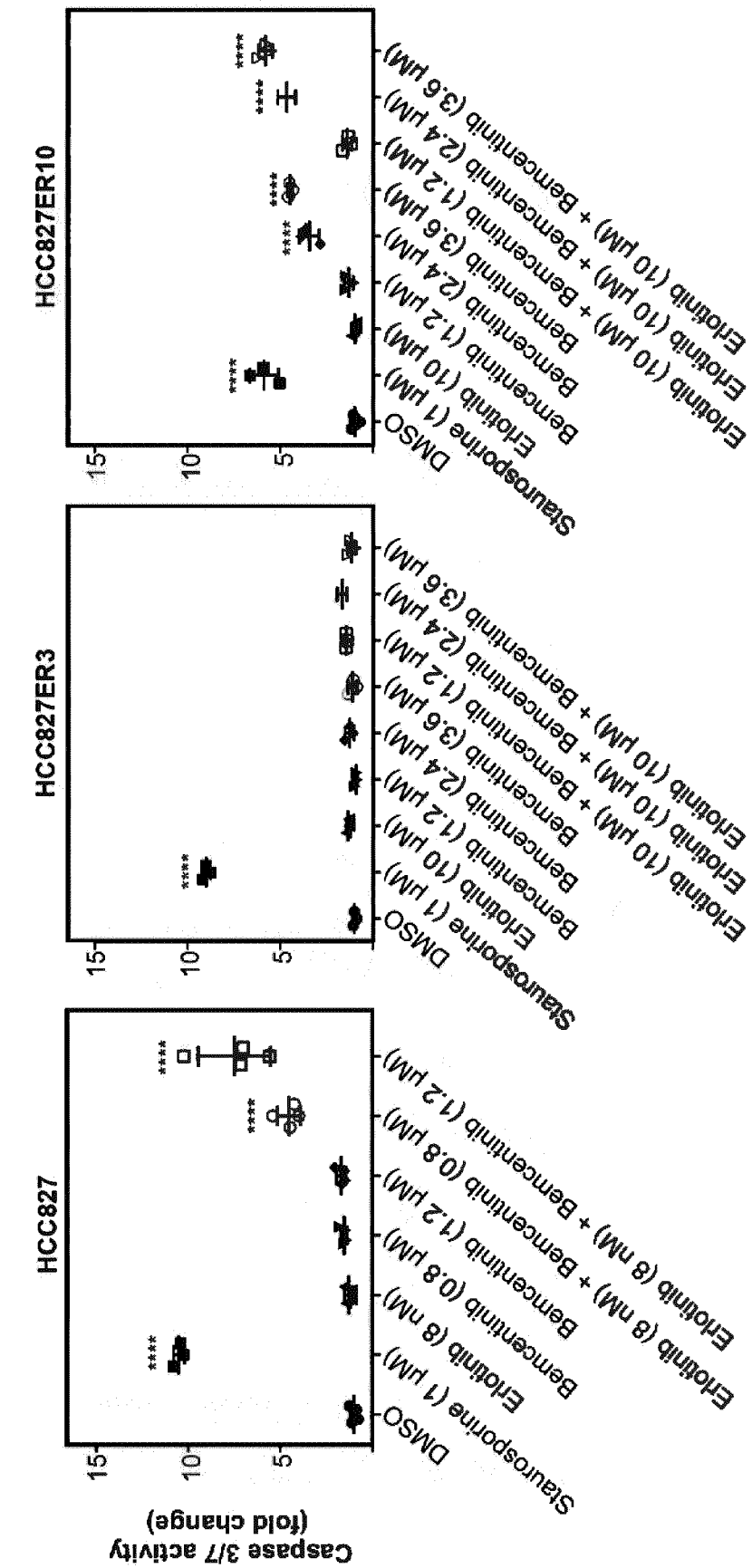


Figure 3



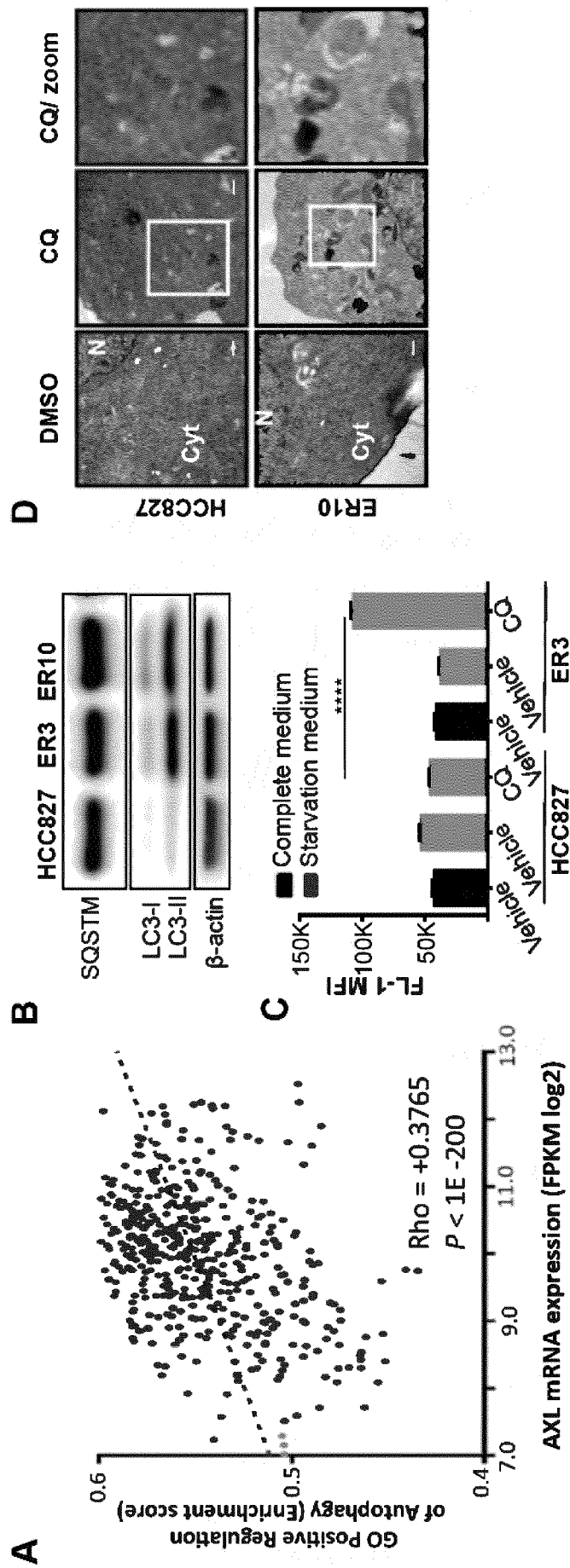


Figure 4

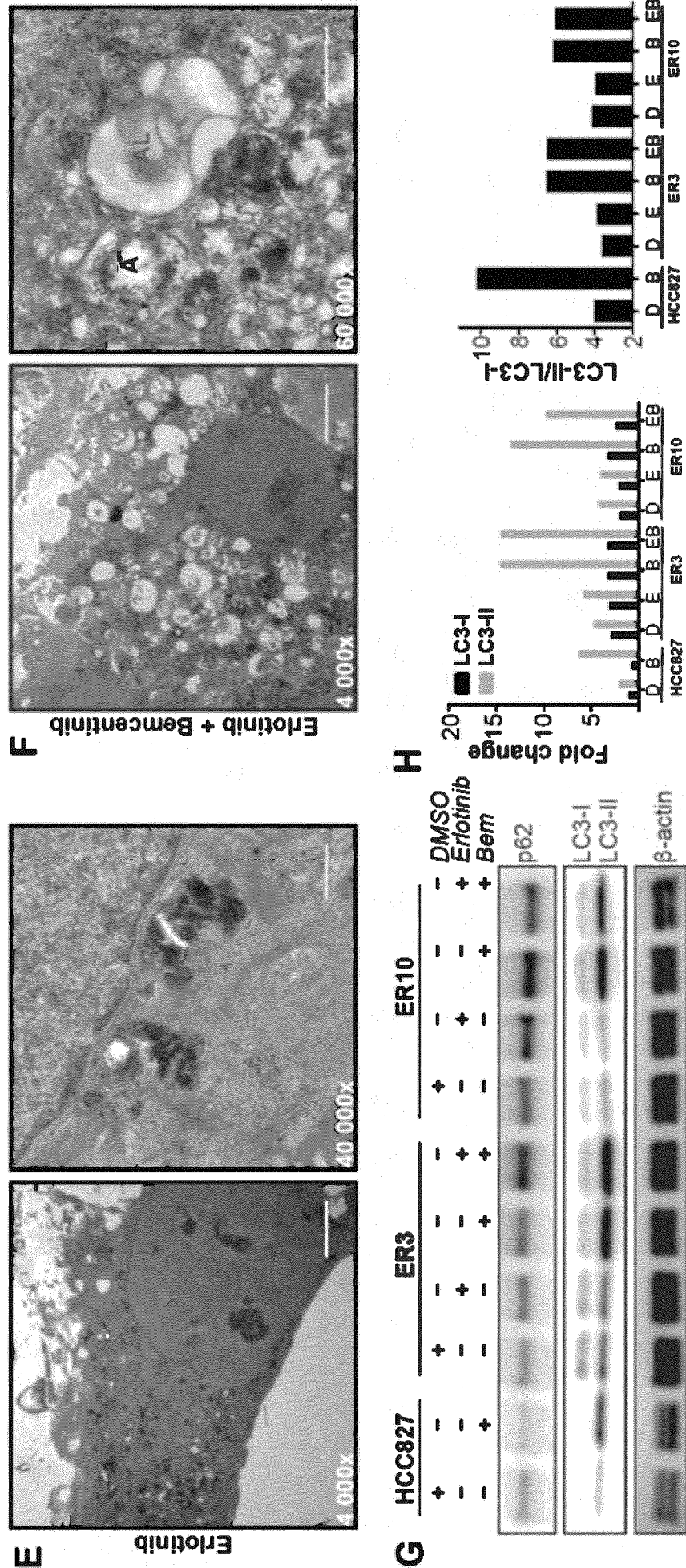


Figure 4

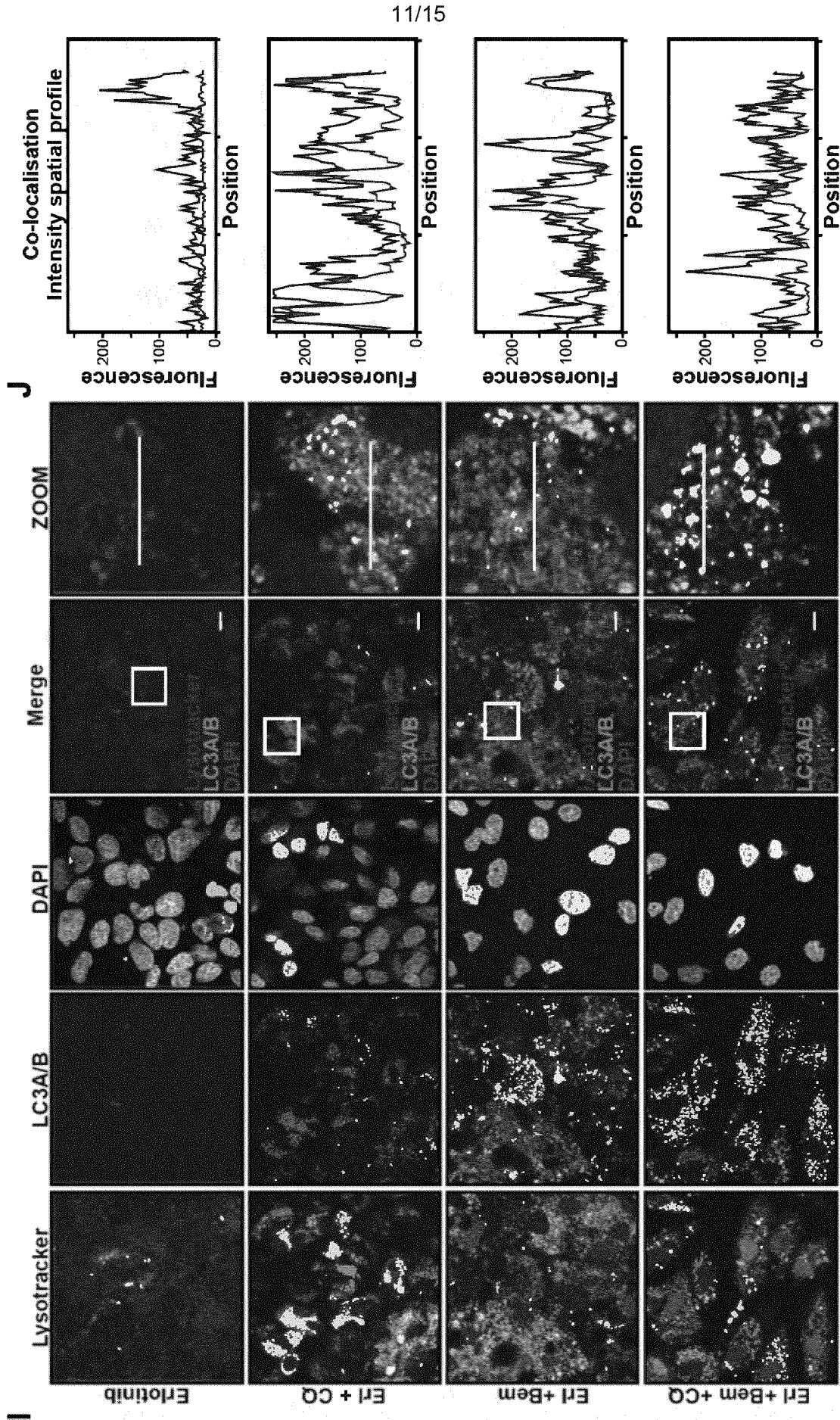


Figure 4

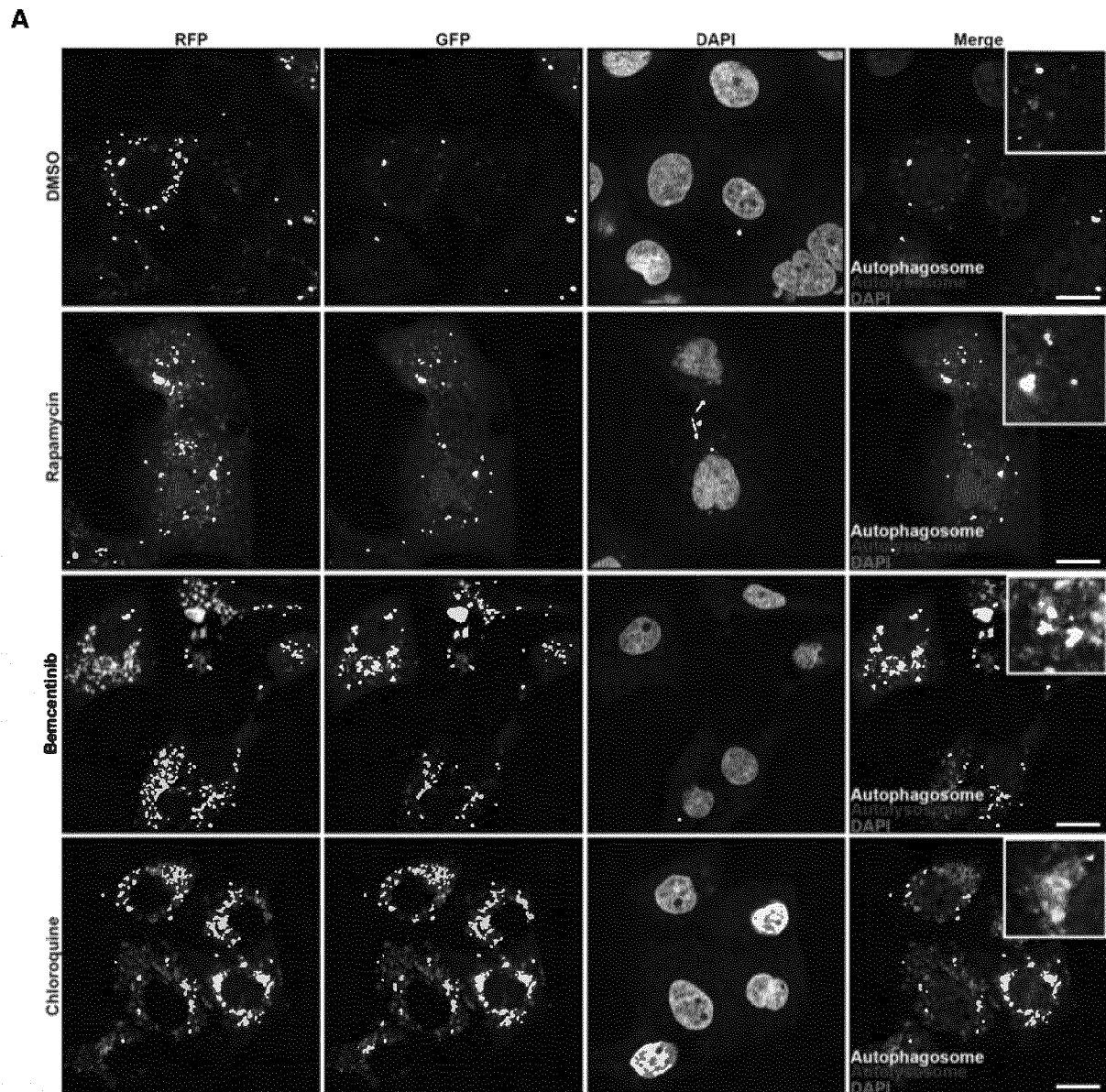


Figure 5

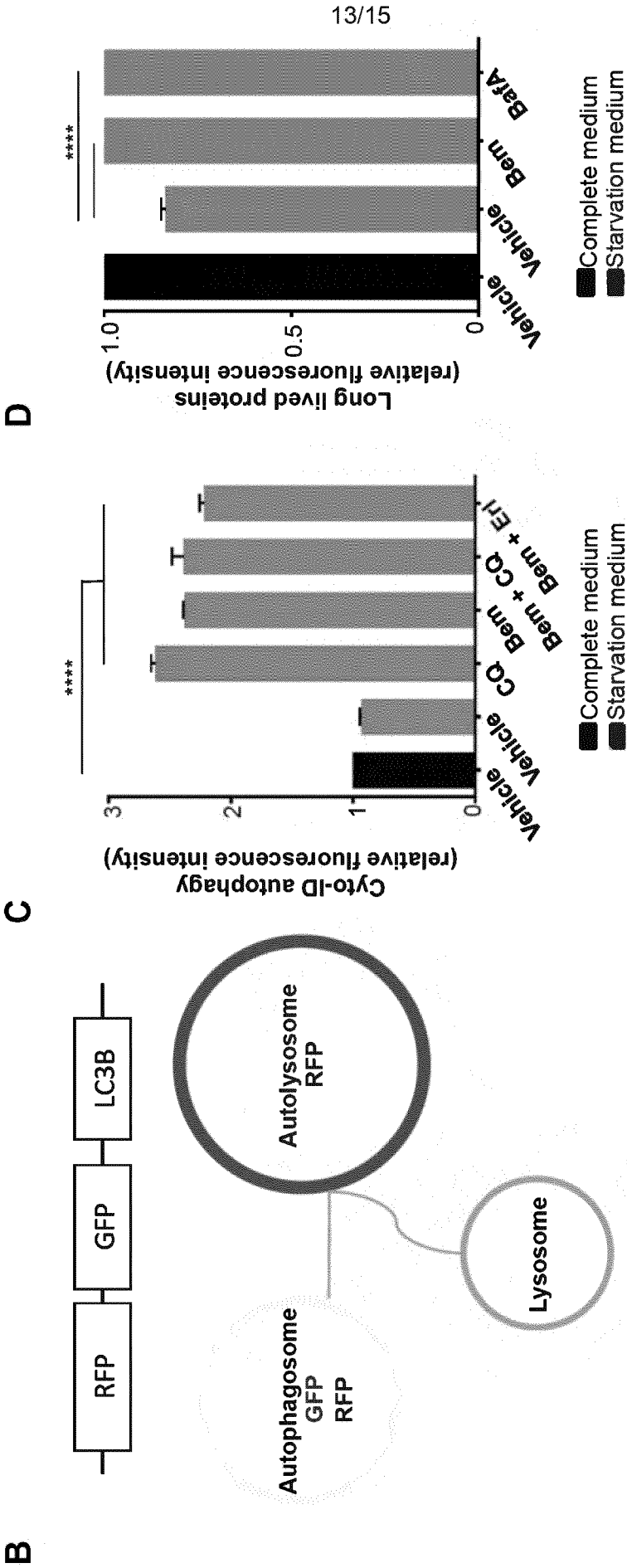


Figure 5

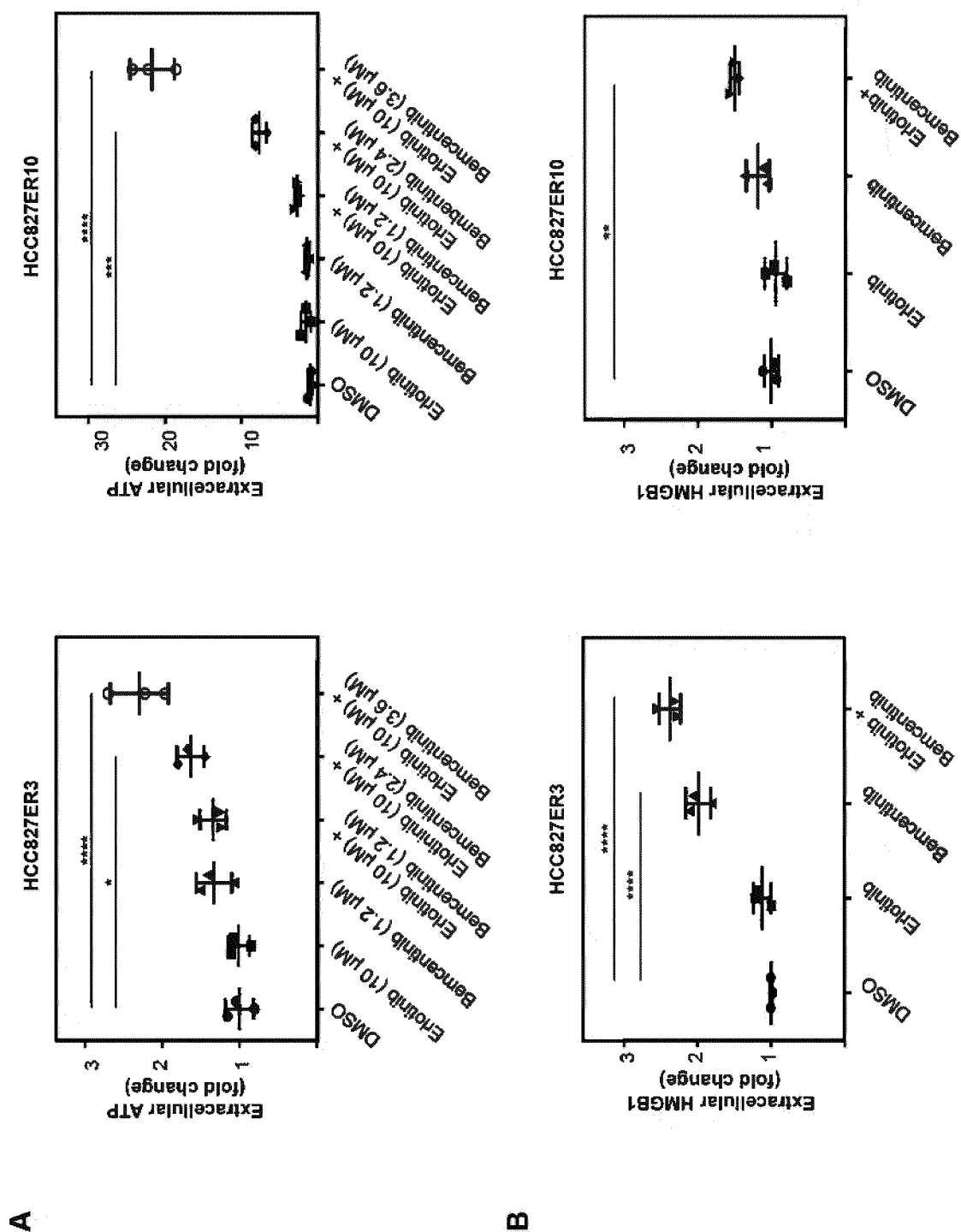
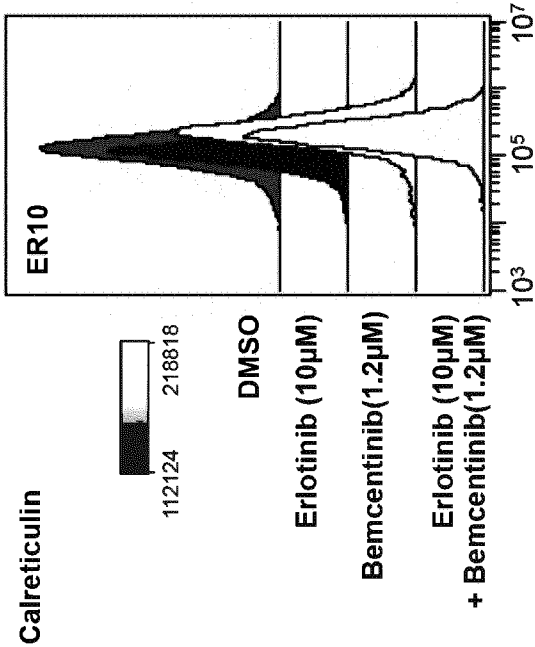


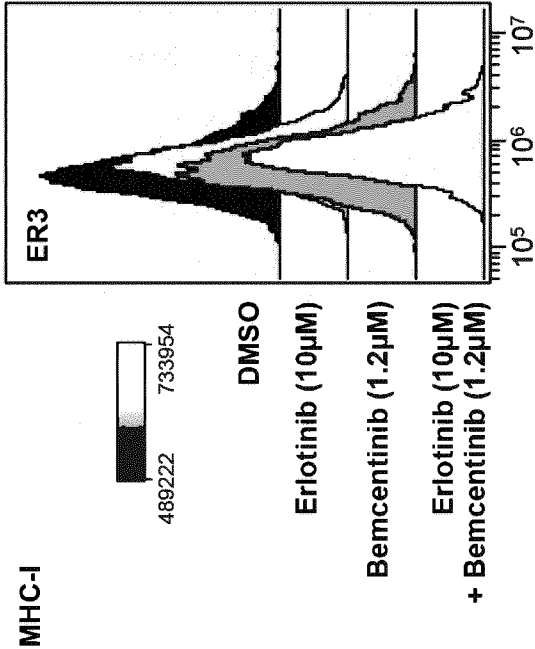
Figure 6

C



Calreticulin	DMSO/ MFI	Bemcentinib/ MFI
HCC827	81 105	107 988
HCC827ER3	95 272	118 531
HCC827ER10	122 854	218 819

D



MHC-I	DMSO/ MFI	Bemcentinib/ MFI
HCC827	921 213	1 178 215
HCC827ER3	489 223	576 377
HCC827ER10	494 544	560 080

Table 6

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2020/073550

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K31/4196 A61K31/50 A61P35/00 ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) A61K A61P		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2016/193680 A1 (BERGENBIO AS [NO]; JONES NICHOLAS ANDREW [GB]) 8 December 2016 (2016-12-08) page 96, line 2 - line 6 -----	1-66, 73-104
X	WO 2015/193428 A1 (BERGENBIO AS [NO]) 23 December 2015 (2015-12-23) page 53, line 28; claims 1, 48 page 52, line 10 - line 25 -----	1-66, 73-104
X	WO 2018/022438 A1 (LILLY CO ELI [US]) 1 February 2018 (2018-02-01) claims 1-4 -----	1-62, 67-104
☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 16 December 2020		Date of mailing of the international search report 12/01/2021
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Scheid, Günther

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2020/073550

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2016193680	A1	08-12-2016	EP 3302481 A1 11-04-2018
			JP 6795585 B2 02-12-2020
			JP 2018521116 A 02-08-2018
			JP 2020105211 A 09-07-2020
			US 2018153888 A1 07-06-2018
			US 2020215064 A1 09-07-2020
			WO 2016193680 A1 08-12-2016

WO 2015193428	A1	23-12-2015	AU 2015276153 A1 05-01-2017
			CA 2952296 A1 23-12-2015
			CN 106573979 A 19-04-2017
			DK 3157559 T3 27-07-2020
			EP 3157559 A1 26-04-2017
			HR P20201091 T1 30-10-2020
			HU E049755 T2 28-10-2020
			JP 6787795 B2 18-11-2020
			JP 2017519501 A 20-07-2017
			KR 20170020476 A 22-02-2017
			LT 3157559 T 25-08-2020
			SI 3157559 T1 30-09-2020
			US 2017129957 A1 11-05-2017
			US 2018371096 A1 27-12-2018
			WO 2015193428 A1 23-12-2015

WO 2018022438	A1	01-02-2018	CN 109562282 A 02-04-2019
			EP 3490676 A1 05-06-2019
			JP 2019525934 A 12-09-2019
			US 2019269666 A1 05-09-2019
			WO 2018022438 A1 01-02-2018
