

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization

International Bureau



(10) International Publication Number

WO 2017/157825 A1

(43) International Publication Date

21 September 2017 (21.09.2017)

WIPO | PCT

(51) International Patent Classification:

*A61K 31/12* (2006.01) *A61K 31/475* (2006.01)  
*A61K 31/135* (2006.01) *A61K 31/495* (2006.01)  
*A61K 31/19* (2006.01) *A61K 31/519* (2006.01)  
*A61K 31/282* (2006.01) *A61K 31/555* (2006.01)  
*A61K 31/337* (2006.01) *A61K 31/704* (2006.01)  
*A61K 31/4045* (2006.01) *A61K 31/7068* (2006.01)  
*A61K 31/4745* (2006.01) *A61P 35/00* (2006.01)

Life Science, New York, NY 10016 (US). **MAES, Tamara**; c/o Oryzon Genomics S.A., C. Sant Ferran 74, 08940 Cornellà de Llobregat (ES). **LUNARDI, Serena**; c/o Oryzon Genomics S.A., C. Sant Ferran 74, 08940 Cornellà de Llobregat (ES).

(74) Agent: **MUELLER-AFRAZ, Simona**; Grenzacherstrasse 124, 4070 Basel (CH).

(21) International Application Number:

PCT/EP2017/055784

(22) International Filing Date:

13 March 2017 (13.03.2017)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/308,529 15 March 2016 (15.03.2016) US

(71) Applicant (for all designated States except US): **F. HOFFMANN-LA ROCHE AG** [CH/CH]; Grenzacherstrasse 124, 4070 Basel (CH).

(71) Applicant (for US only): **HOFFMANN-LA ROCHE INC.** [US/US]; Overlook at Great Notch, 150 Clove Road, 8th Floor, Suite 8 - Legal Department, Little Falls, NJ 07424 (US).

(72) Inventors: **DEMARIO, Mark**; c/o Roche TCRC, Inc. East 29th Street, Alexandria Center for Life Science, New York, NY 10016 (US). **PIERCEALL, William**; c/o Roche TCRC, Inc. East 29th Street, Alexandria Center for Life Science, New York, NY 10016 (US). **MACK, Fiona**; c/o Roche TCRC, Inc. East 29th Street, Alexandria Center for

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))



WO 2017/157825 A1

(54) Title: COMBINATIONS OF LSD1 INHIBITORS FOR USE IN THE TREATMENT OF SOLID TUMORS

(57) Abstract: The instant invention relates to therapeutic combinations of LSD1 inhibitors and one or more other active pharmaceutical ingredient(s) or pharmaceutically acceptable salts thereof. The combinations are particularly useful for treating neoplastic diseases, such as cancer, particularly small cell lung cancer (SCLC).

## COMBINATIONS OF LSD1 INHIBITORS FOR USE IN THE TREATMENT OF SOLID TUMORS

### Field of the invention

The instant invention relates to therapeutic combinations of LSD1 inhibitors and one or more other active pharmaceutical ingredient(s) or pharmaceutically acceptable salts thereof. The combinations are particularly useful for treating neoplastic diseases, such as cancer, particularly  
5 small cell lung cancer (SCLC).

### Background of the invention

Aberrant gene expression in affected tissue as compared to normal tissue is a common characteristic of many human diseases. This is true for cancer and many neurological diseases which are characterized by changes in gene expression patterns. Gene expression patterns are  
10 controlled at multiple levels in the cell. Control of gene expression can occur through modifications of DNA: DNA promoter methylation is associated with suppression of gene expression. Several inhibitors of DNA methylation are approved for clinical use including the blockbuster Vidaza™. Another class of modifications involve histones which form the protein scaffold that DNA is normally associated with (coiled around) in eukaryotic cells. Histones play  
15 a crucial role in organizing DNA and the regulated coiling and uncoiling of DNA around the histones is critical in controlling gene expression – coiled DNA is typically not accessible for gene transcription. A number of histone modifications have been discovered including histone acetylation, histone lysine methylation, histone arginine methylation, histone ubiquinylation, and histone sumoylation, many of which modify accessibility to the associated DNA by the cells  
20 transcriptional machinery. These histone marks serve to recruit various protein complexes involved in transcription and repression. An increasing number of studies are painting an intricate picture of how various combinations of histone marks control gene expression in cell-type specific manner and a new term has been coined to capture this concept: the histone code.

The prototypical histone mark is histone acetylation. Histone acetyl transferase and  
25 histone deacetylases are the catalytic machines involved in modulation of this histone mark although typically these enzymes are parts of multiprotein complexes containing other proteins involved in reading and modifying histone marks. The components of these protein complexes are typically cell-type specific and typically comprise transcriptional regulators, repressors, co-repressors, receptors associated with gene expression modulation (e.g., estrogen or androgen receptor). Histone deacetylase inhibitors alter the histone acetylation profile of chromatin. Accordingly, histone deacetylase inhibitors like Vorinostat (SAHA), Trichostatin A (TSA), and many others have been shown to alter gene expression in various in vitro and in vivo animal models. Clinically, histone deacetylase inhibitors have demonstrated activity in the cancer setting

and are being investigated for oncology indications as well as for neurological conditions and other diseases.

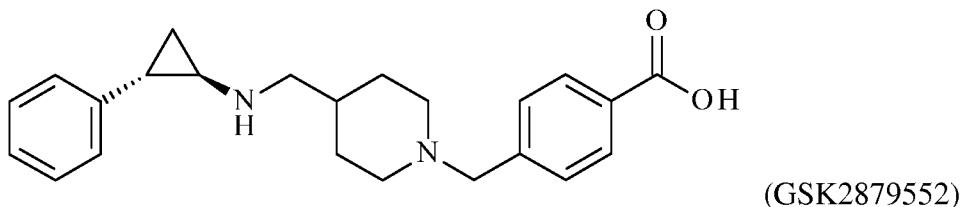
Another modification that is involved in regulating gene expression is histone methylation including lysine and arginine methylation. The methylation status of histone lysines 5 has recently been shown to be important in dynamically regulating gene expression.

A group of enzymes known as histone lysine methyl transferases and histone lysine demethylases are involved in histone lysine modifications. One particular human histone lysine demethylase enzyme called Lysine Specific Demethylase-1 (LSD1) was recently discovered<sup>1</sup> to be involved in this crucial histone modification. LSD1 has a fair degree of structural similarity, 10 and amino acid identity/homology to polyamine oxidases and monoamine oxidases, all of which (i.e., MAO-A, MAO-B and LSD1) are flavin dependent amine oxidases which catalyze the oxidation of nitrogen-hydrogen bonds and/or nitrogen carbon bonds. LSD1 has been recognized as an interesting target for the development of new drugs to treat cancer, neurological diseases 15 and other conditions.

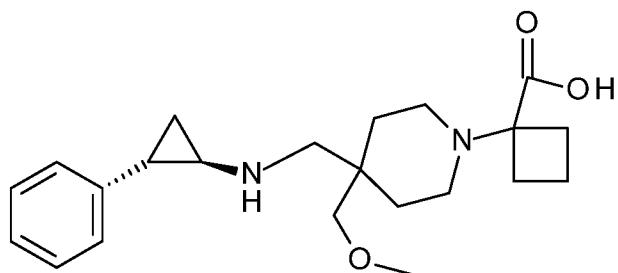
15 Cyclopropylamine containing compounds are known to inhibit a number of medically important targets including amine oxidases like Monoamine Oxidase A (MAO-A; or MAOA), Monoamine Oxidase B (MAO-B; or MAOB), and Lysine Specific Demethylase-1 (LSD1). Tranylcypromine (also known as 2-phenylcyclopropylamine), which is the active ingredient of Parnate® and one of the best known examples of a cyclopropylamine, is known to inhibit all of 20 these enzymes. Since MAO-A inhibition may cause undesired side effects, it would be desirable to identify cyclopropylamine derivatives that exhibit potent LSD1 inhibitory activity while being devoid of or having substantially reduced MAO-A inhibitory activity.

Compounds which act as inhibitors of LSD1 are known in the art. LSD1 inhibitors and methods for making them are for example disclosed in WO 2011/131697<sup>2</sup>, WO 2012/135113<sup>3</sup>, 25 WO 2013/057322<sup>4</sup>, WO 2010/143582<sup>5</sup>, WO 2011/131576<sup>6</sup>, WO 2013/022047<sup>7</sup>, WO 2013/025805<sup>8</sup>, WO 2014/058071<sup>9</sup>, WO 2014/084298<sup>10</sup>, WO 2014/085613<sup>11</sup>, WO 2014/086790<sup>12</sup>, WO2014/164867<sup>13</sup>, WO 2014/194280<sup>14</sup>, WO 2014/205213<sup>15</sup>, WO 2015/021128<sup>16</sup>, WO 2015/031564<sup>17</sup>, WO 2015/089192<sup>18</sup>, WO 2015/120281<sup>19</sup>, WO 2015/123465<sup>20</sup>, WO 2015/123437<sup>21</sup>, WO 2015/123424<sup>22</sup>, WO 2015/123408<sup>23</sup>, WO 2015/134973<sup>24</sup>, WO 30 2015/156417<sup>25</sup>, WO 2015/168466, WO 2015/181380, WO 2015200843, WO 2016003917, WO 2016/004105<sup>26</sup>, WO 2016/007722<sup>27</sup>, WO 2016/007727<sup>28</sup>, WO 2016/007731<sup>29</sup>, WO 2016/007736<sup>30</sup>, WO 2016/034946<sup>31</sup>, WO 2016/037005<sup>32</sup>, CN 105541806<sup>33</sup>, WO 2016/123387<sup>34</sup>, WO 2016/130952<sup>35</sup>, CN 105924362<sup>36</sup>, CN 105985265<sup>37</sup>, WO 2016/161282<sup>38</sup>, CN 106045862<sup>39</sup>, CN 106045881<sup>40</sup>, WO 2016/172496<sup>41</sup>, WO 2016/177656<sup>42</sup>, WO 2017/004519<sup>43</sup>, WO 35 2017/027678<sup>44</sup> which are incorporated in their entirety herein.

WO 2012/135113<sup>3</sup> discloses compounds, for example GSK2879552 [CAS Reg. No. 1401966-69-5], also known as 4-[[4-[[[(1R,2S)-2-phenylcyclopropyl]amino]methyl]-1-piperidinyl]methyl]-benzoic acid (Example 26 on p. 75, Example 29 on p. 81), as selective LSD1 inhibitor.



WO 2017/027678<sup>44</sup> discloses the p-toluenesulfonic acid salt of 1-((4-(methoxymethyl)-4-((1R,2S)-2-phenylcyclopropylamino)methyl)piperidin-1-yl)methyl)cyclobutanecarboxylic acid



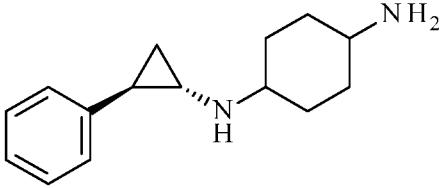
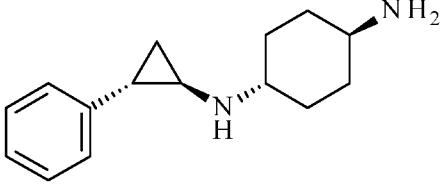
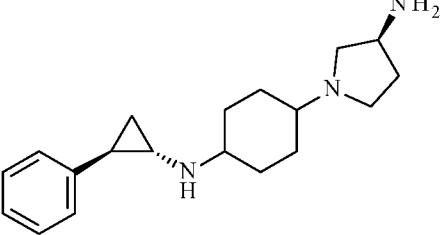
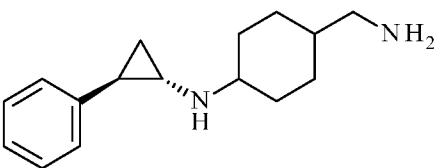
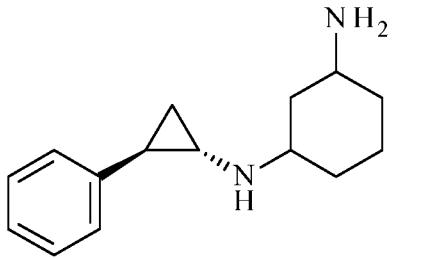
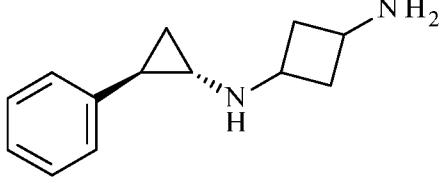
LSD1 inhibitors and methods for making them are for example disclosed in WO 10 2013/022047<sup>7</sup>, particularly examples 1 – 166 (pages 44 to 114 of corresponding EP2743256), in particular N-[4-[2-[(cyclopropylmethylamino)methyl]cyclopropyl]phenyl]-1-methyl-pyrazole-4-carboxamide (Ex. 163) which are incorporated in their entirety herein.

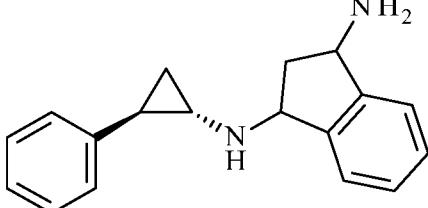
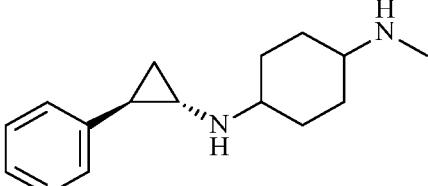
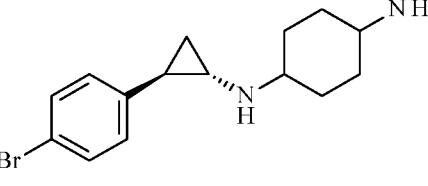
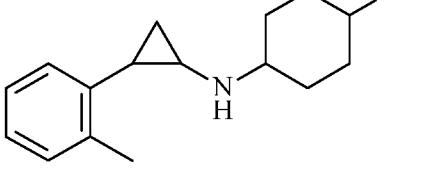
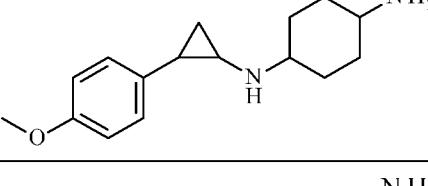
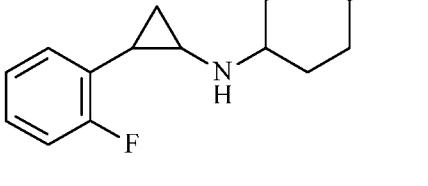
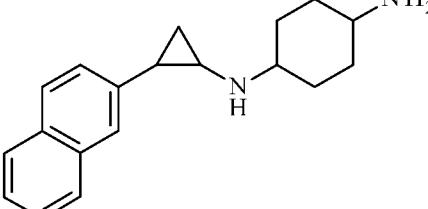
LSD1 inhibitors and methods for making them are for example disclosed in WO 2011/131697<sup>2</sup>, particularly examples 1 – 21 (pages 90 to 103), which are incorporated in their 15 entirety herein.

LSD1 inhibitors and methods for making them are for example disclosed in WO 2013/057322<sup>4</sup>, particularly examples 1 – 108 (pages 155 to 191), which are incorporated in their entirety herein.

Particular LSD1 inhibitors described in WO 2013/057322<sup>4</sup> are provided in Table 1.

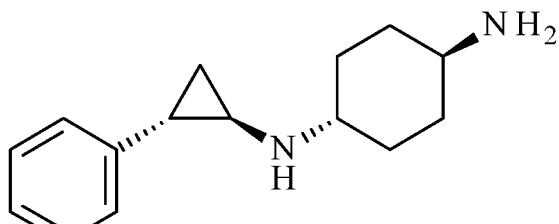
20 Table 1. Particular LSD1 inhibitors disclosed in WO 2013/057322<sup>4</sup>.

Example No of WO 2013/057322 <sup>4</sup>	Substance name	Structure
1	N1-((trans)-2-phenylcyclopropyl)cyclohexane-1,4-diamine	
5	(trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine	
15	(R)-1-((trans)-2-phenylcyclopropyl)amino)cyclohexylpyrrolidin-3-amine	
17	4-(aminomethyl)-N-((trans)-2-phenylcyclopropyl)cyclohexanamine	
18	N1-((trans)-2-phenylcyclopropyl)cyclohexane-1,3-diamine	
19	N1-((trans)-2-phenylcyclopropyl)cyclobutane-1,3-diamine	

Example No of WO 2013/057322 <sup>4</sup>	Substance name	Structure
20	N1-((trans)-2-phenylcyclopropyl)-2,3-dihydro-1H-indene-1,3-diamine	
22	N1-methyl-N4-((trans)-2-phenylcyclopropyl)cyclohexane-1,4-diamine	
26	N1-((trans)-2-(4-bromophenyl)cyclopropyl)cyclohexane-1,4-diamine	
27	N1-(2-(o-tolyl)cyclopropyl)cyclohexane-1,4-diamine	
29	N1-(2-(4-methoxyphenyl)cyclopropyl)cyclohexane-1,4-diamine	
31	N1-(2-(2-fluorophenyl)cyclopropyl)cyclohexane-1,4-diamine	
33	N1-(2-(naphthalen-2-yl)cyclopropyl)cyclohexane-1,4-diamine	

Example No of WO 2013/057322 <sup>4</sup>	Substance name	Structure
50	N-(4'-( <i>trans</i> )-2-((4-aminocyclohexyl)amino)cyclopropyl)-[1,1'-biphenyl]-3-yl)-2-cyanobenzenesulfonamide	
56	N1-(( <i>trans</i> )-2-(4-(pyridin-3-ylmethoxy)phenyl)cyclopropyl)cyclohexane-1,4-diamine	

A more particular LSD1 inhibitor described in WO 2013/057322<sup>4</sup> is (trans)-N1-((1*R*,2*S*)-2-phenylcyclopropyl)cyclohexane-1,4-diamine [CAS Reg. No. 1431304-21-0]



,

corresponding to Example 5 therein, and pharmaceutically acceptable salts thereof. This

5 compound is also known as ORY-1001.

It has been determined that additive or synergistic effects in inhibiting the growth of cancer cells in vitro and in vivo can be achieved by administering LSD1 inhibitors or pharmaceutically acceptable salts thereof in combination with certain other specific agents. The combination and methods may be useful in the treatment of neoplastic diseases such as cancer.

10 Accordingly, present invention provides combinations for use in the treatment of neoplastic diseases in a mammal comprising a LSD1 inhibitor or a pharmaceutically acceptable salt thereof, and one or more active pharmaceutical ingredient(s) selected from Table 2 or pharmaceutically acceptable salts thereof.

Table 2. Active pharmaceutical ingredients suitable to be combined with LSD1 inhibitors.

Compound	INN	Mode of Action	Systematic Name	CAS Number	Literature Reference
ABT-199	Venetoclax	BCL2 inhibitor	4-[4-[[2-(4-Chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl]-N-[[3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino]phenyl]sulfonyl]-2-[(1H-pyrrolo[2,3-b]pyridin-5-yl)oxy]benzamide	1257044-40-8	WO 2010/138588 <sup>45</sup>
ABT-263	Navitoclax	BCL2 inhibitor	4-(4-{{2-(4-Chlorophenyl)-5,5-dimethyl-1-cyclohexen-1-yl}methyl}-1-piperazinyl)-N-[(4-{{(2R)-4-(4-morpholinyl)-1-(phenylsulfanyl)-2-butanyl}amino}-3-[(trifluoromethyl)sulfonyl]phenyl)sulfonyl]benzamide	923564-51-6	US 2007/0027135 <sup>46</sup>
ABT-737		BCL2 inhibitor	4-[4-[[2-(4-chlorophenyl)phenyl]methyl]piperazin-1-yl]-N-[4-[(2R)-4-(dimethylamino)-1-phenylsulfanylbutan-2-yl]amino]-3-nitrophenyl]sulfonylbenzamide	852808-04-9	WO 2005/049594 <sup>47</sup>
ABT-888	Veliparib	PARP inhibitor	2-((R)-2-Methylpyrrolidin-2-yl)-1H-benzimidazole-4-carboxamide	912444-00-9	US 2006/0229289 <sup>48</sup>
ACY-1215	Ricolinostat	HDAC inhibitor	2-(diphenylamino)-N-[7-(hydroxyamino)-7-oxoheptyl]-5-pyrimidinecarboxamide	1316214-52-4	WO 2011/091213 <sup>49</sup>
Belinostat	Belinostat	HDAC (pan-HDAC) inhibitor	(22E)-N-Hydroxy-3-[3-(phenylsulfamoyl)phenyl]prop-2-enamide	866323-14-0	WO 2009/040517 <sup>50</sup>
Bendamustine	Bendamustine	DNA alkylating agent	4-[5-[Bis(2-chloroethyl)amino]-1-methylbenzimidazol-2-yl]butanoic acid	16506-27-7	DD 159877 <sup>51</sup>

Compound	INN	Mode of Action	Systematic Name	CAS Number	Literature Reference
BGJ398	Infigratinib	FGFR kinase inhibitor	3-(2,6-dichloro-3,5-dimethoxyphenyl)-1-(6-((4-(4-ethylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)-1-methylurea	872511-34-7	WO 2006/000420 <sup>52</sup>
BMS-906024		Notch signaling inhibitor	(2R,3S)-N-[(3S)-1-Methyl-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl]-2,3-bis(3,3,3-trifluoropropyl)succinamide	1401066-79-2	WO 2012/129353 <sup>53</sup>
Carboplatin	Carboplatin	DNA alkylating agent (DNA linker)	cis-diammine(cyclobutane-1,1-dicarboxylate-O,O')platinum(II)	41575-94-4	ES 544159 <sup>54</sup>
CGK 733		ATM/ATR kinase inhibitor	$\alpha$ -Phenyl-N-[2,2,2-trichloro-1-[[[(4-fluoro-3-nitrophenyl)amino]thiomethyl]amino]ethyl]benzeneacetamide	905973-89-9	WO 2007/015632 <sup>55</sup>
Cisplatin	Cisplatin	DNA alkylating agent (DNA linker)	(SP-4-2)-diamminedichloroplatinum(II)	15663-27-1	Rosenberg B. <i>et al.</i> <sup>56</sup>
CPI-169		EZH2 inhibitor (EZH1/2 inhibitor)	N-[(1,2-dihydro-4-methoxy-6-methyl-2-oxo-3-pyridinyl)methyl]-1-[1-[1-(ethylsulfonyl)-4-piperidinyl]ethyl]-2-methyl-1H-indole-3-carboxamide	1450655-76-1	WO 2013/120104 <sup>57</sup>
CPI-203		BET inhibitor (BRD2/3/4 inhibitor)	(6S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine-6-acetamide	1446144-04-2	WO 2014/134583 <sup>58</sup>
Docetaxel	Docetaxel	anti-mitotic agent (TUBB1 stabilizer)	1,7 $\beta$ ,10 $\beta$ -trihydroxy-9-oxo-5 $\beta$ ,20-epoxytax-11-ene-2 $\alpha$ ,4,13 $\alpha$ -triyl 4-acetate 2-benzoate 13-{(2R,3S)-3-[(tert-butoxycarbonyl)amino]-2-hydroxy-3-phenylpropanoate}	114977-28-5	EP 253738 <sup>59</sup>

Compound	INN	Mode of Action	Systematic Name	CAS Number	Literature Reference
Doxorubicin	Doxorubicin	topoisomerase inhibitor	(7S,9S)-7-[(2R,4S,5S,6S)-4-amino-5-hydroxy-6-methyloxan-2-yl]oxy-6,9,11-trihydroxy-9-(2-hydroxyacetyl)-4-methoxy-8,10-dihydro-7H-tetracene-5,12-dione	23214-92-8	DE 2510866 <sup>60</sup>
EPZ-004777		DOT1L inhibitor	7-[5-Deoxy-5-[[3-[[[[4-(1,1-dimethylethyl)phenyl]amino]carbonyl]amino]propyl](1-methylethyl)amino]-β-D-ribofuranosyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine	1338466-77-5	Daigle S.R. <i>et al.</i> <sup>61</sup>
EPZ005687		EZH2 inhibitor	1-cyclopentyl-N-[(1,2-dihydro-4,6-dimethyl-2-oxo-3-pyridinyl)methyl]-6-[4-(4-morpholinylmethyl)phenyl]-1H-indazole-4-carboxamide	1396772-26-1	WO 2012/118812 <sup>62</sup>
EPZ-5676	Pinometostat	DOT1L inhibitor	5'-deoxy-5'-[[cis-3-[2-[6-(1,1-dimethylethyl)-1H-benzimidazol-2-yl]ethyl]cyclobutyl](1-methylethyl)amino]-adenosine	1380288-87-8	WO 2012/075381 <sup>63</sup>
EPZ-6438	Tazemetostat	EZH2 inhibitor	N-[(1,2-dihydro-4,6-dimethyl-2-oxo-3-pyridinyl)methyl]-5-[ethyl(tetrahydro-2H-pyran-4-yl)amino]-4-methyl-4'-(4-morpholinylmethyl)-[1,1'-biphenyl]-3-carboxamide	1403254-99-8	WO 2012/142504 <sup>64</sup>
Erlotinib	Erlotinib	tyrosine kinase inhibitor	N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine	183321-74-6	WO 9630347 A1
Etoposide	Etoposide	topoisomerase inhibitor	4'-Demethyl-epipodophyllotoxin 9-[4,6-O-(R)-ethylidene-beta-D-glucopyranoside], 4'-(dihydrogen phosphate)	33419-42-0	CH 514578 <sup>65</sup>

Compound	INN	Mode of Action	Systematic Name	CAS Number	Literature Reference
FLI 06		Notch signaling inhibitor	Cyclohexyl 1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-4-(4-nitrophenyl)-5-oxo-3-quinolinecarboxylate	313967-18-9	WO 2013/178821 <sup>66</sup>
Fluorouracil	Fluorouracil	thymidylate synthase inhibitor	5-Fluoro-1H,3H-pyrimidine-2,4-dione	51-21-8	US 2802005 <sup>67</sup>
GDC-0449	Vismodegib	Hedgehog pathway inhibitor	2-Chloro-N-(4-chloro-3-pyridin-2-ylphenyl)-4-methylsulfonylbenzamide	879085-55-9	WO 2006/028958 <sup>68</sup>
Gemcitabine	Gemcitabine	nucleoside analog	4-amino-1-(2-deoxy-2,2-difluoro- $\beta$ -D-erythro-pentofuranosyl)pyrimidin-2(1H)-on	95058-81-4	GB 2136425 <sup>69</sup>
GSK126		EZH2 inhibitor	N-[(1,2-dihydro-4,6-dimethyl-2-oxo-3-pyridinyl)methyl]-3-methyl-1-[(1S)-1-methylpropyl]-6-[6-(1-piperazinyl)-3-pyridinyl]-1H-indole-4-carboxamide	1346574-57-9	WO 2011/140324 <sup>70</sup>
GSK132472 6A (I-BET726)		BET inhibitor (BRD2/3/4 inhibitor)	4-[(2S,4R)-1-acetyl-4-[(4-chlorophenyl)amino]-1,2,3,4-tetrahydro-2-methyl-6-quinolinyl]-benzoic acid	1300031-52-0	WO 2011/054843 <sup>71</sup>
GSK343		EZH2 inhibitor (EZH1/2 inhibitor)	N-[(1,2-dihydro-6-methyl-2-oxo-4-propyl-3-pyridinyl)methyl]-1-(1-methylethyl)-6-[2-(4-methyl-1-piperazinyl)-4-pyridinyl]-1H-indazole-4-carboxamide	1346704-33-3	WO 2011/140325 <sup>72</sup>
GSK-J1		demethylase inhibitor (JMJD3/UTX inhibitor)	N-[2-(2-Pyridinyl)-6-(1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)-4-pyrimidinyl]- $\beta$ -alanine	1373422-53-7	WO 2012/052390 <sup>73</sup>
GSK121015 1A (I-BET151)		BET inhibitor (BRD2/3/4 inhibitor)	7,3,5-dimethyl-4-isoxazolyl-1,3-dihydro-8-methoxy-1-[1R-1-(2-pyridinyl)ethyl]-2H-imidazo[4,5-c]quinolin-2-one	1300031-49-5	WO 2011/054843 <sup>71</sup>

Compound	INN	Mode of Action	Systematic Name	CAS Number	Literature Reference
Irinotecan	Irinotecan	topoisomerase inhibitor	(S)-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo1H-pyrano[3',4':6,7]-indolizino[1,2-b]quinolin-9-yl-[1,4'bipiperidine]-1'-carboxylate	100286-90-6	US 6121451 <sup>74</sup>
(+)-JQ1		BET inhibitor (BRD2/3/4 inhibitor)	(S)-tert-butyl 2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetate	1268524-70-4	WO 2011/143651 <sup>75</sup>
Lapatinib	Lapatinib	tyrosine kinase inhibitor	N-[3-chloro-4-[(3-fluorophenyl)methoxy]phenyl]-6-[5-[(2-methylsulfonylethylamino)methyl]-2-furyl]quinazolin-4-amine	231277-92-2	WO 99/35146 <sup>76</sup>
LDE225	Sonidegib	Hedgehog pathway inhibitor	N-[6-[(2S,6R)-2,6-Dimethylmorpholin-4-yl]pyridin-3-yl]-2-methyl-3-[4-(trifluoromethoxy)phenyl]benzamide	956697-53-3	WO 2010/033481 <sup>77</sup>
LY2603618		Chk inhibitor	N-[5-bromo-4-methyl-2-[(2S)-2-morpholinylmethoxy]phenyl]-N'-(5-methyl-2-pyrazinyl)-urea	911222-45-2	WO 2006/105262 <sup>78</sup>
LY-3039478		Notch signaling inhibitor	N-[(1S)-2-[[7S)-6,7-dihydro-5-(2-hydroxyethyl)-6-oxo-5H-pyrido[3,2-a][3]benzazepin-7-yl]amino]-1-methyl-2-oxoethyl]-4,4,4-trifluorobutanamide	1421438-81-4	WO 2013/016081 <sup>79</sup>
Menadione	Menadione	1,4-naphthoquinone analogue	2-Methylnaphthalene-1,4-dione	58-27-5	US 2331725 <sup>80</sup>

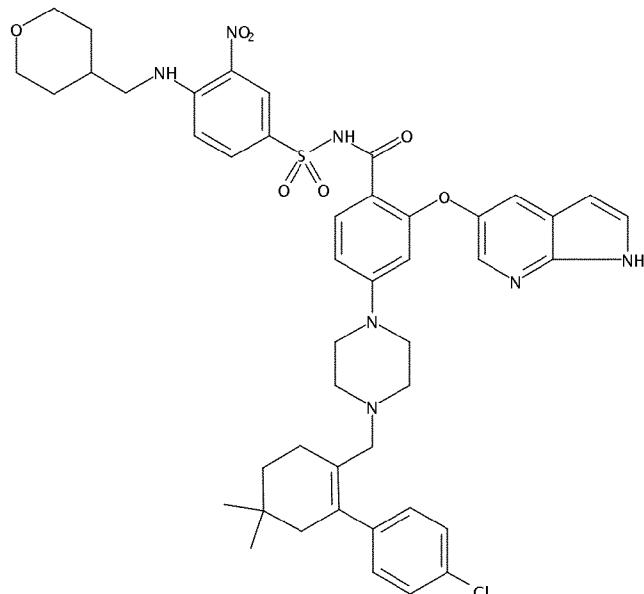
Compound	INN	Mode of Action	Systematic Name	CAS Number	Literature Reference
Methotrexate	Methotrexate	folic acid inhibitor (DHFR inhibitor)	(2S)-2-[(4-{{[(2,4-Diaminopteridin-6-yl)methyl](methyl)amino}benzoyl)amino]pentane dioic acid	59-05-2	US 2512572
MK-0752		Notch signaling inhibitor (gamma secretase inhibitor)	cis-4-[(4-chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)-cyclohexanepropanoic acid	471905-41-6	WO 2002/081435 <sup>81</sup>
MLN8237	Alisertib	Aurora A kinase inhibitor	4-[[9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-pyrimido[5,4-d][2]benzazepin-2-yl]amino]-2-methoxybenzoic acid	1028486-01-2	WO 2008/063525 <sup>82</sup>
MS 436		BET inhibitor (BRD2/3/4 inhibitor)	4-[(1E)-2-(2-amino-4-hydroxy-5-methylphenyl)diazenyl]-N-2-pyridinyl-benzenesulfonamide	1395084-25-9	WO 2012/116170 <sup>83</sup>
Nutlin-3A	Nutlin-3A	MDM2 inhibitor	2-Piperazinone, 4-[[[(4S,5R)-4,5-bis(4-chlorophenyl)-4,5-dihydro-2-[4-methoxy-2-(1-methylethoxy)phenyl]-1H-imidazol-1-yl]carbonyl]-	675576-98-4	US 2005/0282803 <sup>84</sup>
Obatoclax	Obatoclax	BCL2 inhibitor	2-(2-((3,5-Dimethyl-1H-pyrrol-2-yl)methylene)-3-methoxy-2H-pyrrol-5-yl)-1H-indole	803712-67-6	WO 2004/106328 <sup>85</sup>
OTX015		BET inhibitor (BRD2/3/4 inhibitor)	(6S)-4-(4-chlorophenyl)-N-(4-hydroxyphenyl)-2,3,9-trimethyl-6H-Thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine-6-acetamide	202590-98-5	US 5712274 <sup>86</sup>

Compound	INN	Mode of Action	Systematic Name	CAS Number	Literature Reference
Paclitaxel	Paclitaxel	anti-mitotic agent / TUBB stabilizer	(2 $\alpha$ ,4 $\alpha$ ,5 $\beta$ ,7 $\beta$ ,10 $\beta$ ,13 $\alpha$ )-4,10-Bis(acetyloxy)-13-{[(2R,3S)-3-(benzoylamino)-2-hydroxy-3-phenylpropanoyl]oxy}-1,7-dihydroxy-9-oxo-5,20-epoxytax-11-en-2-yl benzoate	33069-62-4	EP 253739 <sup>87</sup>
Panobinostat	Panobinostat	HDAC (pan-HDAC) inhibitor	(2E)-N-hydroxy-3-[4-({[2-(2-methyl-1H-indol-3-yl)ethyl]amino}methyl)phenyl]acrylamide	404950-80-7	WO 2002/022577 <sup>88</sup>
Pemetrexed	Pemetrexed	folic acid inhibitor (TYMS/DHFR/GART inhibitor)	(2S)-2-{{4-[2-(2-amino-4-oxo-1,7-dihydropyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]amino}pentanedioic acid	137281-23-3	EP 432677 <sup>89</sup>
PF-04217903		c-Met inhibitor	4-[1-(6-quinolinylmethyl)-1H-1,2,3-triazolo[4,5-b]pyrazin-6-yl]-1H-pyrazole-1-ethanol	956905-27-4	US 2007/0265272 <sup>90</sup>
PF-3084014		Notch signaling inhibitor (gamma secretase inhibitor)	(2S)-2-[[2S)-6,8-Difluoro-1,2,3,4-tetrahydro-2-naphthalenyl]amino]-N-[1-[2-[(2,2-dimethylpropyl)amino]-1,1-dimethylethyl]-1H-imidazol-4-yl]pentanamide dihydrobromide	865773-15-5	US 2005/0215610 <sup>91</sup>
SAHA	Vorinostat	HDAC inhibitor	suberanilohydroxamic acid	149647-78-9	WO 93/07148 <sup>92</sup>

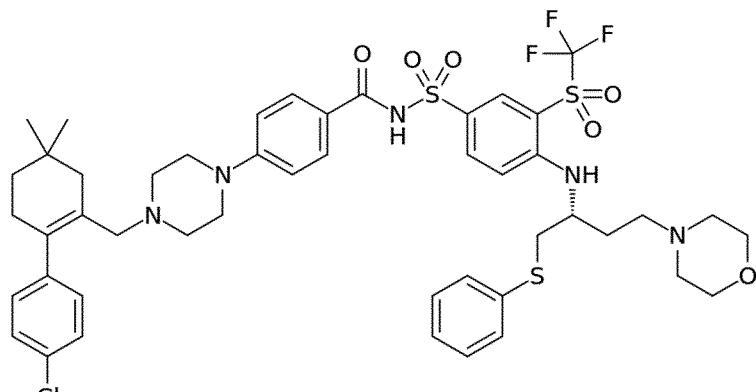
Compound	INN	Mode of Action	Systematic Name	CAS Number	Literature Reference
SGC 0946		DOT1L inhibitor	1-[3-[[[(2R,3S,4R,5R)-5-(4-Amino-5-bromo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-3,4-dihydroxytetrahydrofuran-2-yl]methyl](isopropyl)amino]propyl]-3-[4-(2,2-dimethylethyl)phenyl]urea	1561178-17-3	Yu <i>et al.</i> <sup>93</sup>
SNDX-275	Entinostat	HDAC inhibitor	N-[[4-[(2-aminophenyl)amino]carbonyl]phenyl]methyl]-carbamic acid 3-pyridinylmethyl ester	209783-80-2	JP 10152462 <sup>94</sup>
Taladegib	Taladegib	Hedgehog pathway inhibitor (smoothened inhibitor)	4-fluoro-N-methyl-N-[1-[4-(1-methyl-1H-pyrazol-5-yl)-1-phthalazinyl]-4-piperidinyl]-2-(trifluoromethyl)-benzamide	1258861-20-9	WO 2010/147917 <sup>95</sup>
Temo-zolomide	Temo-zolomide	DNA alkylating agent	4-methyl-5-oxo-2,3,4,6,8-pentazabicyclo[4.3.0]nona-2,7,9-triene-9-carboxamide	85622-93-1	DE 3231255 <sup>96</sup>
Topotecan	Topotecan	topoisomerase inhibitor	(S)-10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione monohydrochloride	123948-87-8	EP 321122 <sup>97</sup>
TW-37		BCL2 inhibitor (BCL2, BCL-xL, MCL-1 inhibitor)	N-[4-[[2-(1,1-dimethylethyl)phenyl]sulfonyl]phenyl]-2,3,4-trihydroxy-5-[[2-(1-methylethyl)phenyl]methyl]-benzamide	877877-35-5	WO 2006/023778 <sup>98</sup>

Compound	INN	Mode of Action	Systematic Name	CAS Number	Literature Reference
Vincristine	Vincristine	anti-mitotic agent (TUBB2 destabilizer)	(3aR,3a1R,4R,5S,5aR,10bR)-Methyl 4-acetoxy-3a-ethyl-9-((5S,7S,9S)-5-ethyl-5-hydroxy-9-(methoxycarbonyl)-2,4,5,6,7,8,9,10-octahydro-1H-3,7-methano[1]azacycloundecino[5,4-b]indol-9-yl)-6-formyl-5-hydroxy-8-methoxy-3a,3a1,4,5,5a,6,11,12-octahydro-1H-indolizino[8,1-cd]carbazole-5-carboxylate	57-22-7	BE 624076 <sup>99</sup>

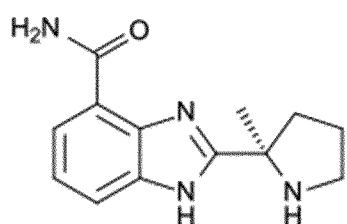
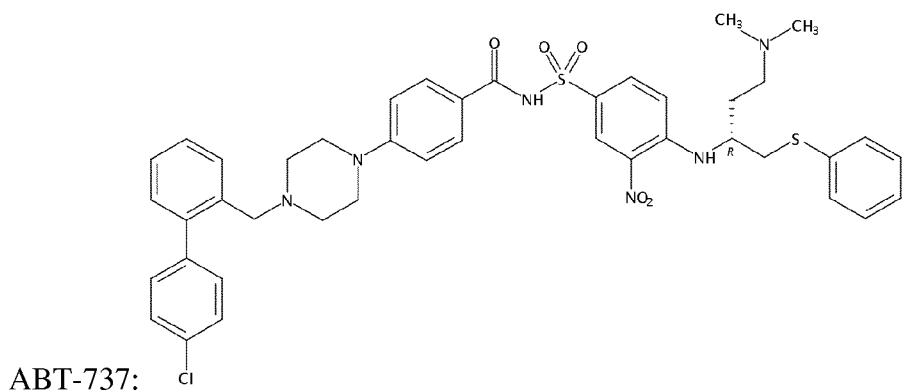
The structures of the compounds of Table 2 are as follows:



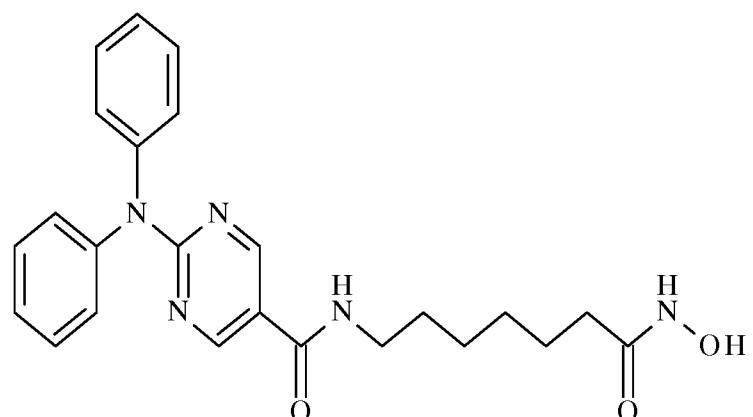
### ABT-199 (Venetoclax):



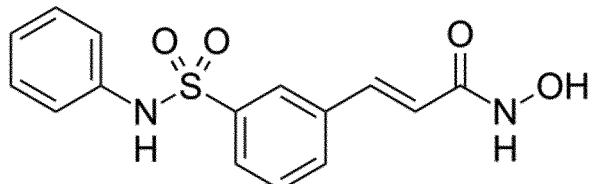
### ABT-263 (Navitoclax):



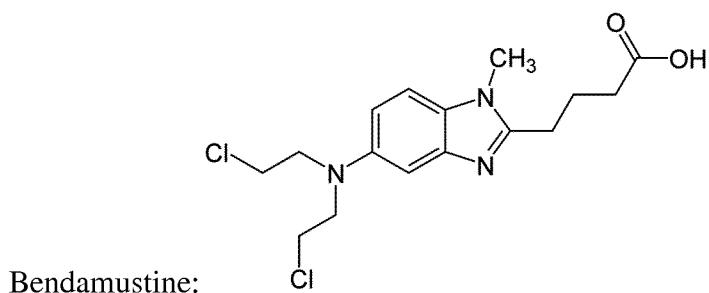
ABT-888 (Veliparib):

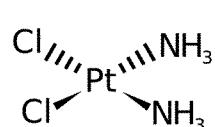
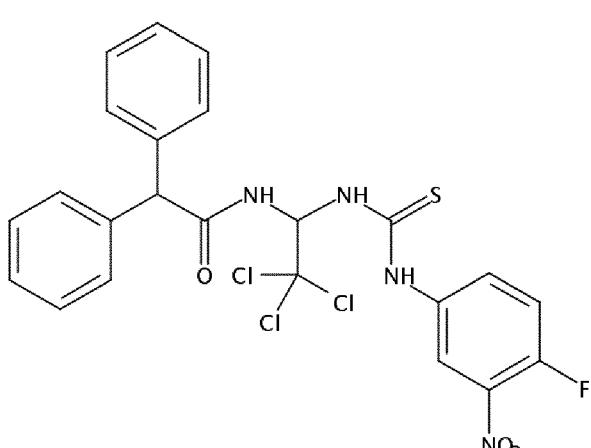
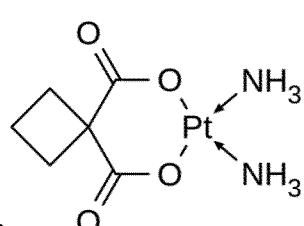
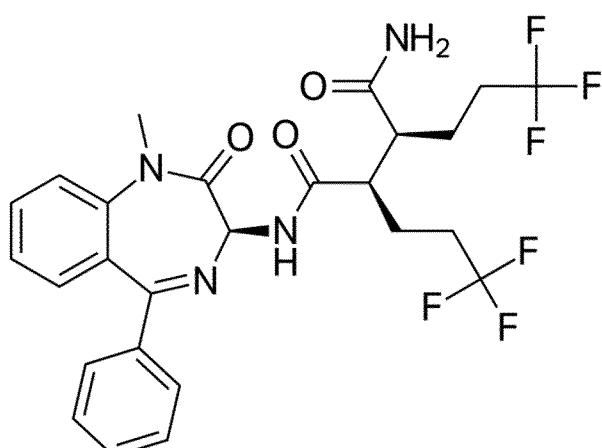
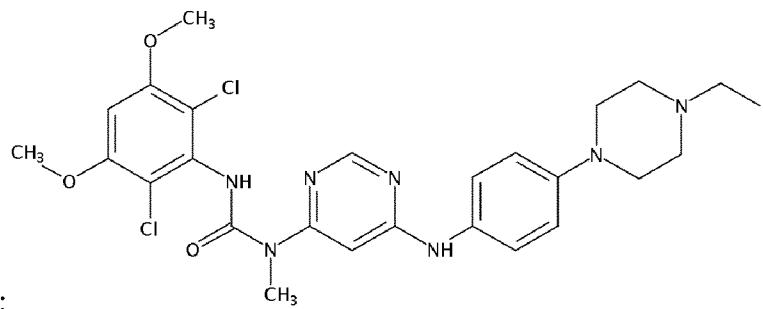


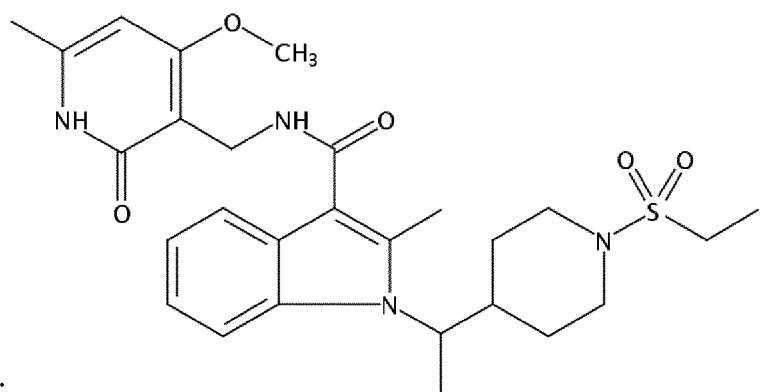
ACY-1215 (Ricolinostat):



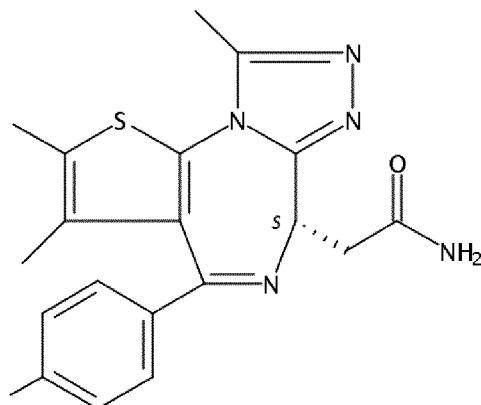
Belinostat:



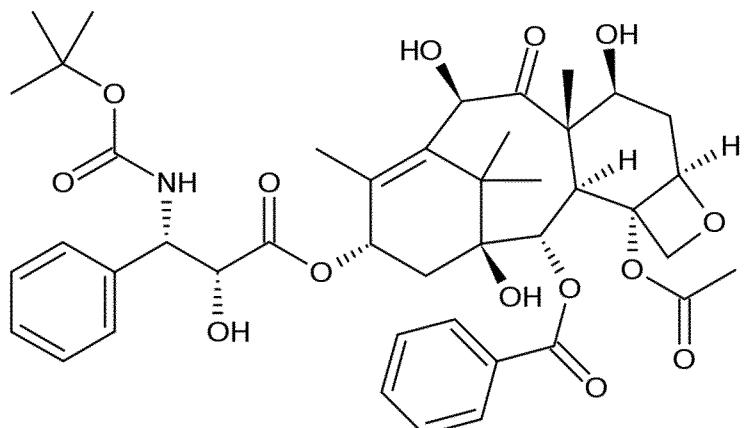




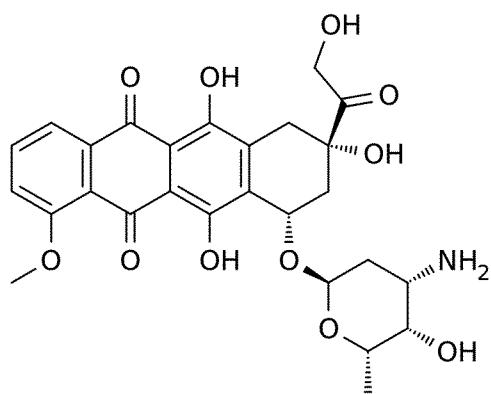
CPI-169:



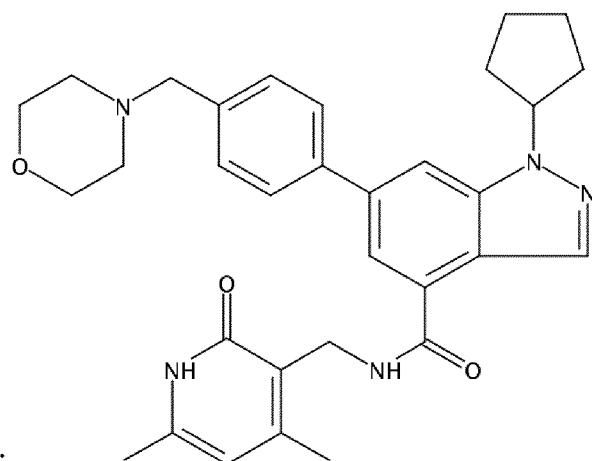
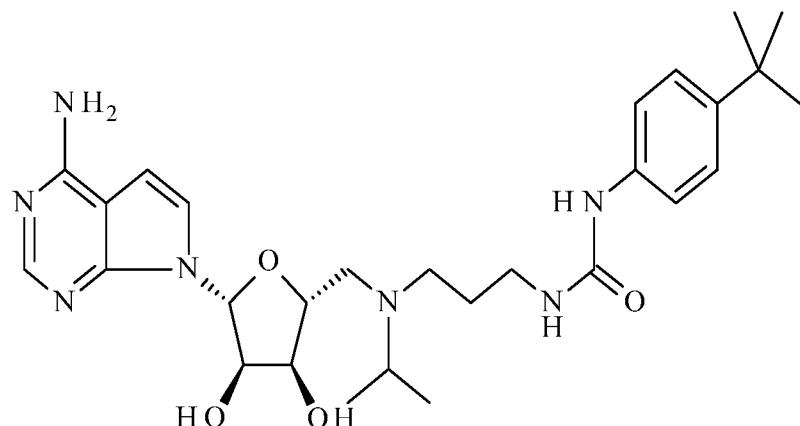
CPI-203: Cl



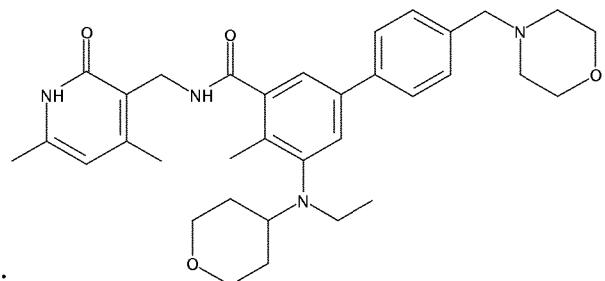
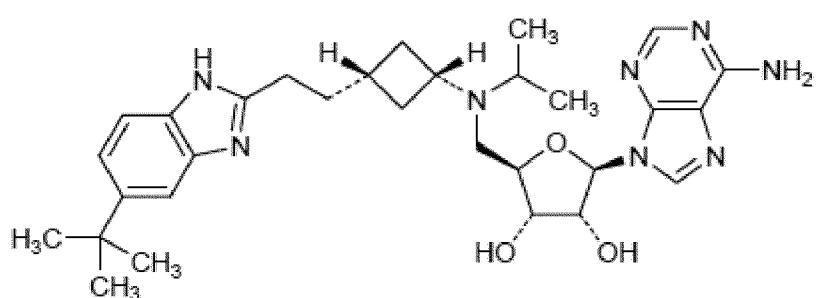
Docetaxel:



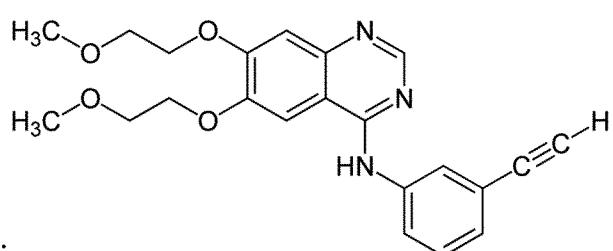
Doxorubicin:



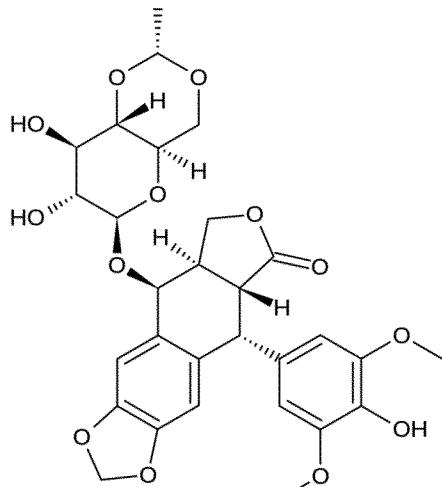
EPZ-5676 (Pinometostat):



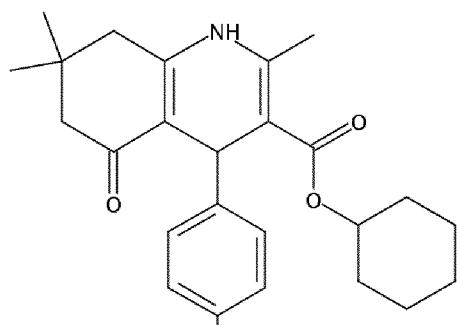
20



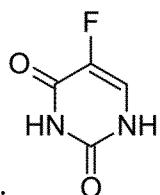
Erlotinib:



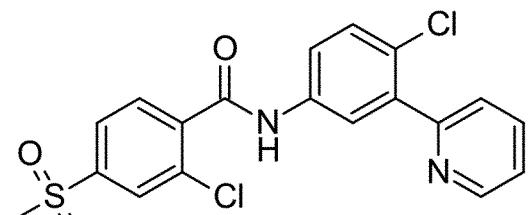
Etoposide:



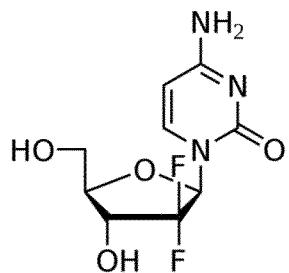
FLI 06:



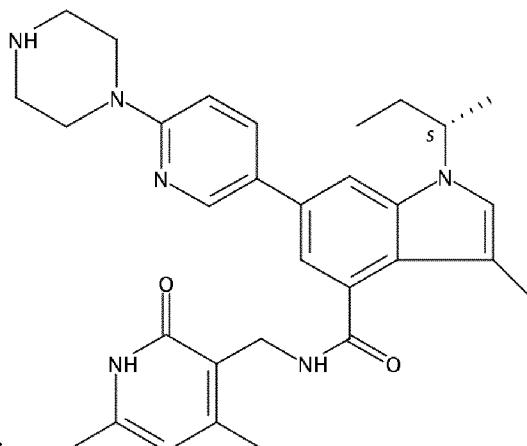
Fluorouracil:



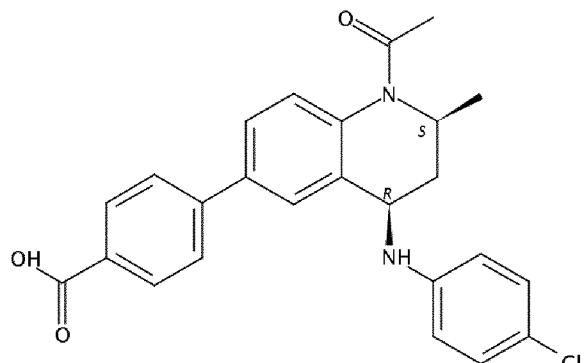
GDC-0449 (Vismodegib):



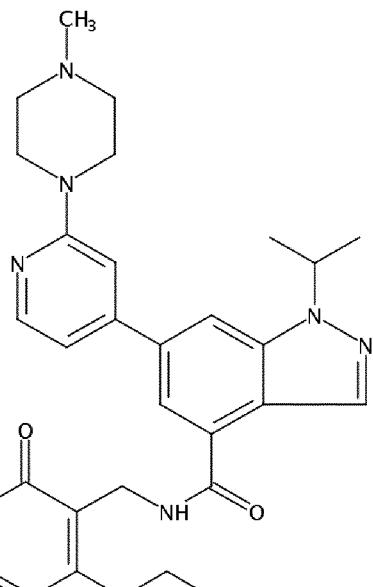
### Gemcitabine:



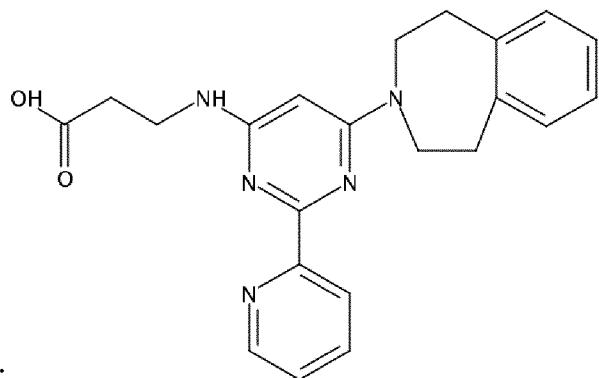
GSK126:



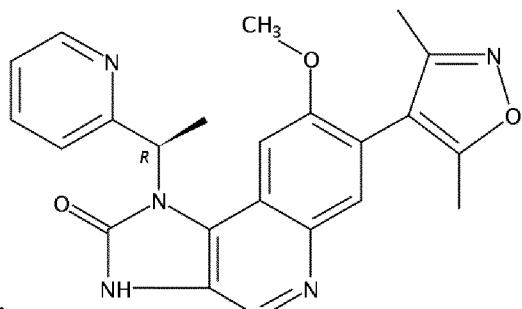
### GSK1324726A (I-BET726):



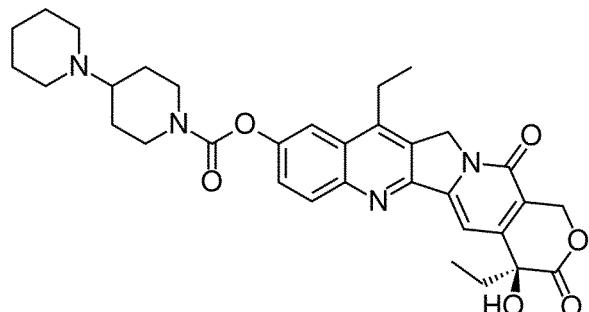
GSK343:



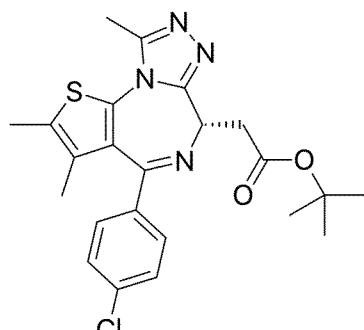
GSK-J1:



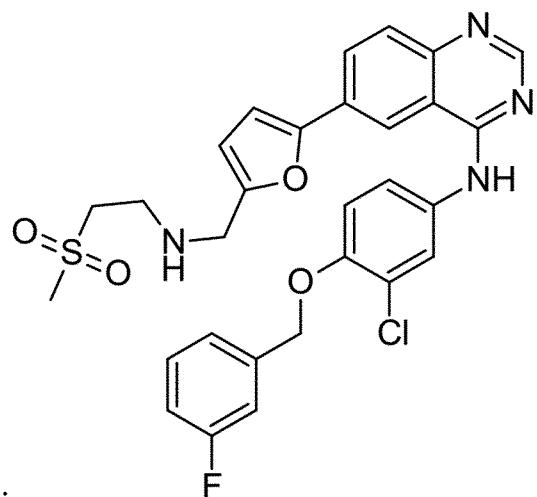
GSK1210151A (I-BET151):



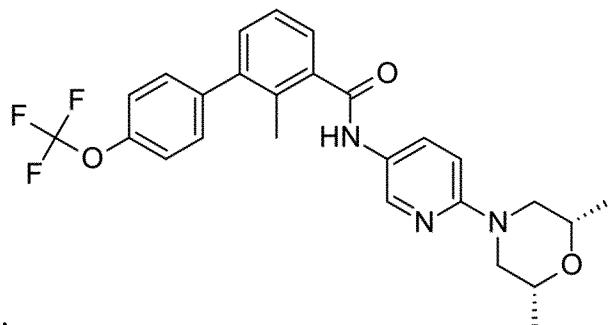
Irinotecan:



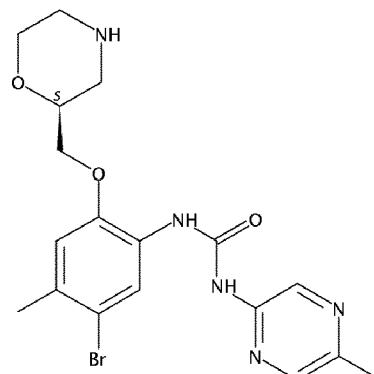
(+)-JQ1:



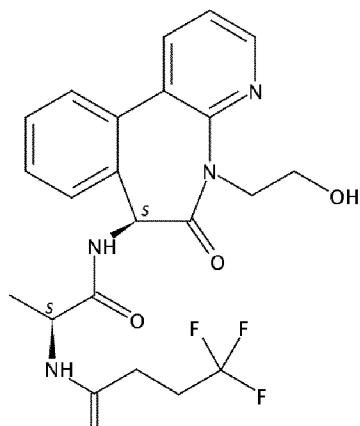
Lapatinib:



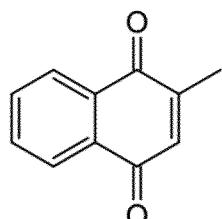
LDE225 (Sonidegib):



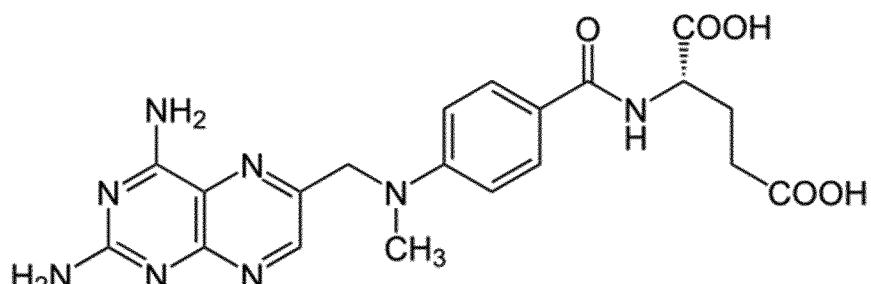
LY2603618:



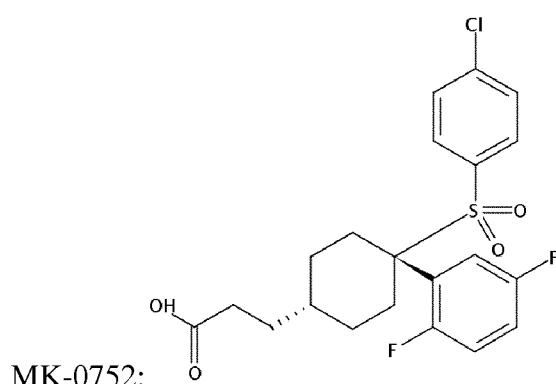
LY-3039478:



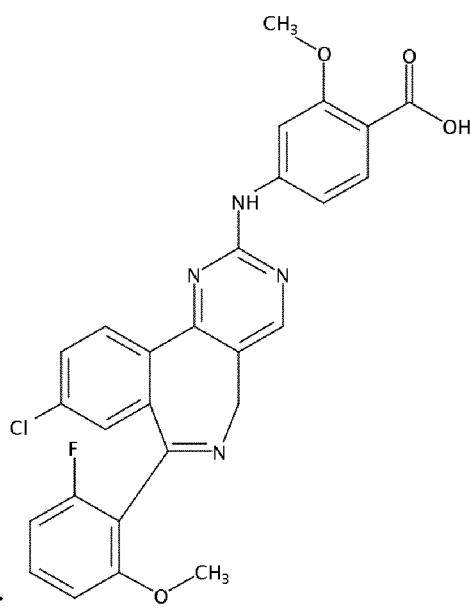
Menadione:



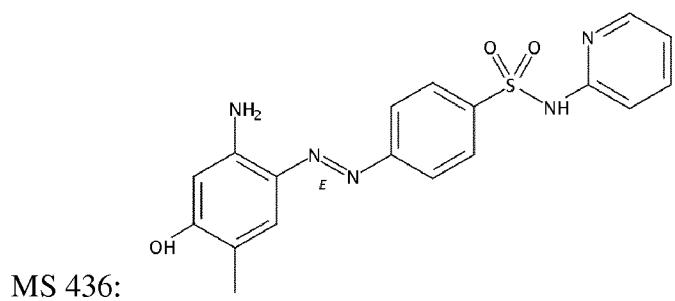
Methotrexate:



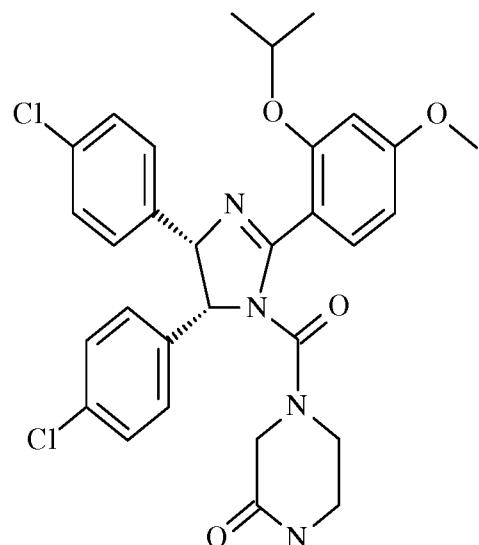
MK-0752:



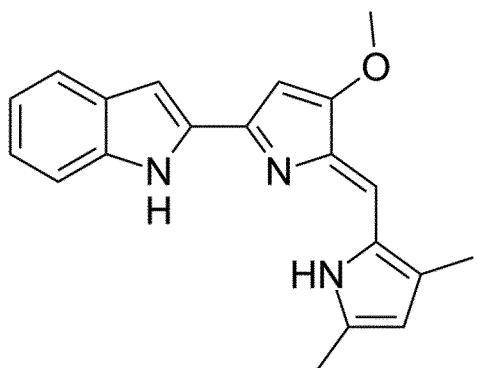
MLN8237 (Alisertib):



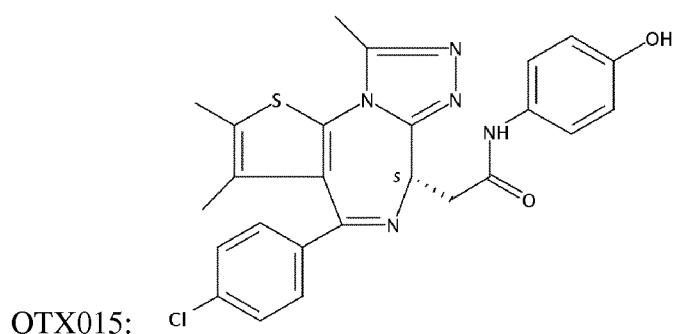
MS 436:



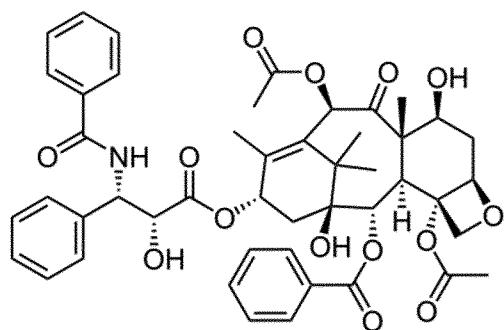
Nutlin-3A:



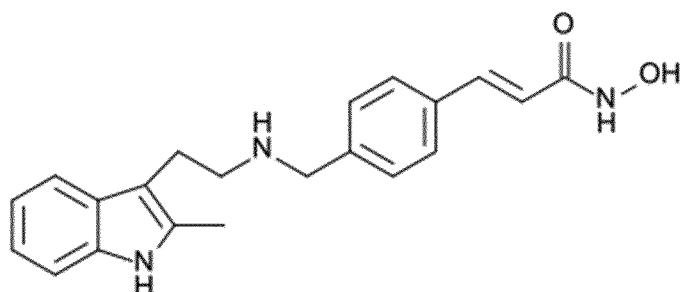
Obatoclax:



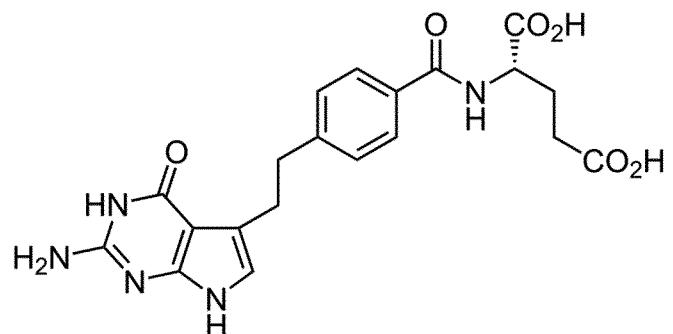
OTX015:



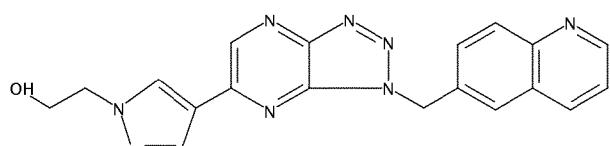
Paclitaxel:



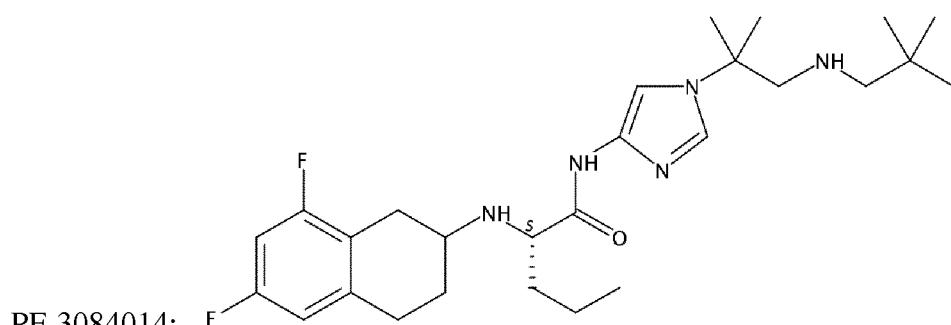
Panobinostat:

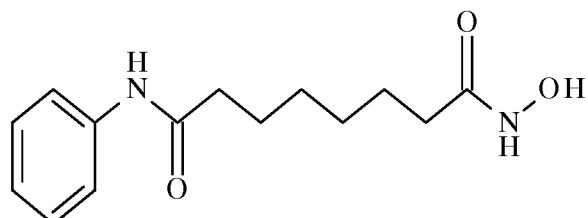


Pemetrexed:

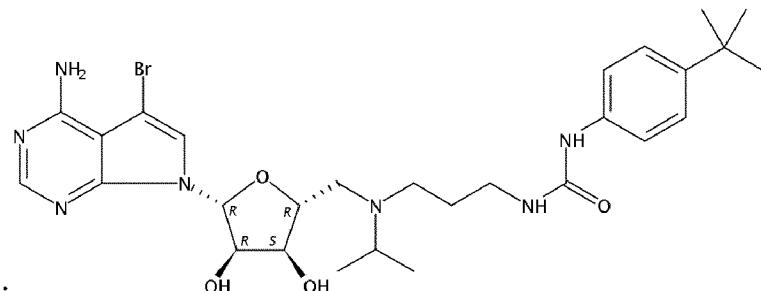


PF-04217903:

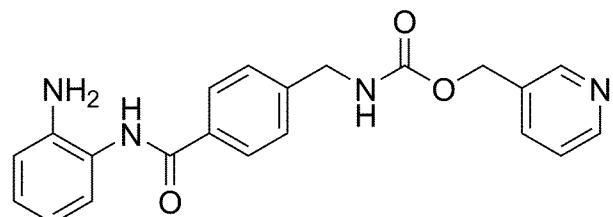




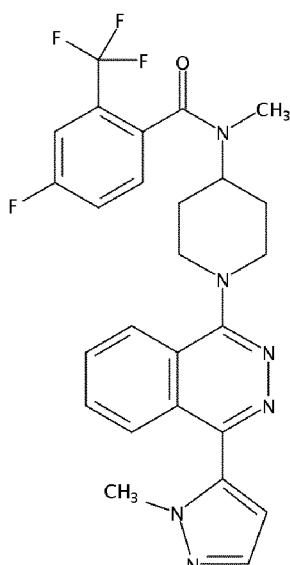
SAHA (Vorinostat):



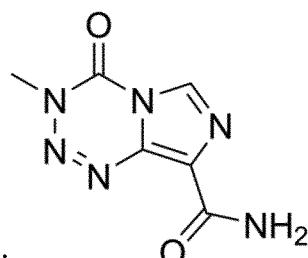
SGC 0946:



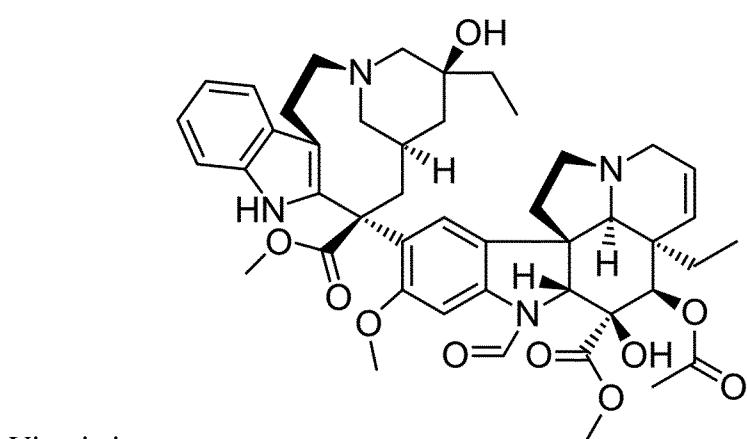
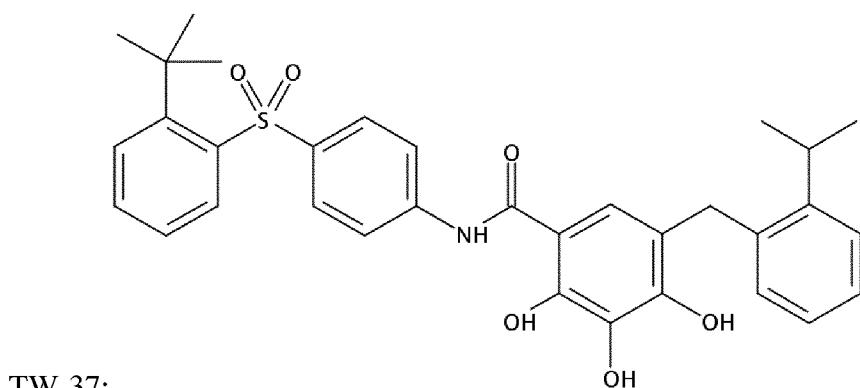
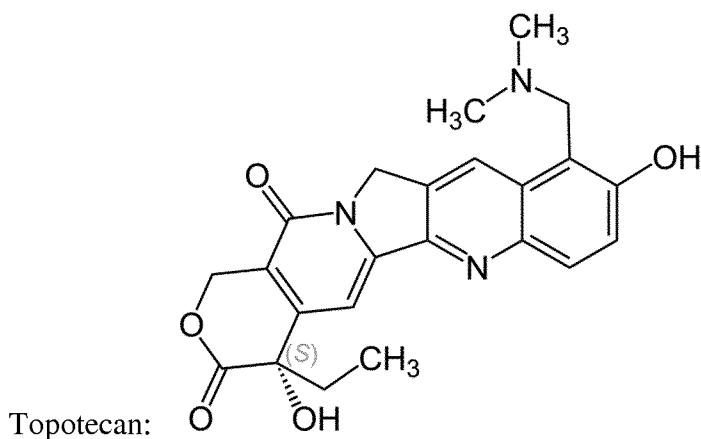
SNDX-275 (Entinostat):



Taladegib:



Temozolomide:



### **Detailed description of the invention**

5 Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, suitable methods and materials are described below.

10 All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety.

The nomenclature used in this Application is based on IUPAC systematic nomenclature, unless indicated otherwise.

Any open valency appearing on a carbon, oxygen, sulfur or nitrogen atom in the structures herein indicates the presence of hydrogen, unless indicated otherwise.

5 When indicating the number of substituents, the term “one or more” refers to the range from one substituent to the highest possible number of substitution, i.e. replacement of one hydrogen up to replacement of all hydrogens by substituents.

10 The term “optional” or “optionally” denotes that a subsequently described event or circumstance can but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not.

“The term “pharmaceutically acceptable salts” denotes salts which are not biologically or otherwise undesirable. Pharmaceutically acceptable salts include both acid and base addition salts.

15 The term “pharmaceutically acceptable acid addition salt” denotes those pharmaceutically acceptable salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, carbonic acid, phosphoric acid, and organic acids selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic, and sulfonic classes of organic acids such as formic acid, acetic acid, propionic acid, glycolic acid, gluconic acid, lactic acid, pyruvic acid, oxalic acid, malic acid, maleic acid, maloneic acid, 20 succinic acid, fumaric acid, tartaric acid, citric acid, aspartic acid, ascorbic acid, glutamic acid, anthranilic acid, benzoic acid, cinnamic acid, mandelic acid, embonic acid, phenylacetic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, and salicylic acid.

25 The term “pharmaceutically acceptable base addition salt” denotes those pharmaceutically acceptable salts formed with an organic or inorganic base. Examples of acceptable inorganic bases include sodium, potassium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, and aluminum salts. Salts derived from pharmaceutically acceptable organic nontoxic bases includes salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, 30 ethanolamine, 2-diethylaminoethanol, trimethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, and polyamine resins.

Stereochemical definitions and conventions used herein generally follow S. P. Parker<sup>100</sup>; and Eliel, E. and Wilen, S.<sup>101</sup>. In describing an optically active compound, the prefixes D and L, or R and S, are used to denote the absolute configuration of the molecule about its chiral center(s). The substituents attached to the chiral center under consideration are ranked in accordance with the Sequence Rule of Cahn, Ingold and Prelog<sup>102</sup>. The prefixes D and L or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or L designating that the compound is levorotatory. A compound prefixed with (+) or D is dextrorotatory.

The terms “pharmaceutical composition” and “pharmaceutical formulation” (or “formulation”) are used interchangeably and denote a mixture or solution comprising a therapeutically effective amount of an active pharmaceutical ingredient together with pharmaceutically acceptable excipients to be administered to a mammal, e.g., a human in need thereof.

The term “pharmaceutically acceptable” denotes an attribute of a material which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic, and neither biologically nor otherwise undesirable and is acceptable for veterinary as well as human pharmaceutical use.

The terms “pharmaceutically acceptable excipient”, “pharmaceutically acceptable carrier” and “therapeutically inert excipient” can be used interchangeably and denote any pharmaceutically acceptable ingredient in a pharmaceutical composition having no therapeutic activity and being non-toxic to the subject administered, such as disintegrators, binders, fillers, solvents, buffers, tonicity agents, stabilizers, antioxidants, surfactants, carriers, diluents or lubricants used in formulating pharmaceutical products.

The term “inhibitor” denotes a compound which competes with, reduces or prevents the binding of a particular ligand to a particular receptor or enzyme and/or which reduces or prevents the activity of a particular protein, e.g. of a receptor or an enzyme.

An “individual” or “subject” is a mammal. Mammals include, but are not limited to, domesticated animals (e.g., cows, sheep, cats, dogs, and horses), primates (e.g., humans and non-human primates such as monkeys), rabbits, and rodents (e.g., mice and rats). In certain embodiments, the individual or subject is a human.

The term “animal” as used herein comprises human beings and non-human animals. In one embodiment, a “non-human animal” is a mammal, for example a rodent such as rat or a mouse. In one embodiment, a non-human animal is a mouse.

The term “half maximal effective concentration” (EC50) denotes the plasma concentration of a particular compound or molecule required for obtaining 50% of the maximum of a particular effect in vivo.

The term “therapeutically effective amount” (or “effective amount”) denotes an amount 5 of a compound or molecule of the present invention that, when administered to a subject, (i) treats or prevents the particular disease, condition or disorder, (ii) attenuates, ameliorates or eliminates one or more symptoms of the particular disease, condition, or disorder, or (iii) prevents or delays the onset of one or more symptoms of the particular disease, condition or disorder described herein. The therapeutically effective amount will vary depending on the 10 compound, the disease state being treated, the severity of the disease treated, the age and relative health of the subject, the route and form of administration, the judgment of the attending medical or veterinary practitioner, and other factors.

The term “treating” or “treatment” of a disease state includes inhibiting the disease state, i.e., arresting the development of the disease state or its clinical symptoms, or relieving the 15 disease state, i.e., causing temporary or permanent regression of the disease state or its clinical symptoms.

The term “assessing a neoplastic disease” is used to indicate that the method according to the present invention will aid a medical professional including, e.g., a physician in assessing whether an individual has a neoplastic disease or is at risk of developing a neoplastic disease. 20 The levels of a gene panel as compared to one or more reference levels indicate whether the individual has a neoplastic disease or whether the individual is at risk of developing a neoplastic disease or prognosing the course of a neoplastic disease. In one embodiment the term assessing a neoplastic disease is used to indicate that the method according to the present invention will aid the medical professional in assessing whether an individual has a neoplastic disease or not. In 25 these embodiment levels of a gene panel as compared to one or more reference levels indicate whether the individual has a neoplastic disease.

The term “assessing a therapy” is used to indicate that the method according to the present invention will aid a medical professional including, e.g., a physician in assessing whether an individual having a neoplastic disease should be treated with an effective amount of an LSD1 30 inhibitor. Levels of the responder genes above the reference level, and/or levels of the non-responder genes below the reference level indicate that the patient should be treated with an effective amount of an LSD1 inhibitor. In certain embodiments, the term “at the reference level” refers to a level of a gene of the gene panel in the sample from the individual or patient that is essentially identical to the reference level or to a level that differs from the reference level by up 35 to 1%, up to 2%, up to 3%, up to 4%, up to 5%.

In certain embodiments, the term “above the reference level” refers to a level of a gene of the gene panel in the sample from the individual or patient above the reference level or to an overall increase of 5%, 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 100% or greater, determined by the methods described herein, as compared to the reference level.

5 In certain embodiments, the term increase refers to the increase in a level of a gene of the gene panel in the sample from the individual or patient wherein, the increase is at least about 1.5-, 1.75-, 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 15-, 20-, 25-, 30-, 40-, 50-, 60-, 70-, 75-, 80-, 90-, or 100-fold higher as compared to the reference level, e.g. predetermined from a reference sample.

In certain embodiments, the term “decrease” or “below” herein to a level of a gene of the gene panel in the sample from the individual or patient below the reference level or to an overall reduction of 5%, 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or greater, determined by the methods described herein, as compared to the reference level. In certain embodiments, the term decrease refers to a decrease in a level of a gene of the gene panel in the sample from the individual or patient wherein the decreased level is 15 at most about 0.9-, 0.8-, 0.7-, 0.6-, 0.5-, 0.4-, 0.3-, 0.2-, 0.1-, 0.05-, or 0.01- fold of the reference level, e.g. predetermined from a reference sample, or lower.

The term “biomarker” as used herein refers generally to a gene, the expression or presence of which in or on a mammalian tissue or cell can be detected by standard methods (or methods disclosed herein) and which may be predictive, diagnostic and/or prognostic for a 20 mammalian cell’s or tissue’s sensitivity to treatment regimens based on LSD1 inhibition by e.g. an LSD1 inhibitor such as (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine bis-hydrochloride. In certain embodiments, the level of such a biomarker is determined to be higher or lower than that observed for a reference sample.

The term “comparing” as used herein refers to comparing the level of the biomarker in 25 the sample from the individual or patient with the reference level of the biomarker specified elsewhere in this description. It is to be understood that comparing as used herein usually refers to a comparison of corresponding parameters or values, e.g., an absolute amount is compared to an absolute reference amount while a concentration is compared to a reference concentration or an intensity signal obtained from the biomarker in a sample is compared to the same type of 30 intensity signal obtained from a reference sample. The comparison may be carried out manually or computer assisted. Thus, the comparison may be carried out by a computing device (e.g., of a system disclosed herein). The value of the measured or detected level of the biomarker in the sample from the individual or patient and the reference level can be, e.g., compared to each other and the said comparison can be automatically carried out by a computer program executing an 35 algorithm for the comparison. The computer program carrying out the said evaluation will provide the desired assessment in a suitable output format. For a computer assisted comparison, the value of the determined amount may be compared to values corresponding to suitable

references which are stored in a database by a computer program. The computer program may further evaluate the result of the comparison, i.e. automatically provide the desired assessment in a suitable output format. For a computer assisted comparison, the value of the determined amount may be compared to values corresponding to suitable references which are stored in a 5 database by a computer program. The computer program may further evaluate the result of the comparison, i.e. automatically provides the desired assessment in a suitable output format.

The term “detecting” a biomarker as used herein refers to methods of detecting the presence of quantity of the biomarker in the sample employing appropriate methods of detection described elsewhere herein.

10 The term “measuring” the level of a biomarker, as used herein refers to the quantification of the biomarker, e.g. to determining the level of the biomarker in the sample, employing appropriate methods of detection described elsewhere herein.

15 The term “monitoring the efficacy of a therapy” is used to indicate that a sample is obtained at least once, including serially, from a patient before and/or under therapy with an LSD1 inhibitor and that gene panel levels are measured therein to obtain an indication whether the therapy is efficient or not.

20 In the monitoring of the efficacy of a therapy the gene panel levels are measured and in one embodiment compared to a reference value for the gene panel, or, in a further embodiment, it is compared to the gene panel levels in a sample obtained from the same patient at an earlier point in time, e.g. while said patient was already under therapy or before start of a therapy in said patient.

25 A “patient” or “subject” herein is any single human subject eligible for treatment who is experiencing or has experienced one or more signs, symptoms, or other indicators of a neoplastic disease. Intended to be included as a subject are any subjects involved in clinical research trials not showing any clinical sign of disease, or subjects involved in epidemiological studies, or subjects once used as controls. The subject may have been previously treated with an LSD1 inhibitor or another drug, or not so treated. The subject may be naïve to an additional drug(s) being used when the treatment herein is started, i.e., the subject may not have been previously treated with, for example, a therapy other than an LSD1 inhibitor at “baseline” (i.e., at a set point 30 in time before the administration of a first dose of Drug D in the treatment method herein, such as the day of screening the subject before treatment is commenced). Such “naïve” subjects are generally considered to be candidates for treatment with such additional drug(s).

35 The phrase “providing a diagnosis/assessment” as used herein refers to using the information or data generated relating to the gene panel levels in a sample of a patient to diagnose/assess a neoplastic disease in the patient. The information or data may be in any form,

written, oral or electronic. In some embodiments, using the information or data generated includes communicating, presenting, reporting, storing, sending, transferring, supplying, transmitting, dispensing, or combinations thereof. In some embodiments, communicating, presenting, reporting, storing, sending, transferring, supplying, transmitting, dispensing, or combinations thereof are performed by a computing device, analyzer unit or combination thereof. In some further embodiments, communicating, presenting, reporting, storing, sending, transferring, supplying, transmitting, dispensing, or combinations thereof are performed by a laboratory or medical professional. In some embodiments, the information or data includes a comparison of the gene panel levels to a reference level.

The phrase “recommending a treatment” as used herein refers to using the information or data generated relating to the gene panel levels in a sample of a patient to identify the patient as suitably treated or not suitably treated with a therapy. In some embodiment the therapy may comprise an LSD1 inhibitor. In some embodiments the phrase “recommending a treatment/therapy” includes the identification of a patient who requires adaptation of an effective amount of an LSD1 inhibitor being administered. In some embodiments recommending a treatment includes recommending that the amount of an LSD1 inhibitor being administered is adapted. The phrase “recommending a treatment” as used herein also may refer to using the information or data generated for proposing or selecting a therapy comprising an LSD1 inhibitor for a patient identified or selected as more or less likely to respond to the therapy comprising a LSD1 inhibitor. The information or data used or generated may be in any form, written, oral or electronic. In some embodiments, using the information or data generated includes communicating, presenting, reporting, storing, sending, transferring, supplying, transmitting, dispensing, or combinations thereof. In some embodiments, communicating, presenting, reporting, storing, sending, transferring, supplying, transmitting, dispensing, or combinations thereof are performed by a computing device, analyzer unit or combination thereof. In some further embodiments, communicating, presenting, reporting, storing, sending, transferring, supplying, transmitting, dispensing, or combinations thereof are performed by a laboratory or medical professional. In some embodiments, the information or data includes a comparison of the gene panel levels to a reference level. In some embodiments, the information or data includes an indication that the patient is suitably treated or not suitably treated with a therapy comprising an LSD1 inhibitor.

In certain embodiments, the term “reference level” herein refers to a predetermined value. In this context “level” encompasses the absolute amount, the relative amount or concentration as well as any value or parameter which correlates thereto or can be derived therefrom. As the skilled artisan will appreciate the reference level is predetermined and set to meet routine requirements in terms of e.g. specificity and/or sensitivity. These requirements can vary, e.g. from regulatory body to regulatory body. It may for example be that assay sensitivity or specificity, respectively, has to be set to certain limits, e.g. 80%, 90%, 95% or 98%, respectively.

These requirements may also be defined in terms of positive or negative predictive values. Nonetheless, based on the teaching given in the present invention it will always be possible for a skilled artisan to arrive at the reference level meeting those requirements. In one embodiment the reference level is determined in reference samples from healthy individuals. The reference level 5 in one embodiment has been predetermined in reference samples from the disease entity to which the patient belongs. In certain embodiments the reference level can e.g. be set to any percentage between 25% and 75% of the overall distribution of the values in a disease entity investigated. In other embodiments the reference level can e.g. be set to the median, tertiles or quartiles as determined from the overall distribution of the values in reference samples from a 10 disease entity investigated. In one embodiment the reference level is set to the median value as determined from the overall distribution of the values in a disease entity investigated. The reference level may vary depending on various physiological parameters such as age, gender or subpopulation, as well as on the means used for the determination of the gene panel levels referred to herein. In one embodiment, the reference sample is from essentially the same type of 15 cells, tissue, organ or body fluid source as the sample from the individual or patient subjected to the method of the invention, e.g. if according to the invention blood is used as a sample to determine the gene panel levels in the individual, the reference level is also determined in blood or a part thereof.

The phrase “responsive to” in the context of the present invention indicates that a patient 20 suffering from, being suspected to suffer or being prone to suffer from, or diagnosed with a disorder as described herein, shows a response to therapy comprising an LSD1 inhibitor.

The term “sample” refers to a sample of a body fluid, to a sample of separated cells or to a sample from a tissue or an organ. Samples of body fluids can be obtained by well-known 25 techniques and include, samples of blood, plasma, serum, urine, lymphatic fluid, sputum, ascites, bronchial lavage or any other bodily secretion or derivative thereof. Tissue or organ samples may be obtained from any tissue or organ by, e.g., biopsy. Separated cells may be obtained from the body fluids or the tissues or organs by separating techniques such as centrifugation or cell sorting. E.g., cell-, tissue- or organ samples may be obtained from those cells, tissues or organs which express or produce the biomarker. The sample may be frozen, fresh, fixed (e.g. formalin fixed), 30 centrifuged, and/or embedded (e.g. paraffin embedded), etc. The cell sample can, of course, be subjected to a variety of well-known post-collection preparative and storage techniques (e.g., nucleic acid and/or protein extraction, fixation, storage, freezing, ultrafiltration, concentration, evaporation, centrifugation, etc.) prior to assessing the amount of the marker in the sample. Likewise, biopsies may also be subjected to post-collection preparative and storage techniques, 35 e.g., fixation.

The phrase “selecting a patient” or “identifying a patient” as used herein refers to using the information or data generated relating to the gene panel levels in a sample of a patient to

identify or selecting the patient as more likely to benefit or less likely to benefit from a therapy comprising an LSD1 inhibitor. The information or data used or generated may be in any form, written, oral or electronic. In some embodiments, using the information or data generated includes communicating, presenting, reporting, storing, sending, transferring, supplying, 5 transmitting, dispensing, or combinations thereof. In some embodiments, communicating, presenting, reporting, storing, sending, transferring, supplying, transmitting, dispensing, or combinations thereof are performed by a computing device, analyzer unit or combination thereof. In some further embodiments, communicating, presenting, reporting, storing, sending, transferring, supplying, transmitting, dispensing, or combinations thereof are performed by a 10 laboratory or medical professional. In some embodiments, the information or data includes a comparison of the gene panel levels to a reference level. In some embodiments, the information or data includes an indication that the patient is more likely or less likely to respond to a therapy comprising an LSD1 inhibitor.

The phrase “selecting a therapy” as used herein refers to using the information or data 15 generated relating to the gene panel levels in a sample of a patient to identify or selecting a therapy for a patient. In some embodiment the therapy may comprise an LSD1 inhibitor. In some embodiments the phrase “identifying/selecting a therapy” includes the identification of a patient who requires adaptation of an effective amount of an LSD1 inhibitor being administered. In some embodiments recommending a treatment includes recommending that the amount of LSD1 20 inhibitor being administered is adapted. The phrase “recommending a treatment” as used herein also may refer to using the information or data generated for proposing or selecting a therapy comprising an LSD1 inhibitor for a patient identified or selected as more or less likely to respond to the therapy comprising an LSD1 inhibitor. The information or data used or generated may be in any form, written, oral or electronic. In some embodiments, using the information or data 25 generated includes communicating, presenting, reporting, storing, sending, transferring, supplying, transmitting, dispensing, or combinations thereof. In some embodiments, communicating, presenting, reporting, storing, sending, transferring, supplying, transmitting, dispensing, or combinations thereof are performed by a computing device, analyzer unit or combination thereof. In some further embodiments, communicating, presenting, reporting, 30 storing, sending, transferring, supplying, transmitting, dispensing, or combinations thereof are performed by a laboratory or medical professional. In some embodiments, the information or data includes a comparison of the gene panel levels to a reference level. In some embodiments, the information or data includes an indication that a therapy comprising an LSD1 inhibitor is suitable for the patient.

35 The term “responder gene” refers to the group of genes comprising ASCL1, HOXA10, NCAM1, NCAM2, NEUROD1, DDC, GRP, KRT8, ENO2, AVP, OXT, SYP, CHGA, CHGB, SOX21 and BCL2.

The term “non-responder gene” refers to the oncogene MYC.

The term “solid tumor” relates to an abnormal mass of tissue that usually does not contain cysts or liquid areas. Solid tumors may be benign (not cancer), or malignant (cancer). Different types of solid tumors are named for the type of cells that form them. Examples of solid tumors are sarcomas, carcinomas, and lymphomas. Leukemias (cancers of the blood) generally do not form solid tumors.

### Therapeutic Combinations

In detail, the present invention provides a therapeutic combination comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof, and one or more active pharmaceutical ingredients selected from a compound of Table 2 and pharmaceutically acceptable salts thereof.

In detail, the present invention provides a therapeutic combination comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof, and one or more active pharmaceutical ingredients selected from the list of ABT-199, ABT-263, ABT-737, ABT-888, ACY-1215, Belinostat, Bendamustine, BGJ398, BMS-906024, Carboplatin, CGK 733, Cisplatin, CPI-169, CPI-203, Docetaxel, Doxorubicin, EPZ-004777, EPZ005687, EPZ-5676, EPZ-6438, Erlotinib, Etoposide, FLI 06, Fluorouracil, GDC-0449, Gemcitabine, GSK126, GSK1324726A, GSK343, GSK-J1, GSK1210151A, Irinotecan, (+)-JQ1, Lapatinib, LDE225, LY2603618, LY-3039478, Menadione, Methotrexate, MK-0752, MLN8237, MS 436, Nutlin-3A, Obatoclax, OTX015, Paclitaxel, Panobinostat, Pemetrexed, PF-04217903, PF-3084014, SAHA, SGC 0946, SNDX-275, Taladegib, Temozolomide, Topotecan, TW-37, Vincristine and pharmaceutically acceptable salts thereof.

In detail, the present invention provides a therapeutic combination comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof, and one or more active pharmaceutical ingredients selected from BCL2 inhibitors, BET inhibitors, EZH2 inhibitors, DOT1L inhibitors, Chk inhibitors, DNA alkylating agents, HDAC inhibitors, topoisomerase inhibitors, anti-mitotic agents, Aurora kinase inhibitors and pharmaceutically acceptable salts thereof.

In detail, the present invention provides a therapeutic combination comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof, and one or more active pharmaceutical ingredients selected from BCL2 inhibitors, BET inhibitors, EZH2 inhibitors, DOT1L inhibitors and pharmaceutically acceptable salts thereof.

In detail, the present invention provides a therapeutic combination comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof, and one or more active pharmaceutical ingredients selected from BCL2 inhibitors, BET inhibitors and pharmaceutically acceptable salts thereof.

In detail, the present invention provides a therapeutic combination comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof, and one BCL2 inhibitor or a pharmaceutically acceptable salt thereof.

5 In detail, the present invention provides a therapeutic combination comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof, and one BCL2 inhibitor selected from the list of ABT-199, ABT-263, ABT-737, Obatoclax, TW-37 and a pharmaceutically acceptable salt thereof.

10 In detail, the present invention provides a therapeutic combination comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof, and one BET inhibitor or a pharmaceutically acceptable salt thereof.

15 In detail, the present invention provides a therapeutic combination comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof, and one BET inhibitor selected from the list of CPI-203, GSK1324726A, GSK1210151A, (+)-JQ1, MS 436, OTX015 and a pharmaceutically acceptable salt thereof.

20 In detail, the present invention provides a therapeutic combination comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof, and one EZH2 inhibitor or a pharmaceutically acceptable salt thereof.

25 In detail, the present invention provides a therapeutic combination comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof, and one EZH2 inhibitor selected from the list of CPI-169, EPZ005687, EPZ-6438, GSK126, GSK343 and a pharmaceutically acceptable salt thereof.

30 In detail, the present invention provides a therapeutic combination comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof, and one DOT1L inhibitor or a pharmaceutically acceptable salt thereof.

25 In detail, the present invention provides a therapeutic combination comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof, and one DOT1L inhibitor selected from the list of EPZ-004777, EPZ-5676, SGC 0946 and a pharmaceutically acceptable salt thereof.

30 In detail, the present invention provides a therapeutic combination comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof, and one Chk inhibitor or a pharmaceutically acceptable salt thereof.

25 In detail, the present invention provides a therapeutic combination comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof, and one Chk inhibitor selected from LY2603618 and a pharmaceutically acceptable salt thereof.

In detail, the present invention provides a therapeutic combination comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof, and one DNA alkylating agent or a pharmaceutically acceptable salt thereof.

5 In detail, the present invention provides a therapeutic combination comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof, and one DNA alkylating agent selected from the list of Bendamustine, Carboplatin, Cisplatin, Temozolomide and a pharmaceutically acceptable salt thereof.

10 In detail, the present invention provides a therapeutic combination comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof, and one HDAC inhibitor or a pharmaceutically acceptable salt thereof.

In detail, the present invention provides a therapeutic combination comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof, and one HDAC inhibitor selected from the list of ACY-1215, Belinostat, Panobinostat, SAHA, SNDX-275 or and a pharmaceutically acceptable salt thereof.

15 In detail, the present invention provides a therapeutic combination comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof, and one topoisomerase inhibitor or a pharmaceutically acceptable salt thereof.

20 In detail, the present invention provides a therapeutic combination comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof, and one topoisomerase inhibitor selected from the list of Etoposide, Irinotecan, Topotecan and a pharmaceutically acceptable salt thereof.

In detail, the present invention provides a therapeutic combination comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof, and one Aurora kinase inhibitor or a pharmaceutically acceptable salt thereof.

25 In detail, the present invention provides a therapeutic combination comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof, and one Aurora kinase inhibitor selected from the list of MLN8237 and a pharmaceutically acceptable salt thereof.

In detail, the present invention provides a therapeutic combination comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof, and one anti-mitotic agent or a pharmaceutically acceptable salt thereof.

30 In detail, the present invention provides a therapeutic combination comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof, and one anti-mitotic agent selected from Docetaxel, Paclitaxel, Vincristine and a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a therapeutic combination comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof, a topoisomerase inhibitor or a pharmaceutically acceptable salt thereof, and a DNA alkylating agent or a pharmaceutically acceptable salt thereof.

5 In one embodiment, the present invention provides a therapeutic combination comprising (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine or a pharmaceutically acceptable salt thereof, a topoisomerase inhibitor or a pharmaceutically acceptable salt thereof, and a DNA alkylating agent or a pharmaceutically acceptable salt thereof.

10 In one embodiment, the present invention provides a therapeutic combination comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof, etoposide or a pharmaceutically acceptable salt thereof, and carboplatin or a pharmaceutically acceptable salt thereof.

15 In one embodiment, the present invention provides a therapeutic combination comprising (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine or a pharmaceutically acceptable salt thereof, etoposide or a pharmaceutically acceptable salt thereof, and carboplatin or a pharmaceutically acceptable salt thereof.

In one embodiment of the invention, the therapeutic combination yields a synergy score above 6.4, particularly above 8, more particularly above 10, most particularly above 15.

20 In one embodiment of the invention, the therapeutic combination yields a synergy score above 6.4, particularly above 8, more particularly above 10, most particularly above 15, wherein the synergy score was calculated as:

$$\text{Synergy Score} = \log f_X \log f_Y \sum \max(0, I_{\text{data}})(I_{\text{data}} - I_{\text{Loewe}})$$

### LSD1 inhibitors

In one aspect of the present invention, the LSD1 inhibitor is selected from a compound as described in WO 2011/131697<sup>2</sup>, WO 2012135113<sup>3</sup> and WO 2013/057322<sup>4</sup>.

25 In a particular embodiment of the invention the LSD1 inhibitor is selected from the list of:

4-[[4-[[[(1R,2S)-2-phenylcyclopropyl]amino]methyl]-1-piperidinyl]methyl]-benzoic acid, (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine,

(R)-1-(4-((trans)-2-phenylcyclopropyl)amino)cyclohexyl)pyrrolidin-3-amine,

4-(aminomethyl)-N-((trans)-2-phenylcyclopropyl)cyclohexanamine,

30 N1-((trans)-2-phenylcyclopropyl)cyclohexane-1,3-diamine,

N1-((trans)-2-phenylcyclopropyl)cyclobutane-1,3-diamine,

N1-((trans)-2-phenylcyclopropyl)-2,3-dihydro-1H-indene-1,3-diamine,

N1-methyl-N4-((trans)-2-phenylcyclopropyl)cyclohexane-1,4-diamine,  
N1-((trans)-2-(4-bromophenyl)cyclopropyl)cyclohexane-1,4-diamine,  
N1-(2-(o-tolyl)cyclopropyl)cyclohexane-1,4-diamine,  
N1-(2-(4-methoxyphenyl)cyclopropyl)cyclohexane-1,4-diamine,  
5 N1-(2-(2-fluorophenyl)cyclopropyl)cyclohexane-1,4-diamine,  
N1-(2-(naphthalen-2-yl)cyclopropyl)cyclohexane-1,4-diamine,  
N-(4'-((trans)-2-((4-aminocyclohexyl)amino)cyclopropyl)-[1,1'-biphenyl]-3-yl)-2-  
cyanobenzenesulfonamide,  
N1-((trans)-2-(4-(pyridin-3-ylmethoxy)phenyl)cyclopropyl)cyclohexane-1,4-diamine,  
10 and a pharmaceutically acceptable salt thereof.

In a particular embodiment of the invention the LSD1 inhibitor is selected from the list of:

4-[[4-[[[(1R,2S)-2-phenylcyclopropyl]amino]methyl]-1-piperidinyl]methyl]-benzoic acid,  
(trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine,  
(R)-1-(4-(((trans)-2-phenylcyclopropyl)amino)cyclohexyl)pyrrolidin-3-amine,  
15 4-(aminomethyl)-N-((trans)-2-phenylcyclopropyl)cyclohexanamine,  
N1-((trans)-2-phenylcyclopropyl)cyclohexane-1,3-diamine,  
N1-((trans)-2-phenylcyclopropyl)cyclobutane-1,3-diamine,  
N1-((trans)-2-phenylcyclopropyl)-2,3-dihydro-1H-indene-1,3-diamine,  
N1-methyl-N4-((trans)-2-phenylcyclopropyl)cyclohexane-1,4-diamine,  
20 N1-((trans)-2-(4-bromophenyl)cyclopropyl)cyclohexane-1,4-diamine,  
N1-(2-(o-tolyl)cyclopropyl)cyclohexane-1,4-diamine,  
N1-(2-(4-methoxyphenyl)cyclopropyl)cyclohexane-1,4-diamine,  
N1-(2-(2-fluorophenyl)cyclopropyl)cyclohexane-1,4-diamine,  
N1-(2-(naphthalen-2-yl)cyclopropyl)cyclohexane-1,4-diamine,  
25 N-(4'-((trans)-2-((4-aminocyclohexyl)amino)cyclopropyl)-[1,1'-biphenyl]-3-yl)-2-  
cyanobenzenesulfonamide, and  
N1-((trans)-2-(4-(pyridin-3-ylmethoxy)phenyl)cyclopropyl)cyclohexane-1,4-diamine,  
or a pharmaceutically acceptable salt thereof.

In a particular embodiment of the invention the LSD1 inhibitor is selected from the list of:

30 4-[[4-[[[(1R,2S)-2-phenylcyclopropyl]amino]methyl]-1-piperidinyl]methyl]-benzoic acid (trans)-  
N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine,  
(R)-1-(4-(((trans)-2-phenylcyclopropyl)amino)cyclohexyl)pyrrolidin-3-amine,  
4-(aminomethyl)-N-((trans)-2-phenylcyclopropyl)cyclohexanamine,  
N1-((trans)-2-phenylcyclopropyl)cyclohexane-1,3-diamine,  
35 N1-((trans)-2-phenylcyclopropyl)cyclobutane-1,3-diamine,  
N1-((trans)-2-phenylcyclopropyl)-2,3-dihydro-1H-indene-1,3-diamine,  
N1-methyl-N4-((trans)-2-phenylcyclopropyl)cyclohexane-1,4-diamine,

N1-((trans)-2-(4-bromophenyl)cyclopropyl)cyclohexane-1,4-diamine,  
N1-(2-(o-tolyl)cyclopropyl)cyclohexane-1,4-diamine,  
N1-(2-(4-methoxyphenyl)cyclopropyl)cyclohexane-1,4-diamine,  
N1-(2-(2-fluorophenyl)cyclopropyl)cyclohexane-1,4-diamine,  
5 N1-(2-(naphthalen-2-yl)cyclopropyl)cyclohexane-1,4-diamine,  
N-(4'-((trans)-2-((4-aminocyclohexyl)amino)cyclopropyl)-[1,1'-biphenyl]-3-yl)-2-  
cyanobenzenesulfonamide,  
N1-((trans)-2-(4-(pyridin-3-ylmethoxy)phenyl)cyclopropyl)cyclohexane-1,4-diamine,  
and a pharmaceutically acceptable salt thereof.

10 In a particular embodiment of the invention the LSD1 inhibitor is GSK2879552 [CAS Reg. No. 1401966-69-5], also known as 4-[[4-[[[(1R,2S)-2-phenylcyclopropyl]amino]methyl]-1-piperidinyl]methyl]-benzoic acid, or a pharmaceutically acceptable salt thereof.

In a particular embodiment of the invention the LSD1 inhibitor is selected from the list of:  
(trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine,

15 (R)-1-(4-(((trans)-2-phenylcyclopropyl)amino)cyclohexyl)pyrrolidin-3-amine,

4-(aminomethyl)-N-((trans)-2-phenylcyclopropyl)cyclohexanamine,

N1-((trans)-2-phenylcyclopropyl)cyclohexane-1,3-diamine,

N1-((trans)-2-phenylcyclopropyl)cyclobutane-1,3-diamine,

N1-((trans)-2-phenylcyclopropyl)-2,3-dihydro-1H-indene-1,3-diamine,

20 N1-methyl-N4-((trans)-2-phenylcyclopropyl)cyclohexane-1,4-diamine,

N1-((trans)-2-(4-bromophenyl)cyclopropyl)cyclohexane-1,4-diamine,

N1-(2-(o-tolyl)cyclopropyl)cyclohexane-1,4-diamine,

N1-(2-(4-methoxyphenyl)cyclopropyl)cyclohexane-1,4-diamine,

N1-(2-(2-fluorophenyl)cyclopropyl)cyclohexane-1,4-diamine,

25 N1-(2-(naphthalen-2-yl)cyclopropyl)cyclohexane-1,4-diamine,

N-(4'-((trans)-2-((4-aminocyclohexyl)amino)cyclopropyl)-[1,1'-biphenyl]-3-yl)-2-  
cyanobenzenesulfonamide,

N1-((trans)-2-(4-(pyridin-3-ylmethoxy)phenyl)cyclopropyl)cyclohexane-1,4-diamine,

and a pharmaceutically acceptable salt thereof.

30 In a particular embodiment of the invention the LSD1 inhibitor is (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine [CAS Reg. No. 1431304-21-0] or a pharmaceutically acceptable salt thereof.

In a particular embodiment of the invention the LSD1 inhibitor is (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine [CAS Reg. No. 1431304-21-0] or a hydrochloride salt thereof.

In a particular embodiment of the invention the LSD1 inhibitor is (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine bis-hydrochloride [CAS Reg. No. 1431303-72-8].

### Combination Therapies

The therapeutic combinations may be used for the treatment of a hyperproliferative disease or disorder, including tumors, cancers, and neoplastic tissue, along with pre-malignant and non-neoplastic or non-malignant hyperproliferative disorders. In certain embodiments, a combination of the invention is combined in a dosing regimen as combination therapy, with another compound that has anti-hyperproliferative properties or that is useful for treating the hyperproliferative disorder. The additional compound of the dosing regimen preferably has complementary activities to the combination, and such that they do not adversely affect each other. Such compounds may be administered in amounts that are effective for the purpose intended. In one embodiment, the therapeutic combination is administered by a dosing regimen wherein the therapeutically effective amount of an LSD1 inhibitor or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt thereof is administered in a range from twice daily to once every three weeks (q3wk), and the therapeutically effective amount of one or more active pharmaceutical ingredients selected from a compound of Table 2 and pharmaceutically acceptable salts thereof is administered in a range from twice daily to once every three weeks.

The combination therapy may be administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations. The combined administration includes coadministration, using separate formulation, and consecutive administration in either order, wherein preferably there is a time period while both (or all) active agents simultaneously exert their biological activities.

In one specific aspect of the invention, the LSD1 inhibitor or a pharmaceutically acceptable salt thereof can be administered for a time period of about 1 to about 10 days after administration of the one or more active pharmaceutical ingredients selected from a compound of Table 2 and pharmaceutically acceptable salts thereof begins. In another specific aspect of the invention, the LSD1 inhibitor or a pharmaceutically acceptable salt thereof can be administered for a time period of about 1 to 10 days before administration of the one or more active pharmaceutical ingredients selected from a compound of Table 2 and pharmaceutically acceptable salts thereof begins. In another specific aspect of the invention, administration of the LSD1 inhibitor or a pharmaceutically acceptable salt thereof and administration of the one or more active pharmaceutical ingredients selected from a compound of Table 2 and pharmaceutically acceptable salts thereof begin on the same day.

In one specific aspect of the invention, the one or more active pharmaceutical ingredients selected from a compound of Table 2 and pharmaceutically acceptable salts thereof can be

administered for a time period of about 1 to about 10 days after administration of the LSD1 inhibitor or a pharmaceutically acceptable salt thereof begins. In another specific aspect of the invention, the one or more active pharmaceutical ingredients selected from a compound of Table 2 and pharmaceutically acceptable salts thereof can be administered for a time period of about 1

5 to 10 days before administration of the LSD1 inhibitor or a pharmaceutically acceptable salt thereof begins. In another specific aspect of the invention, administration of one or more active pharmaceutical ingredients selected from a compound of Table 2 and pharmaceutically acceptable salts thereof and administration of the LSD1 inhibitor or a pharmaceutically acceptable salt thereof begin on the same day.

10 Suitable dosages for any of the above co-administered agents are those presently used and may be lowered due to the combined action (synergy) of the newly identified agent and other chemotherapeutic agents or treatments, such as to increase the therapeutic index or mitigate toxicity or other side-effects or consequences.

15 In a particular embodiment of anti-cancer therapy, the therapeutic combination may be combined with surgical therapy and radiotherapy. The amounts of the combination and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.

20 In one particular embodiment of the invention, the SCLC cells are sensitized through administration of an LSD1 inhibitor prior to administration of the therapeutic combinations as described herein.

In one particular embodiment of the invention, the SCLC cells are sensitized through administration of (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine, or a pharmaceutically acceptable salt thereof, prior to administration of the therapeutic combinations as described herein.

25 In one particular embodiment of the invention, the SCLC cells are sensitized through administration of (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine, or a pharmaceutically acceptable salt thereof, five days on/two days off (5/2) for three weeks prior to administration of the therapeutic combinations as described herein.

30 In one particular embodiment of the invention, the SCLC cells are sensitized through administration of (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine, or a pharmaceutically acceptable salt thereof, at a dose of 40 µg per kg (upk) five days on/two days off (5/2) for three weeks prior to administration of the therapeutic combinations as described herein.

In one particular embodiment of the invention, the SCLC cells are sensitized through administration of (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine, or a pharmaceutically acceptable salt thereof, at a dose of 40 µg per kg (upk) five days on/two days off (5/2) for three weeks prior to administration of a therapeutic combination comprising

5 Etoposide, Carboplatin and (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine, or a pharmaceutically acceptable salt thereof.

In one particular embodiment of the invention, the SCLC cells are sensitized through administration of (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine, or a pharmaceutically acceptable salt thereof, at a dose of 40 µg per kg (upk) five days on/two days off (5/2) for three weeks prior to administration of a therapeutic combination comprising

10 Etoposide at a dose of 5 mg per kg (mpk) daily for five days (qdx5), Carboplatin at a dose of 100 mpk weekly for three weeks (qwkx3) and (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine, or a pharmaceutically acceptable salt thereof, at a dose of 20 upk five days on/two days off for three weeks.

15 One particular embodiment of the invention relates to a method for the treatment of a neoplastic disease, which method comprises sensitizing through administration of an LSD1 inhibitor followed by administering an effective amount of a therapeutic combination as described herein to a human being or animal.

20 One particular embodiment of the invention relates to a method for the treatment of a neoplastic disease, which method comprises sensitizing through administration of (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine or a pharmaceutically acceptable salt thereof followed by administering an effective amount of a therapeutic combination as described herein to a human being or animal.

25 One particular embodiment of the invention relates to a method for the treatment of a neoplastic disease, which method comprises sensitizing through administration of (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine or a pharmaceutically acceptable salt thereof five days on/two days off (5/2) for three weeks followed by administering an effective amount of a therapeutic combination as described herein to a human being or animal.

30 One particular embodiment of the invention relates to a method for the treatment of a neoplastic disease, which method comprises sensitizing through administration of (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine or a pharmaceutically acceptable salt thereof at a dose of 40 µg per kg (upk) five days on/two days off (5/2) for three weeks followed by administering an effective amount of a therapeutic combination as described herein to a human being or animal.

One particular embodiment of the invention relates to a method for the treatment of a neoplastic disease, which method comprises sensitizing through administration of (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine or a pharmaceutically acceptable salt thereof at a dose of 40 µg per kg (upk) five days on/two days off (5/2) for three weeks followed

5 by administering an effective amount of a therapeutic combination comprising Etoposide, Carboplatin and (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine to a human being or animal.

One particular embodiment of the invention relates to a method for the treatment of a neoplastic disease, which method comprises sensitizing through administration of (trans)-N1-

10 ((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine or a pharmaceutically acceptable salt thereof at a dose of 40 µg per kg (upk) five days on/two days off (5/2) for three weeks followed by administering an effective amount of a therapeutic combination comprising Etoposide at a dose of 5 mg per kg (mpk) daily for five days (qdx5), Carboplatin at a dose of 100 mpk weekly for three weeks (qwkx3) and (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine

15 at a dose of 20 upk five days on/two days off for three weeks to a human being or animal.

### Pharmaceutical Compositions

Another embodiment provides pharmaceutical compositions or medicaments comprising a therapeutic combination as described herein and a pharmaceutically acceptable excipient.

Compositions are formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners.

The therapeutic combinations as described herein may be administered by any suitable means, including oral, topical (including buccal and sublingual), rectal, vaginal, transdermal, parenteral, subcutaneous, intraperitoneal, intrapulmonary, intradermal, intrathecal and epidural and intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration.

30 The therapeutic combinations as described herein may be administered in any convenient administrative form, e.g., tablets, powders, capsules, solutions, dispersions, suspensions, syrups, sprays, suppositories, gels, emulsions, patches, etc. Such compositions may comprise components conventional in pharmaceutical preparations, e.g., diluents, carriers, pH modifiers, preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants,

flavorants, salts for varying the osmotic pressure, buffers, masking agents, antioxidants, and further active agents. They can also comprise still other therapeutically valuable substances.

A typical formulation is prepared by mixing a therapeutic combination as described herein and a pharmaceutically acceptable excipient. Suitable excipients are well known to those skilled in the art and are described in detail in, e.g., Ansel H.C. *et al.*<sup>103</sup>; Rowe R.C.<sup>104</sup> and Gennaro A.R. *et al.*<sup>105</sup>. The formulations may also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents, diluents and other known additives to provide an elegant presentation of the drug (i.e., a compound of the present invention or pharmaceutical composition thereof) or aid in the manufacturing of the pharmaceutical product (i.e., medicament).

The dosage at which therapeutic combination as described herein can be administered can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case.

An example of a suitable oral dosage form is a tablet comprising about 0.01 mg to 10 mg of a therapeutic combination as described herein compounded with about 90 to 30 mg anhydrous lactose, about 5 to 40 mg sodium croscarmellose, about 5 to 30 mg polyvinylpyrrolidone (PVP) K30, and about 1 to 10 mg magnesium stearate. The powdered ingredients are first mixed together and then mixed with a solution of the PVP. The resulting composition can be dried, granulated, mixed with the magnesium stearate and compressed to tablet form using conventional equipment.

An example of an aerosol formulation can be prepared by dissolving a therapeutic combination as described herein, for example 0.1 to 100 mg, in a suitable buffer solution, e.g. a phosphate buffer, adding a tonicifier, e.g. a salt such as sodium chloride, if desired. The solution may be filtered, e.g., using a 0.2  $\mu$ m filter, to remove impurities and contaminants.

Another embodiment relates to a pharmaceutical composition comprising a therapeutic combination as described herein and one or more pharmaceutically acceptable excipient.

### **Articles of Manufacture**

In another embodiment of the invention, an article of manufacture, or "kit", containing a combination useful for the treatment of the diseases and disorders described above is provided.

In one embodiment, the kit comprises a container and a therapeutic combination as described herein.

One embodiment of the invention provides an article of manufacture comprising a therapeutic combination as described herein useful in the treatment of a neoplastic disease.

The kit may further comprise a label or package insert, on or associated with the container. The term "package insert" is used to refer to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications, usage, dosage, administration, contraindications and/or warnings concerning the use of such therapeutic products. Suitable containers include, for example, bottles, vials, syringes, blister pack, etc. The container may be formed from a variety of materials such as glass or plastic. The container may hold a combination, or a formulation thereof, which is effective for treating the condition and may have a sterile access port (for example, the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). The label or package insert indicates that the composition is used for treating the condition of choice, such as cancer. In one embodiment, the label or package inserts indicates that the composition comprising the combination can be used to treat a disorder resulting from abnormal cell growth.

The label or package insert may also indicate that the composition can be used to treat other disorders. Alternatively, or additionally, the article of manufacture may further comprise a second container comprising a pharmaceutically acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

The kit may further comprise directions for the administration of the combination, and, if present, the second pharmaceutical formulation. For example, if the kit comprises a first composition comprising the LSD1 inhibitor or a pharmaceutically acceptable salt thereof and a second pharmaceutical formulation comprising one or more active pharmaceutical ingredients selected from a compound of Table 2 and pharmaceutically acceptable salts thereof, the kit may further comprise directions for the simultaneous, sequential or separate administration of the first and second pharmaceutical compositions to a patient in need thereof.

In another embodiment, the kits are suitable for the delivery of solid oral forms of a combination, such as tablets or capsules. Such a kit preferably includes a number of unit dosages. Such kits can include a card having the dosages oriented in the order of their intended use. An example of such a kit is a "blister pack". Blister packs are well known in the packaging industry and are widely used for packaging pharmaceutical unit dosage forms. If desired, a memory aid can be provided, for example in the form of numbers, letters, or other markings or with a calendar insert, designating the days in the treatment schedule in which the dosages can be administered.

According to one embodiment, a kit may comprise (a) a first container with the LSD1 inhibitor or a pharmaceutically acceptable salt thereof contained therein; (b) a second container with one or more active pharmaceutical ingredients selected from a compound of Table 2 and pharmaceutically acceptable salts thereof and (c) a third container with a third pharmaceutical formulation contained therein, wherein the third pharmaceutical formulation comprises another compound with anti-hyperproliferative activity. Alternatively, or additionally, the kit may comprise another container comprising a pharmaceutically-acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

Where the kit comprises a composition of the LSD1 inhibitor or a pharmaceutically acceptable salt thereof and one or more active pharmaceutical ingredients selected from a compound of Table 2 and pharmaceutically acceptable salts thereof, the kit may comprise a container for containing the separate compositions such as a divided bottle or a divided foil packet, however, the separate compositions may also be contained within a single, undivided container. Typically, the kit comprises directions for the administration of the separate components. The kit form is particularly advantageous when the separate components are preferably administered in different dosage forms (e.g., oral and parenteral), are administered at different dosage intervals, or when titration of the individual components of the combination is desired by the prescribing physician.

### **Medical Uses and Methods of Treatment**

Another embodiment relates to a therapeutic combination as described herein for use as therapeutically active substance.

Another embodiment relates to a therapeutic combination as described herein for use in the treatment of a neoplastic disease.

Another embodiment relates to a method for the treatment of a neoplastic disease, which method comprises administering an effective amount of a therapeutic combination as described herein to a human being or animal.

Another embodiment relates to the use of a therapeutic combination as described herein for the treatment of a neoplastic disease.

Another embodiment relates to the use of a therapeutic combination as described herein for the preparation of medicaments useful in the treatment of a neoplastic disease.

In a particular embodiment of the invention the therapeutic combination as described herein is administered to a patient in need thereof orally, such as an oral solution.

In a particular embodiment of the invention the neoplastic disease that is potentially treatable by the therapeutic combination as described herein is a cancer, particularly a cancer selected from the group consisting of breast cancer, prostate cancer, cervical cancer, ovarian cancer, gastric cancer, colorectal cancer (i.e. including colon cancer and rectal cancer),  
5 pancreatic cancer, liver cancer, brain cancer, neuroendocrine cancer, lung cancer, kidney cancer, hematological malignancies, melanoma and sarcomas.

In a particular embodiment of the invention the cancer that is potentially treatable by the therapeutic combination as described herein is selected from the group consisting of hematological malignancies, neuroendocrine cancer, breast cancer, cervical cancer, ovarian  
10 cancer, colorectal cancer, melanoma and lung cancer.

In a particular embodiment of the invention the neoplastic disease is a cancer selected from the group consisting of blood cancer or lung cancer, more particularly acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), chronic neutrophilic leukemia, chronic eosinophilic leukemia, chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia  
15 (ALL), hairy cell leukemia, small cell lung carcinoma (SCLC) and non-small-cell lung carcinoma (NSCLC).

In a particular embodiment of the invention the neoplastic disease is a blood cancer or lung cancer selected from the group of acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), chronic neutrophilic leukemia, chronic eosinophilic leukemia,  
20 chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), hairy cell leukemia, small cell lung carcinoma (SCLC) and non-small-cell lung carcinoma (NSCLC).

In a particular embodiment of the invention the neoplastic disease is a cancer is selected from the group consisting of acute myeloid leukemia (AML), non-Hodgkin's lymphoma, small cell lung cancer (SCLC), thyroid cancer, and melanoma.

25 In a particular embodiment of the invention the neoplastic disease is a cancer selected from the group consisting of acute myeloid leukemia (AML), thyroid cancer, melanoma, or small cell lung cancer (SCLC).

In a particular embodiment of the invention the neoplastic disease is a cancer selected from the group consisting of acute myeloid leukemia (AML) and small cell lung cancer (SCLC).

30 In a particular embodiment of the invention the neoplastic disease is neuroendocrine cancer.

In a particular embodiment of the invention the neoplastic disease is a solid tumor.

In a particular embodiment of the invention the neoplastic disease is a malignant solid tumor selected from sarcomas, carcinomas, and lymphomas.

In a particular embodiment of the invention the neoplastic disease is lung cancer.

5 In a particular embodiment of the invention the neoplastic disease is small cell lung cancer (SCLC).

In a particular embodiment of the invention the neoplastic disease is small cell lung cancer (SCLC), wherein the SCLC cells areis sensitive to LSD1 inhibitor-based therapy.

10 In a particular embodiment of the invention the neoplastic disease is small cell lung cancer (SCLC), wherein the SCLC cells are sensitive to LSD1 inhibitor-based therapy, wherein the sensitivity to LSD 1 inhibitor-based therapy is assessed based on predictive mRNA expression levels as described herein.

In a particular embodiment of the invention the neoplastic disease is small cell lung cancer (SCLC), wherein the SCLC cells are sensitive to LSD1 inhibitor-based therapy, wherein the sensitivity to LSD 1 inhibitor-based therapy is assessed using an in vitro method comprising:

15 a) measuring in a sample from the patient the levels of a gene panel, wherein the gene panel comprises one or more genes selected from responder genes and non-responder genes,

b) calculating a signature score from the measured levels of the gene panel,

c) comparing the signature score calculated to a threshold level, and

20 d) identifying the patient as more likely to respond to the therapy comprising an LSD1 inhibitor when the signature score is above the threshold level.

In a particular embodiment of the invention the neoplastic disease is small cell lung cancer (SCLC), wherein the SCLC cells exhibit response to single agent treatment with LSD1 inhibitors.

25 In a particular embodiment of the invention the neoplastic disease is small cell lung cancer (SCLC), wherein the SCLC cells exhibit response to single agent treatment with LSD1 inhibitors, wherein the response to single agent treatment with LSD1 inhibitors is assessed based on predictive mRNA expression levels as described herein.

30 In a particular embodiment of the invention the neoplastic disease is small cell lung cancer (SCLC), wherein the SCLC cells exhibit response to single agent treatment with LSD1

inhibitors, wherein the response to single agent treatment with LSD1 inhibitors is assessed using an in vitro method comprising:

5 a) measuring in a sample from the patient the levels of a gene panel, wherein the gene panel comprises one or more genes selected from responder genes and non-responder genes,

b) calculating a signature score from the measured levels of the gene panel,

c) comparing the signature score calculated to a threshold level, and

d) identifying the patient as more likely to respond to the therapy comprising an LSD1 inhibitor when the signature score is above the threshold level.

10

## Gene Panels and mRNA Signatures

Table 3 provides a list including description of the genes employed in present invention.

Gene	Ensembl Gene ID*	Description	Synonyms	Location: Chromosome
ASCL1	ENSG00000139352	achaete-scute family bHLH transcription factor 1	ASH1, bHLHa46, HASH1	Chromosome 12: 102,957,686-102,960,516 forward strand.
DDC	ENSG00000132437	dopa decarboxylase	AADC	Chromosome 7: 50,458,436-50,565,457 reverse strand.
CEACAM6	ENSG00000086548	carcinoembryonic antigen-related cell adhesion molecule 6	CD66c, NCA	Chromosome 19: 41,750,977-41,772,208 forward strand.
LRRIQ4	ENSG00000188306	leucine-rich repeats and IQ motif containing 4	LRRC64	Chromosome 3: 169,821,922-169,837,775 forward strand.
NR0B2	ENSG00000131910	nuclear receptor subfamily 0, group B, member 2	SHP	Chromosome 1: 26,911,489-26,913,966 reverse strand.
GRP	ENSG00000134443	gastrin-releasing peptide		Chromosome 18: 59,220,168-59,230,774 forward strand.
CEACAM5	ENSG00000105388	carcinoembryonic antigen-related cell adhesion molecule 5	CD66e, CEA	Chromosome 19: 41,576,273-41,729,798 forward strand.
SOX21	ENSG00000125285	SRY (sex determining region Y)-box 21	SOX25	Chromosome 13: 94,709,622-94,712,399 reverse strand.

Gene	Ensembl Gene ID*	Description	Synonyms	Location: Chromosome
OR51E2	ENSG00000167332	olfactory receptor, family 51, subfamily E, member 2	PSGR	Chromosome 11: 4,680,171-4,697,854 reverse strand.
SEC11C	ENSG00000166562	SEC11 homolog C, signal peptidase complex subunit	SEC11L3, SPC21, SPCS4C	Chromosome 18: 59,139,477-59,158,836 forward strand.
BAALC	ENSG00000164929	brain and acute leukemia, cytoplasmic		Chromosome 8: 103,140,710-103,230,305 forward strand.
CCDC40	ENSG00000141519	coiled-coil domain containing 40	CILD15, FAP172, FLJ20753, FLJ32021, KIAA1640	Chromosome 17: 80,036,632-80,100,613 forward strand.
RAB3B	ENSG00000169213	RAB3B, member RAS oncogene family		Chromosome 1: 51,907,956-51,990,764 reverse strand.
RGS17	ENSG00000091844	regulator of G-protein signaling 17	RGS-17, RGSZ2	Chromosome 6: 153,004,459-153,131,249 reverse strand.
ABCE1	ENSG00000164163	ATP-binding cassette, sub-family E (OABP), member 1	OABP, RLI, RNASEL1, RNASELI, RNS4I	Chromosome 4: 145,097,932-145,129,179 forward strand.
ETS2	ENSG00000157557	v-ets avian erythroblastosis virus E26 oncogene homolog 2		Chromosome 21: 38,805,307-38,824,955 forward strand.
CCDC154	ENSG00000197599	coiled-coil domain containing 154	C16orf29, LOC645811	Chromosome 16: 1,434,383-1,444,556 reverse strand.
SPAG6	ENSG00000077327	sperm associated antigen 6	CT141, pf16, Repro-SA-1	Chromosome 10: 22,345,445-22,454,224 forward strand.
PON1	ENSG0000005421	paraoxonase 1	ESA, PON	Chromosome 7: 95,297,676-95,324,707 reverse strand.
TMEM176A	ENSG0000002933	transmembrane protein 176A	HCA112, MS4B1	Chromosome 7: 150,800,403-150,805,120 forward strand.
C1orf127	ENSG00000175262	chromosome 1 open reading frame 127	FLJ37118	Chromosome 1: 10,946,471-10,982,037 reverse strand.
IGF2BP2	ENSG00000073792	insulin-like growth factor 2 mRNA binding protein 2	IMP-2	Chromosome 3: 185,643,739-185,825,056 reverse strand.

Gene	Ensembl Gene ID*	Description	Synonyms	Location: Chromosome
IGFBP5	ENSG00000115461	insulin-like growth factor binding protein 5		Chromosome 2: 216,672,105-216,695,525 reverse strand.
FAM84A	ENSG00000162981	family with sequence similarity 84, member A	FLJ35392, NSE1	Chromosome 2: 14,632,686-14,650,814 forward strand.
FOXA2	ENSG00000125798	forkhead box A2	HNF3B	Chromosome 20: 22,581,005-22,585,455 reverse strand.
HOXA10	ENSG00000253293	homeobox A10	HOX1, HOX1H	Chromosome 7: 27,170,591-27,180,261 reverse strand.
MYC	ENSG00000136997	v-myc avian myelocytomatisis viral oncogene homolog	bHLHe39, c-Myc, MYCC	Chromosome 8: 127,735,434-127,741,434 forward strand.
NCAM1	ENSG00000149294	neural cell adhesion molecule 1	CD56, NCAM	Chromosome 11: 112,961,247-113,278,436 forward strand.
NCAM2	ENSG00000154654	neural cell adhesion molecule 2	MGC51008, NCAM21	Chromosome 21: 20,998,315-21,543,329 forward strand.
NEUROD1	ENSG00000162992	neuronal differentiation 1	BETA2, BHF-1, bHLHa3, MODY6, NEUROD	Chromosome 2: 181,673,088-181,680,876 reverse strand.
KRT8	ENSG00000170421	keratin 8, type II	CARD2, CK8, CYK8, K2C8, K8, KO	Chromosome 12: 52,897,187-52,949,954 reverse strand.
ENO2	ENSG00000111674	enolase 2 (gamma, neuronal)		Chromosome 12: 6,913,745-6,923,698 forward strand.
AVP	ENSG00000101200	arginine vasopressin	ADH, ARVP	Chromosome 20: 3,082,556-3,084,724 reverse strand.
OXT	ENSG00000101405	oxytocin/neurophysin I prepropeptide	OT, OT-NPI, OXT-NPI	Chromosome 20: 3,071,620-3,072,517 forward strand.
SYP	ENSG00000102003	synaptophysin	MRX96	Chromosome X: 49,187,804-49,200,259 reverse strand.

Gene	Ensembl Gene ID*	Description	Synonyms	Location: Chromosome
CHGA	ENSG00000100604	chromogranin A		Chromosome 14: 92,923,080-92,935,293 forward strand.
CHGB	ENSG00000089199	chromogranin B	SCG1, SgI	Chromosome 20: 5,911,430-5,925,361 forward strand.
BCL2	ENSG00000171791	B-cell CLL/lymphoma 2	Bcl-2, PPP1R50	Chromosome 18: 63,123,346-63,320,128 reverse strand.

Table 3. Description of the genes employed in the invention (\*<http://www.ensembl.org/>, Cunningham F. *et al.*<sup>106</sup>).

The present invention identifies a gene panel (also referred to as “multi-gene panel”, “gene expression panel” or “panel of genes”) whose mRNA expression signature based on *in vitro* data may serve to identify patients most likely to respond to LSD1 inhibitor containing therapy regimens. The genes listed are characteristic of the SCLC classic phenotype (generally of neuroendocrine origin) to the exclusion of those cell lines of “variant” phenotype. The expression of these genes may have predictive benefit in identifying responder patients of other histological subtypes in additional tumor settings.

It has been found that the mRNA signature is characterized by high expression in responder genes: ASCL1, HOXA10, NCAM1, NCAM2, NEUROD1, DDC, GRP, KRT8, ENO2, AVP, OXT, SYP, CHGA, CHGB, SOX21 and BCL2.

It has further been found, that non-responder lines may be characterized by high levels of the oncogene MYC.

The baseline expression levels of responder genes and non-responder genes listed herein may yield, alone or in combination with one another, a composite score that discriminates between cell lines and patient-derived clinical specimens that are resistant to therapy, and identifies those that are sensitive (responsive) to therapy using an LSD1 inhibitor.

Thus higher levels of responder genes and/or lower expression levels of non-responder genes are indicative for the response to a therapy using an LSD1 inhibitor. Combining the expression levels of several responder and/or non-responder genes may provide a multi-gene signature with improved confidence regarding responsiveness as compared to the readout from single gene expression levels.

The present invention identifies mRNAs associated with and for identifying responses to

LSD1 inhibition.

The present invention also relates to a method for identifying sensitivity to LSD1 inhibitor-based therapy.

The present invention also relates to the use of a gene panel in order to determine a patient's response to a neoplastic disease when a patient is to be treated with an LSD1 inhibitor-based therapy.

The present invention also identifies mRNAs expression for monitoring the treatment of neoplastic diseases in a patient with an LSD1 inhibitor.

The present invention also provides the predictive mRNA values in determining the effectiveness of LSD1 inhibitor-based therapy to neoplastic diseases.

One embodiment of the invention provides an *in vitro* method of identifying a patient having a neoplastic disease as likely to respond to a therapy comprising an LSD1 inhibitor, the method comprising

a) measuring in a sample from the patient the levels of a gene panel, wherein the gene panel comprises one or more genes selected from responder genes and non-responder genes,

b) comparing the levels of the gene panel measured in a) to a reference level, and

c) identifying the patient as more likely to respond to the therapy comprising an LSD1 inhibitor when the levels of the responder genes of the gene panel measured in a) in the sample from the patient are above the reference level, and/or when the levels of the non-responder genes of the gene panel measured in a) in the sample from the patient are below the reference level.

One embodiment of the invention provides an in vitro method of identifying a patient having a neoplastic disease as likely to respond to a therapy comprising an LSD1 inhibitor, the method comprising

a) measuring in a sample from the patient the levels of a gene panel, wherein the gene panel comprises one or more genes selected from responder genes and non-responder genes,

b) calculating a signature score from the measured levels of the gene panel,

c) comparing the signature score calculated to a threshold level, and

d) identifying the patient as more likely to respond to the therapy comprising an LSD1 inhibitor when the signature score is above the threshold level.

Another embodiment of the invention provides an *in vitro* method of identifying a patient having a neoplastic disease as likely to respond to a therapy comprising an LSD1 inhibitor, the method comprising

- 5 a) measuring in a sample from the patient the levels of a gene panel, wherein the gene panel comprises one or more genes selected from responder genes and non-responder genes,
- b) comparing the levels of the gene panel measured in a) to a reference level,
- c) identifying the patient as more likely to respond to the therapy comprising an LSD1 inhibitor when the levels of the responder genes of the gene panel measured in a) in the sample from the patient are above the reference level, and/or when the levels of the non-responder genes of the gene panel measured in a) in the sample from the patient are below the reference level, and
- 10 d) administering an effective amount of LSD1 inhibitor.

One embodiment of the invention provides an in vitro method of identifying a patient having a neoplastic disease as likely to respond to a therapy comprising an LSD1 inhibitor, the method comprising

- 15 a) measuring in a sample from the patient the levels of a gene panel, wherein the gene panel comprises one or more genes selected from responder genes and non-responder genes,
- b) calculating a signature score from the measured levels of the gene panel,
- c) comparing the signature score calculated to a threshold level,
- d) identifying the patient as more likely to respond to the therapy comprising an LSD1 inhibitor when the signature score is above the threshold level, and
- 20 e) administering an effective amount of LSD1 inhibitor.

25 Another embodiment of the invention provides an *in vitro* method of monitoring efficacy of therapy comprising an LSD1 inhibitor in patient having a neoplastic disease, the method comprising

- 30 a) measuring in a sample from the patient prior to start of the therapy the levels of a gene panel, wherein the gene panel comprises one or more genes selected from responder genes and non-responder genes,

b) using the levels of the gene panel measured in a) to calculate the patient's signature score prior to start of the therapy,

c) measuring in a sample from the patient after start of the therapy the levels of the gene panel,

5 d) using the levels of the gene panel measured in c) to calculate the patient's signature score after start of the therapy,

e) comparing the patient's signature score obtained in d) after start of the therapy with the signature score obtained in b) prior to start of the therapy, and

10 f) identifying the patient as responding to the therapy when the signature score obtained in d) after start of the therapy are higher than the signature score obtained in b) prior to start of the therapy.

15 In this application, the term "readout levels" denotes a value which can be in any form of mRNA expression measurement, such as for example expression levels derived from RNA-sequencing such as normalized read counts and RPKM (Reads per Kilobase of Million mapped reads); RT-qPCR; or microarrays.

In this application, the term "normalized read count" denotes the read count which is obtained directly from a RNA-sequencing experiment and which is normalized to make it comparable across experiments.

20 In this application, the term "normalized expression level" denotes a value which is obtained in a particular kind of expression measurement and which is normalized to make it comparable across experiments (e.g. normalized expression from microarrays, normalized expression from RNA-sequencing).

In one aspect of the invention, the normalized expression level is the normalized read count.

25 In one aspect of the invention, the levels measured are mRNA expression levels.

In one aspect of the invention, the levels measured are mRNA expression levels derived from RNA-sequencing, RT-qPCR or microarrays.

In one aspect of the invention, the reference level is a standard value from a patient with the same neoplastic disease.

30 In another embodiment, the reference level is median mRNA expression measured in a population of patients with the same neoplastic disease.

In one aspect of the invention, the reference level for certain genes of the gene panel are as follows (indicated as normalized read counts): ASCL1 (4515.83); DDC (2005.02); GRP (426.01); HOXA10 (10.04).

The reference levels reported above were obtained by selecting the lower normalized 5 read count for the corresponding gene among two small cell lung cancer cell lines  $C_S$  and  $C_R$ , wherein  $C_S$  is the sensitive cell line with the lowest expression of the selected gene, and  $C_R$  is the resistant cell line with the highest expression of the selected gene.

A signature score as used herein is a gene-based algorithm-derived score (a multi-gene 10 signature) composed of values indicative for up-regulations of responder genes and for down- regulation or copy number variation of non-responder genes.

A signature score larger than a threshold level predicts response to therapy comprising an LSD1 inhibitor. The higher the threshold level for predicting response is selected for the signature score, the higher the specificity obtained. The lower the threshold level for predicting response is selected for the signature score, the higher the sensitivity obtained.

15 In one embodiment of the invention, the threshold level corresponds to a Signature Score 1 of 0.4 to 0.6, particularly  $0.5 \pm 20\%$ , most particularly 0.5, wherein the signature score is obtained by partial least square (PLS) analysis using the second principal component:

Signature Score 1 =

0.0900693

20 + (Normalized expression level of ASCL1)  $\times 0.00000211296$   
+ (Normalized expression level of DDC)  $\times 0.000000536658$   
+ (Normalized expression level of GRP)  $\times 0.00000297345$   
+ (Normalized expression level of HOXA10)  $\times 0.000234721$   
– (Copy number variation of MYC)  $\times 0.0537056$ .

25 In one embodiment of the invention, the threshold level corresponds to a Signature Score 2 of 0.4 to 0.6, particularly  $0.5 \pm 20\%$ , most particularly 0.5, wherein the signature score is obtained by partial least square (PLS) analysis using the first principal component:

Signature Score 2 =

0.483918

30 + (Normalized expression level of ASCL1)  $\times 0.$  0000188066  
+ (Normalized expression level of DDC)  $\times 0.$  0000188066  
+ (Normalized expression level of GRP)  $\times 0.$  0000352033  
– (Copy number variation of MYC)  $\times 0.0407898$ .

In one embodiment of the invention, the threshold level corresponds to a Signature Score 3 of 0.4 to 0.6, particularly  $0.5 \pm 20\%$ , most particularly 0.5, wherein the signature score is obtained by partial least square (PLS) analysis using the first principal component:

Signature Score 3 =

$$\begin{aligned} 5 \quad & 0.393569 \\ & + (\text{Normalized expression level of ASCL1}) \times 0.0000182731 \\ & + (\text{Normalized expression level of DDC}) \times 0.0000189664 \\ & + (\text{Normalized expression level of GRP}) \times 0.00000342046. \end{aligned}$$

A signature score above the threshold level indicates a high likelihood of response to treatment with an LSD1 inhibitor, whereas a signature score below said level indicates a lower likelihood to respond to such treatment. A higher score is associated with higher mRNA expression of ASCL1, DDC, GRP and HOXA10, and with lower copy number variations in MYC.

In one embodiment of the invention, the reference level is the threshold level of a signature score.

In one embodiment of the invention, the signature score to predict response to therapy comprising an LSD1 inhibitor may be obtained by performing the following steps:

a. Select a gene panel which comprises m genes, wherein m is an integer greater than 1, selected among the genes disclosed in Table 9, and optionally HOXA10 and MYC.

b. Select a set of one or more sensitive and a set of one or more resistant cancer cell lines, particularly originating from neuroendocrine tumors such as small cell lung cancer (SCLC), as for example described in Table 6. Alternatively select a set of one or more classic and set of one or more variant small cell lung cancer cell lines.

c. Generate an  $n \times m$  matrix, wherein m is as defined above and n is the total number of small cell lung cancer cell lines selected. The matrix contains expression levels of the selected genes (and/or copy number variations in case of the MYC). Gene expression levels may be reported as RPKM or as normalized read counts.

d. Generate a response vector of size n, which describes each cell line as being sensitive ("S") or resistant ("R"), as defined in Table 6. Alternatively, this vector may describe each cell line as being of "classic" (C") or "variant" (V") subtype.

e. Apply a machine learning algorithm for classification of the matrix described above in point c. Examples of such machine learning algorithms include, but are

not limited to, decision trees, support-vector machines, neural networks, nearest neighbor analysis, naïve Bayes, random forest, partial least square, etc.

5 f. Perform appropriate cross-validation using either cell lines included in the analysis and/or cell lines not included in the analysis to optimize the model's predictive power.

10 g. Select a function  $f(x)$ , as appropriate for the machine learning algorithm selected, to obtain a signature score  $y$  ( $y=f(x)$ ). This function  $f(x)$  comprises a set of coefficients  $a_1 \dots a_p$  calculated by the machine learning algorithm (where  $p$  is the number of coefficients selected by a given algorithm) and gene expression levels ( $x_1 \dots x_m$ ) of the genes selected.

h. Select a threshold, as proposed by the machine learning method, to determine whether the signature score predicts sensitivity or resistance to an LSD1 inhibition therapy.

15 In a particular embodiment of the invention the gene panel comprises one or more genes selected from the group of ASCL1, MYC, HOXA10, DDC, GRP, NCAM1, NCAM2, NEUROD1, KRT8, ENO2, AVP, OXT, SYP, CHGA, CHGB, SOX21 and BCL2.

In a particular embodiment of the invention the gene panel comprises one or more genes selected from the group of ASCL1, MYC, HOXA10, DDC, GRP, NCAM1, NCAM2, NEUROD1, SOX21 and BCL2.

20 In a particular embodiment of the invention the gene panel comprises two, three, four or five genes selected from the group of ASCL1, MYC, HOXA10, DDC, GRP, NCAM1, NCAM2, NEUROD1, SOX21 and BCL2.

In a particular embodiment of the invention the gene panel comprises one or more genes selected from the group of ASCL1, MYC, HOXA10, DDC and GRP.

25 In a particular embodiment of the invention the gene panel comprises two, three, four or five genes selected from the group of ASCL1, MYC, HOXA10, DDC and GRP.

In a particular embodiment of the invention the gene panel comprises one or more genes selected from the group of ASCL1, MYC and HOXA10.

In a particular embodiment of the invention the gene panel comprises the ASCL1 gene.

30 In a particular embodiment of the invention the gene panel comprises the MYC gene.

In a particular embodiment of the invention the gene panel comprises the HOXA10 gene.

In a particular embodiment of the invention the gene panel comprises the DDC gene.

In a particular embodiment of the invention the gene panel comprises the GRP gene.

In a particular embodiment of the invention the gene panel consists of one, two, three, four or five genes.

5 In a particular embodiment of the invention the gene panel consists of two, three or four genes.

In a particular embodiment of the invention the responder genes are selected from the group of ASCL1, HOXA10, DDC, GRP, NCAM1, NCAM2, NEUROD1, KTR8, ENO2, AVP, OXT, SYP, CHGA, CHGB, SOX21 and BCL2.

10 In a particular embodiment of the invention the non-responder genes are selected from MYC.

### Description of the drawings

Figure 1: In vitro differential activity of LSD1 inhibitors (i.e. (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine) in a panel of SCLC cell lines treated for 7 days. 15 “Classic” neuroendocrine cell lines such as NCI-H1876 (Figure 1A) and NCI-H510 (Figure 1B) maintained a high level of sensitivity.

Figure 2: LSD1 inhibitors (i.e. (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine) improve potency and duration of SCLC standards of care (SOC) etoposide and carboplatin in vivo (Figure 2A) as well as in vivo in mice (Figure 20 2B).

Figure 3: Principal component analysis score plot for principal component 1 (t[1], x-axis) and principal component 2 (t[2], y-axis) separates classic cell lines (C, black) from variant cell lines (V, gray) according to Example 5.

Figure 4: Heat Map showing mRNA expression (as z-scores) for the gene panel of 25 Example 6 comprising the genes of Table 8, Table 6 and MYC. These genes best predict response to an LSD1 inhibition therapy in the 19 cell lines of Table 6. Higher z-scores correlate with better sensitivity.

Figure 5: Heat Map showing mRNA expression (as z-scores) for the neuroendocrine genes of Example 7 in the 19 cell lines of Table 6. Sensitive cell-lines display a stronger 30 expression (higher z-score) of such neuroendocrine markers.

**Figure 6:** Signature scores obtained by PLS analysis using the second principal component according to Example 8. Cell lines with  $\text{score\_1} > 0.5$  are more likely to be sensitive to an LSD1 inhibition therapy.

**Figure 7:** Signature scores obtained by PLS analysis using the first principal component according to Example 8. Cell lines with  $\text{score\_2} > 0.5$  are more likely to be sensitive to an LSD1 inhibition therapy.

**Figure 8:** Signature scores obtained by PLS analysis using the first principal component according to Example 8. Cell lines with  $\text{score\_3} > 0.45$  are more likely to be sensitive to an LSD1 inhibition therapy.

**Figure 9:** *in vivo* tumor growth inhibition of (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine in classic (C) cell line H-510A.

**Figure 10:** Heat Map showing mRNA expression (as z-scores) patterns in SCLC patient samples.

## Examples

The following examples 1 to 9 are provided for illustration of the invention. They should not be considered as limiting the scope of the invention, but merely as being representative thereof.

## Methods

### Expression data

Expression data were obtained from whole transcriptomic RNA sequencing (RNA-seq) by Illumina, Inc. (San Diego, CA). The Illumina HiSeq machine generates raw base calls in reads of 50 or 100 bp length, which are subjected to several data analysis steps. The RNA-seq is conducted at 40 to 50 million reads per sample. This number provides relatively high sensitivity to detect low-expressed genes while allowing for cost-effective multiplexing of samples. RNA is prepared by standard kits and RNA libraries by polyA TruSeq Illumina kits. 100 ng of mRNA per cell line is used for each RNA-seq reaction. A number of quality control procedures are applied to the RNA-seq data for each sample. The Illumina HiSeq software reports the total number of clusters (DNA fragments) loaded in each lane, percent passing sequencing quality filters (which identifies errors due to overloading and sequencing chemistry), a phred quality score for each base of each sequence read, overall average phred scores for each sequencing cycle, and overall percent error (based on alignment to the reference genome). For each RNA-seq sample, the percentage of reads that contain mitochondrial and ribosomal RNA is calculated. The FASTQC package is used to provide additional QC metrics (base distribution, sequence duplication, overrepresented sequences, and enriched kmers) and a graphical summary. Raw

reads were aligned against the human genome (hg19) using GSNAP and recommended options for RNASeq data. In addition to the genome sequence, GSNAP is given a database of human splice junctions and transcripts based on Ensembl v73. Resulting SAM files are then converted to sorted BAM files using Samtools. Gene expression values are calculated both as RPKM 5 values following (Mortazavi *et al.*<sup>107</sup>) and as read counts. Normalized read counts were obtained using the R package DESeq2.

#### Copy number variations (CNV)

To obtain copy number variation data genomic DNA were extracted and array CGH analysis were performed by Roche NimbleGen (Madison, WI) using their standard protocols. Normalized 10 signal intensities and copy number changes were obtained using the segMNT algorithm. CGH microarrays contain isothermal, 45- to 85-mer oligonucleotide probes that are synthesized directly on a silica surface using light-directed photochemistry (Selzer *et al.*<sup>108</sup>). The genomic DNA samples are randomly fragmented into lower molecular weight species and differentially labeled with fluorescent dyes.

#### 15 Principal component analysis

Principal component analysis was carried out with Simca v 14 (Umetrics AB, Umeå, Sweden).

#### Differential gene expression analysis

Differential gene expression analysis used to generate data in Table 9 was carried out with the R package DESeq2 starting from raw read counts for 19 cell lines.

#### 20 Heat maps of cell lines

Heat maps of cell lines (as in Figure 4 and 5) were generated using GenePattern v 3.9.4 (Reich M. *et al.*<sup>109</sup>) to visualize color-coded gene expression levels. GenePattern takes in input the logarithm of normalized read counts (as reported in Table 10) plus one and applies a row-based normalization which consists of calculating z-scores for all expression levels of a given gene 25 across the cell lines tested. A z-score of 0 corresponds to the mean of a distribution, and positive or negative value represent normalized gene expression levels above or below the mean, respectively. The color mapping capped the z-score range from -1.5 to +1.5, that is, z-scores above +1.5 are displayed in black and z-scores below -1.5 are in white. Intermediate values are displayed in different shades of gray. Gene Pattern performs hierarchical clustering to group and 30 sort cell lines based on their gene expression profile.

#### Example 1 – Differential Activity of LSD1 inhibitors in SCLC Cell Lines

The differential activity of (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine in SCLC Cell Lines is presented in Figures 1A-1B. The activity of (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine was assessed in vitro in a panel of SCLC cell 35 lines treated for 7 days. Cell lines characterized as “classic” neuroendocrine lineages, such as

NCI-H1876 (Figure 1A) and NCI-H510 (Figure 1B), maintained a high level of sensitivity to (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine.

The compound potency determination was performed by culturing small cell lung cancer cell lines for 7 days at 37 degrees C at 5% CO<sub>2</sub> in humidified incubators in the presence of 15 - 5 serially dilutions (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine at the indicated concentration. Each of the cell lines was propagated and tested in distinct optimized media as recommended by ATCC or cell line source.

Cells were thawed from a liquid nitrogen preserved state. Once cells have been expanded and divided at their expected doubling times, screening was started. Cells were seeded in growth 10 media in black 384-well tissue culture treated plates at 500 cells per well (except where noted in Analyzer). Cells were equilibrated in assay plates via centrifugation and placed in incubators attached to the Dosing Modules at 37°C for twenty-four hours before treatment. At the time of treatment, a set of assay plates (which did not receive treatment) were collected and ATP levels 15 were measured by adding ATPLite (Perkin Elmer). These Tzero (T0) plates were read using ultra-sensitive luminescence on Envision Plate Readers. Treated assay plates were incubated with (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine for one-hundred and sixty-eight hours. After one-hundred and sixty-eight hours, plates were developed for endpoint 20 analysis using ATPLite. All data points were collected via automated processes; quality controlled; and analyzed using Horizon CombinatoRx proprietary software. Assay plates were accepted if they passed the following quality control standards: relative luciferase values were consistent throughout the entire experiment, Z-factor scores were greater than 0.6, untreated/vehicle controls behaved consistently on the plate.

Horizon Discovery utilizes Growth Inhibition (GI) as a measure of cell viability. The cell 25 viability of vehicle was measured at the time of dosing (T0) and after one hundred and sixty-eight hours (T168). A GI reading of 0% represents no growth inhibition - cells treated with (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine and T168 vehicle signals were matched. A GI 100% represents complete growth inhibition - cells treated by compound 30 and T0 vehicle signals were matched. Cell numbers have not increased during the treatment period in wells with GI 100% and may suggest a cytostatic effect for compounds reaching a plateau at this effect level. A GI 200% represents complete death of all cells in the culture well. Compounds reaching an activity plateau of GI 200% were considered cytotoxic. Horizon CombinatoRx calculates GI by applying the following test and equation:

$$\text{If } T < V_0 : 100 * (1 - \frac{T-V_0}{V_0})$$

$$\text{If } T \geq V_0 : 100 * (1 - \frac{T-V_0}{V-V_0})$$

where T is the signal measure for a test article, V is the vehicle-treated control measure, and Vo is the vehicle control measure at time zero. This formula was derived from the Growth Inhibition calculation used in the National Cancer Institute's NCI-60 high throughput screen.

**Example 2 - Synergistic Effects of LSD1 inhibitors combined with other active**

**5 pharmaceutical ingredients**

Table 4 provides a heat map of synergy scores, the values indicating the strength of the synergistic effects. Synergy scores > 6.4 were considered significant and warranted further validations. Cell lines that exhibited particular single agent response to (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine (NCI-H187, NCI-H1417, NCI-H1876, NCI-H510) 10 were sensitized to the effects of a broad range of drug classes including HDAC and BET inhibitors, DNA alkylating agents, topoisomerase inhibitors, anti-mitotic agents, Aurora kinase inhibitors, BCL2 family inhibitors and Chk inhibitors. Similar levels of synergy were not uniformly observed in cell lines that were insensitive to (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine (NSCLC cell lines and SCLC cell line NCI- 15 H1048, NCI-H446 and SBC-5). These data suggest the LSD1 inhibition may broadly sensitize SCLC cell lines to intervention by chemotherapeutics and targeted therapies.

Cells were thawed from a liquid nitrogen preserved state and expanded until they reached their expected doubling times. Each of the cell lines was propagated and tested in distinct optimized media as recommended by ATCC or cell line source.

20 Cells were seeded in 384-well assay plates at assigned densities (determined in the optimization phase). Cells were then equilibrated via centrifugation in incubators attached to the Dosing Modules for 24 hours before (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine pre-treatment. Assay plates were then treated with the assigned concentrations of (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine (determined in the 25 optimization phase).

At the time of (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine treatment, a set of assay plates (which do not contain treatment) were collected and ATP levels measured by adding ATPLite (Perkin Elmer). These Tzero (T0) plates were read on Envision Plate Readers to measure luminescence. Treated assay plates were incubated with 30 (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine for 96 hours before treatment with the second compound. After this time, assay plates were then treated with 8 point serial dilutions of enhancer compound in a 9x9 extended matrix and harvested after another 72 hours incubation. After a total of 168 hours from the initial (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine treatment time, plates were developed for endpoint 35 analysis using ATPLite. All data points were collected via automated processes; quality controlled; and analyzed using Horizon CombinatoRx proprietary software. Assay plates were

accepted if they passed the following quality control standards: relative luciferase values were consistent throughout the entire experiment, Z-factor scores were greater than 0.6, untreated/vehicle controls behaved consistently on the plate.

Horizon Discovery utilizes Growth Inhibition (GI) as a measure of cell viability. The cell 5 viability of vehicle is measured at the time of dosing (T0) and after one hundred and sixty-eight hours (T168). A GI reading of 0% represents no growth inhibition - cells treated with compound and T168 vehicle signals are matched. A GI 100% represents complete growth inhibition - cells treated by compound and T0 vehicle signals are matched. Cell numbers have not increased during the treatment period in wells with GI 100% and may suggest a cytostatic effect for 10 compounds reaching a plateau at this effect level. A GI 200% represents complete death of all cells in the culture well. Compounds reaching an activity plateau of GI 200% are considered cytotoxic. Horizon CombinatoRx calculates GI by applying the following test and equation:

$$\text{If } T < V_0 : 100 * (1 - \frac{T-V_0}{V_0})$$

$$\text{If } T \geq V_0 : 100 * (1 - \frac{T-V_0}{V-V_0})$$

15 where T is the signal measure for a test article, V is the vehicle-treated control measure, and V<sub>0</sub> is the vehicle control measure at time zero. This formula is derived from the Growth Inhibition calculation used in the National Cancer Institute's NCI-60 high throughput screen.

Loewe additivity model is dose-based and applies only to the activity levels achieved by the single agents. Loewe Volume is used to assess the overall magnitude of the combination 20 interaction in excess of the Loewe additivity model. Loewe Volume is particularly useful when distinguishing synergistic increases in a phenotypic activity (positive Loewe Volume) versus synergistic antagonisms (negative Loewe Volume). When antagonisms are observed, as in the current dataset, the Loewe Volume should be assessed to examine if there is any correlation between antagonism and a particular drug target-activity or cellular genotype. This model 25 defines additivity as a non-synergistic combination interaction where the combination dose matrix surface should be indistinguishable from either drug crossed with itself. The calculation for additivity is:

$$I_{\text{Loewe}} \text{ that satisfies } (X/X_I) + (Y/Y_I) = 1$$

30 where X<sub>I</sub> and Y<sub>I</sub> are the single agent effective concentrations for the observed combination effect I. For example, if 50% inhibition is achieved separately by 1mM of drug A or 1mM of drug B, a combination of 0.5mM of A and 0.5mM of B should also inhibit by 50%.

To measure combination effects in excess of Loewe additivity, the Horizon Discovery platform was utilized. This method devised a scalar measure to characterize the strength of synergistic interaction termed the Synergy Score. The Synergy Score is calculated as:

$$\text{Synergy Score} = \log f_X \log f_Y \sum \max(0, I_{\text{data}})(I_{\text{data}} - I_{\text{Loewe}})$$

The fractional inhibition for each component agent and combination point in the matrix is calculated relative to the median of all vehicle-treated control wells. The Synergy Score equation integrates the experimentally-observed activity volume at each point in the matrix in excess of a

5 model surface numerically derived from the activity of the component agents using the Loewe model for additivity. Additional terms in the Synergy Score equation (above) are used to normalize for various dilution factors used for individual agents and to allow for comparison of synergy scores across an entire experiment.

Activity over Loewe additivity is most easily calculated using a simple volume score,

10 where  $V_{\text{Loewe}} = \log f_X \log f_Y \sum (I_{\text{data}} - I_{\text{Loewe}})$ , summed over all non-single agent concentration pairs and where  $\log f_{X,Y}$  are the natural logarithm of the dilution factors used for each single agent. This effectively calculates a volume between the measured and Loewe additive response surfaces, corrected for varying dilution factors. This volume score emphasizes the overall synergistic or antagonistic effect of the combination, thus minimizing the effects of outlying data 15 spikes and identifying combinations with a robust synergy across a wide range of concentrations and at high effect levels.  $V_{\text{Loewe}}$  is positive for mostly synergistic combinations and negative for antagonism. The uncertainty  $\sigma_V$  can be calculated based on the measured errors  $\sigma_I$  and standard error propagation.

"Synergy Score"  $S = f_{\text{cov}} \ln f_X \ln f_Y \sum \max(0, I_{\text{data}}) \max(0, I_{\text{data}} - I_{\text{Loewe}})$ , which is a positive-

20 gated, inhibition-weighted volume over Loewe additivity. This provides an additional prioritization favoring combinations whose synergy occurs at high effect levels, ignoring antagonistic portions of the response surface. Here  $f_{X,Y}$  are the dilution factors used for each single agent and the coverage factor  $f_{\text{cov}}$  accounts for missing data, scaling the score up by the ratio of total/tested combination dose matrix points.  $S$  is always positive, and its uncertainty  $\sigma_S$  25 can be calculated based on the measured errors  $\sigma_I$  and standard error propagation. An alternative to the synergy score is the "Hit Score"  $H = f_{\text{cov}} \log f_X \log f_Y \sum \max(0, I_{\text{data}}) \max(0, I_{\text{data}} - I_{\text{HSA}})$ , which refers to the HSA model. The key distinctions between  $S$  and  $H$  lie in the different underlying models and also in how the single agents are used in the model calculations. In the Chalice Analyzer, the HSA model is calculated directly from the single agent responses at 30 corresponding concentrations, while the Loewe additive model is derived from the sigmoidal fits to the single agent response curves.

To prioritize hits, distributions of a score ( $S$  or  $H$ ) and its error can be used to define an appropriate selection cutoff. For example, combinations with  $S > 3\sigma_S$  are "individually significant" at ~99% confidence, assuming normal errors. To estimate systematic experimental

35 errors that are not tested by replicate plates, the distribution of synergy scores for any drug-with-itself combinations acquired during the experiment can be used to determine a plausible range

for non-detections. Alternatively, the score distribution for the whole experiment can be used to identify outliers at a chosen confidence level.

**Example 3 – in vitro Synergistic Effects for SCLC of LSD1 inhibitors combined with other active pharmaceutical ingredients**

5 Table 5 provides a heat map of synergy scores, the values indicating the strength of the synergistic effects. Synergy scores > 6.4 were considered significant and warranted further validations. A select panel of drug classes were prioritized for further evaluation in an expanded panel of SCLC cell lines based upon the level of synergy observed and potential clinical use of the compounds in a therapeutic regimen in SCLC. Targeted therapies and chemical probes that  
10 inhibited the epigenetic regulator BET (particularly Brd4) ((+)-JQ1, CPI-203, MS 436, GSK1324726A, GSK1210151A and OTX015) and anti-apoptotic regulator BCL2 (Obatoclax, ABT-199, ABT-737, and TW-37) were highly synergistic with LSD1 inhibition. Synergy was also observed with other epigenetic regulators, EZH2 (e.g. CPI-169, EPZ005687, EPZ-6438, GSK126, GSK343) and DOT1L (e.g. EPZ-5676, SGC 0946), albeit at a low level compared to  
15 BET (particularly BRD4) and BCL2 inhibitors..

Inhibitors of the Notch, Hedgehog or Smoothened pathway were not synergistic with (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine treatment, indicating that LSD1 inhibition sensitizes cell lines to select compound and drug classes that include HDAC and BET inhibitors, DNA alkylating agents, topoisomerase inhibitors, anti-mitotic agents,  
20 Aurora kinase inhibitors, BCL2 family inhibitors, EZH2, DOT1L and Chk inhibitors.

Cells were treated and data analyzed as described in Example 2 above.

Table 4. Synergistic effects of combinations of (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine with a panel of suitable active pharmaceutical ingredients (API).

2nd API:	Synergy Scores in NSCLC			Synergy Scores in SCLC						
	CA L-12T	A549	NCI-H441	NCI-H187	NCI-H1417	NCI-H1876	NCI-H510	NCI-H1048	NCI-H446	SB C-5
(+)-JQ1	0.51	0.07	0.12	11.29	39.59	18.65	11.88	0.68	1.74	0.15
ABT-263	0.01	0.89	0.75	14.31	19.10	23.63	18.16	14.92	0.29	3.35
ABT-888	0.22	0.02	0.04	2.26	3.26	8.62	4.10	0.40	0.05	0.27
Belinostat	0.42	0.52	0.66	14.35	19.12	9.05	15.72	1.61	3.21	1.84
Benda-mustine	0.10	0.02	0.01	8.19	5.20	12.38	1.12	2.01	0.10	0.37
BGJ398	0.49	0.16	0.17	9.26	9.66	19.85	4.42	9.55	17.33	0.69
Carbo-	0.06	0.03	1.27	7.49	10.45	10.90	9.96	1.47	1.58	0.22

2nd API:	Synergy Scores in NSCLC			Synergy Scores in SCLC						
	CA L-12T	A549	NCI-H441	NCI-H187	NCI-H1417	NCI-H1876	NCI-H510	NCI-H1048	NCI-H446	SB C-5
platin										
CGK 733	0.39	3.07	0.27	3.35	0.91	4.59	3.03	1.21	5.16	0.78
Cisplatin	0.85	0.04	1.80	4.91	15.96	5.34	9.89	3.72	1.56	0.48
Docetaxel	1.42	1.21	1.82	13.67	11.72	19.92	31.60	0.50	3.33	0.88
Doxo-rubicin	0.76	0.45	6.86	6.85	33.43	3.74	15.96	3.13	4.93	1.20
Erlotinib	0.43	0.18	0.70	3.17	2.87	5.21	3.29	0.50	1.99	0.32
Etoposide	0.15	0.00	5.83	8.28	13.22	11.17	11.55	1.04	0.12	0.54
Fluorou-racil	0.07	0.00	0.68	1.97	1.63	4.91	0.62	0.80	0.09	0.42
Gem-citabine	0.58	0.93	6.78	19.43	15.18	2.74	23.37	1.11	1.01	0.33
GSK-J1	0.01	0.07	0.09	2.14	2.26	10.21	3.80	0.23	0.03	0.85
Irinotecan	0.14	0.02	3.45	13.74	21.62	8.75	17.17	2.00	1.16	0.48
Lapatinib	1.23	0.00	0.36	1.23	7.00	5.69	20.64	0.75	20.44	0.03
LY-2603618	1.46	0.20	2.22	6.47	1.05	11.98	14.09	1.47	0.37	0.87
Menadione	0.01	0.06	0.02	3.89	4.18	8.81	3.63	0.45	0.06	0.52
Metho-trexate	0.25	1.95	0.29	1.45	1.82	4.20	1.75	0.62	0.74	0.34
MLN8237	0.76	0.08	0.81	7.60	9.15	23.31	28.91	1.02	1.16	0.51
Nutlin-3A	0.11	0.04	0.36	1.56	2.56	7.24	1.63	0.29	0.36	0.48
Paclitaxel	0.83	1.11	1.33	12.68	14.10	20.99	28.03	2.26	2.64	1.83
Pano-binostat	1.11	1.34	0.45	10.41	17.19	2.60	12.47	0.58	15.30	1.13
Peme-trexed	2.12	0.01	2.76	4.10	2.54	4.27	0.86	0.20	0.18	0.11
PF-04217903	0.15	0.07	0.16	0.99	0.81	6.68	1.11	0.56	0.01	0.49
Temozo-lomide	0.04	0.00	4.12	2.52	21.79	8.49	5.43	0.81	0.37	0.10
Topotecan	0.08	1.92	1.98	11.49	2.24	6.23	23.12	3.73	6.87	0.20
Vincristine	0.49	1.23	0.04	18.07	27.52	7.80	10.01	0.08	2.31	0.15

Table 5. in vitro Synergistic Effects in SCLC cell lines of combinations of (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine with a panel of suitable active pharmaceutical ingredients (API).

2nd API	Synergy Scores of SCLC cell lines									
	NCI-H1876	NCI-H510	NCI-H1417	NCI-H187	NCI-H2171	NCI-H69	SHP-77	NCI-H526	DMS-114	NCI-H446
(+)-JQ1	9.15	24.21	7.87	2.83	8.69	6.44	0.45	8.06	1.55	4.03
ABT-199	4.63	13.46	11.01	1.95	0.04	5.07	0.33	3.47	0.03	0.07
ABT-263	21.80	10.70	12.21	2.51	6.19	8.22	3.59	4.18	0.26	1.41
ABT-737	19.84	11.80	25.26	4.17	3.15	4.01	1.88	11.44	0.42	1.73
BMS-906024	0.22	0.00	0.33	0.45	0.19	8.46	0.03	5.80	0.02	0.12
CPI-169	8.50	5.76	0.38	0.09	0.00	0.03	0.03	2.46	0.06	0.31
CPI-203	15.25	25.41	13.47	1.24	6.83	8.68	0.37	11.09	1.58	0.58
EPZ005687	4.57	10.77	0.46	0.10	0.48	0.80	0.23	3.66	0.14	0.35
EPZ-5676	6.68	19.72	0.87	0.11	0.05	0.70	0.12	1.20	0.00	0.24
EPZ-6438	8.18	9.06	0.31	0.03	0.01	0.68	0.02	1.82	0.04	0.00
FLI 06	6.95	0.83	0.28	1.71	1.76	4.01	6.32	2.18	5.48	3.29
GDC-0449	5.64	3.05	0.25	0.16	0.10	0.90	0.24	1.76	0.01	0.16
GSK1210151A	11.42	15.35	15.13	1.77	10.11	10.38	0.66	12.65	0.67	0.32
GSK126	10.80	12.69	0.41	0.35	0.80	1.63	0.02	3.20	0.51	0.41
GSK1324726A	15.98	21.32	21.84	2.66	9.12	10.17	0.72	12.18	1.22	1.25
GSK343	0.81	4.25	0.24	0.15	0.36	0.81	0.13	2.48	0.05	0.01
LDE225	0.57	5.81	1.01	0.73	0.34	0.78	0.53	2.17	0.08	0.02
LY-3039478	0.19	0.00	0.21	0.47	0.30	4.94	0.12	7.90	0.00	0.28
MK-0752	0.69	0.71	0.15	0.32	0.17	3.88	0.03	6.03	0.04	0.43
MS 436	5.74	5.52	12.37	0.06	1.37	3.82	0.23	15.84	0.18	0.42
Obatoclax	6.11	6.31	2.36	0.81	0.61	6.01	4.76	8.19	1.87	2.57
OTX015	14.88	11.52	14.26	0.88	5.30	8.65	0.78	16.72	0.10	0.44
PF-3084014	0.25	0.03	0.02	0.10	1.02	1.53	0.19	8.64	0.02	1.31
SGC 0946	6.81	24.63	0.28	0.12	0.07	4.50	0.06	1.80	0.00	0.06
Taladegib	1.64	2.50	0.19	0.09	0.11	2.35	0.19	3.66	0.10	0.01
TW-37	0.86	6.95	8.08	0.57	0.72	2.23	0.45	3.60	0.59	0.28

**Example 4. LSD1 inhibitors improve potency and duration of SCLC- SOC in vivo**

In vivo, the effects of (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine treatment synergized with both etoposide and carboplatin to induce a cytotoxic response as can be seen from Figure 2A. In the clinic the one standard of care (SOC) for SCLC is to 5 combine etoposide and carboplatin.

In vivo, the combination of etoposide and carboplatin promotes rapid tumor regression during the dosing period in the NCI-H526 model as can be seen from Figure 2B. The addition of (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine to SOC improved the duration of tumor regression and significantly delayed tumor regrowth by 30 days after the 10 suspension of dosing. Together the data suggest that LSD1 inhibition can sensitize cells to select chemotherapeutics and targeted agents in vitro and in vivo.

**NCI-H526 Models:**

8-12-week old nu/nu mice were injected with 1x10<sup>7</sup> H526 cells or 5x10<sup>6</sup> SHP-77 resuspended in 100 µL of 1:1 mixture of Matrigel® and PBS. Tumors were staged at 100-150 mm<sup>3</sup> animals and 15 distributed into dosing groups. (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine was administered at a dose of 40 µg per kg (upk) five days on/two days off (5/2) for three weeks. Etoposide was administered i.p. at a dose of 5 mg per kg (mpk) daily for five days (qdx5). Carboplatin was administered i.p. at a dose of 100 mpk weekly for three weeks (qwrx3). In 20 combination with etoposide and carboplatin, (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine was administered at a dose of 20 upk five days on/two days off for three weeks. Tumor volume was measure biweekly using a digital caliber. The endpoint of the experiment was a tumor volume of 1000 mm<sup>3</sup> or 90 days, whichever came first. Statistical analysis was performed using unpaired t-test and Gehan-Breslow-Wilcoxon test.

**Example 5. Cell response to LSD1 inhibition**

25 The compound potency determination was performed by culturing 19 small cell lung cancer cell lines (of various tumor origins) for 4 days at 37 degrees C at 5% CO<sub>2</sub> in humidified incubators in the presence of serially diluted (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine bis-hydrochloride.

As a positive control for cytotoxicity the Hsp90 inhibitor 17-N-allylamino-17-30 demethoxygeldanamycin (17-AAG, a geldanamycin analogue) was used as positive control in serial dilution. Each of the cell lines was propagated and tested in distinct optimized media as recommended by ATCC or cell line source.

Small cell lung cancer cell lines can be categorized as “classic” or “variant”, based on their enzymatic activities, cellular morphologies, and growth phenotypes (Desmond *et al*<sup>110</sup>).

Shoemaker R.H.<sup>111</sup>). Classic cell lines express elevated levels of L-dopa decarboxylase, bombesin-like immunoreactivity, neuron-specific enolase, and the brain isozyme of creatine kinase; variant cell lines continue to express neuron-specific enolase and the brain isozyme of creatine kinase, but have undetectable levels of L-dopa decarboxylase and bombesin-like immunoreactivity. Unlike classic cell lines, some variant cell lines are amplified for and have increased expression of the c-myc (MYC)oncogene.

Some cell lines exhibit features specific to both a classic and variant subtype. For example, SHP-77 has biochemical properties of classic SCLC (e.g. elevated levels of L-dopa decarboxylase and bombesin-like immunoreactivity) but the morphology of a variant. According to the literature, SHP-77 is considered classic based on its biochemical profile but variant based on its morphology and growth characteristic.

For NCI-H2029 and SBC-5 no subtype is reported in literature however their transcriptomic profile (mRNA expression levels of DDC/GRP) clearly shows their class membership which is provided in brackets in Table 6.

Depending on their responses to (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine bis-hydrochloride, cell lines are classified as either “sensitive” [S], defined as having EC50 < 0.05 μM, or “resistant”, defined as having EC50 >= 0.05 μM [R].

Cell-based response to (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine bis-hydrochloride was greater in classic SCLC cell lines compared to variant SCLC cell lines (p-value 0.0055 Table 6). Out of the 19 SCLC cell lines tested, 9 out of 11 classic cell lines [C] are sensitive [S], and 7 out of 8 variant cell lines [V] are resistant [R] (Table 7).

The variant and classic subtypes predict response to an LSD1 inhibitor therapy with a sensitivity of 82% and specificity of 88%.

Higher copy number variations (CNV) in the MYC gene (Ensemble Gene ID: ENSG00000136997) are associated with small cell lung cancer of variant subtype (V) (Am J Pathol. 1988 Jul; 132(1): 13–17). Indeed, among the 19 cell lines here described, high copy number variations of the MYC gene (CNV >> 2) were found exclusively in cell lines with a variant subtype (NCI-H2171, NCI-H446, NCI-H82, see Table 6). Furthermore, all three cell lines with high copy number variations of MYC were resistant to LSD1 inhibition, indicating that the presence of MYC amplification can predict resistance (R) to an LSD1 inhibition therapy.

Principal component analysis carried out from RNA-seq data for the cell lines of Table 6 surprisingly revealed that classic and variant SCLC cell lines form distinct clusters. (Figure 3).

Cell Line	SubType Lit.	Max. Response (%)	EC50 (μM)	Sensitivity to LSD1 inh.	MYC CNV
NCI-H1876	C	145	$4.32 \times 10^{-5}$	S	0.81
NCI-H69	C	44	$5.85 \times 10^{-4}$	S	1.14
NCI-H510A	C	68	$3.15 \times 10^{-4}$	S	2.56
NCI-H146	C	48	$1.00 \times 10^{-4}$	S	1.24
NCI-H187	C	61	$1.36 \times 10^{-4}$	S	1.12
NCI-H2081	C	10	$9.20 \times 10^{-4}$	S	2.22
NCI-H345	C	7	$2.75 \times 10^{-5}$	S	1.26
NCI-H526	V	35	$6.32 \times 10^{-4}$	S	1.07
NCI-H748	C	13	$3.00 \times 10^{-4}$	S	1.05
NCI-H1417	C	77	$3.02 \times 10^{-4}$	S	NA
DMS-114	V	0	$>5 \times 10^{-2}$	R	1.21
NCI-H1048	V	27	$>5 \times 10^{-2}$	R	0.98
NCI-H2029	(C)	0	$>5 \times 10^{-2}$	R	1.23
NCI-H2171	V	0	$>5 \times 10^{-2}$	R	7.46
NCI-H2227	C	0	$>5 \times 10^{-2}$	R	0.81
NCI-H446	V	7	$>5 \times 10^{-2}$	R	6.72
NCI-H82	V	0	$>5 \times 10^{-2}$	R	9.44
SHP-77	V (C)	0	$>5 \times 10^{-2}$	R	1.36
SBC-5	(V)	23	$>5 \times 10^{-2}$	R	1.21

Table 6. Cell-based response to (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine bis-hydrochloride in classic SCLC cell lines [C] as compared to variant SCLC cell lines [V].

	Classic [C]	Variant [V]
Sensitive [S]	9	1
Resistant [R]	2	7

Table 7. Contingency matrix showing the number of classic and variant cell lines that are

5 sensitive or resistant to an LSD1 inhibition therapy.

#### **Example 6. Gene panel to predict response to LSD1 inhibition**

Differential gene expression analysis between two resistant cell lines that have features of a classic subtype (SHP-77 and NCI-2029) and classic and variant cell lines which are sensitive (NCI-H1876, NCI-H69, NCI-H510A, NCI-H146, NCI-H187, NCI-H2081, NCI-H345, NCI-H526, NCI-H748) interestingly revealed that lower mRNA expression levels of HOXA10 correlate with resistance to an LSD1 inhibition therapy (Table 8). This suggests that low levels of HOXA10 mRNA may predict resistance to an LSD1 inhibition therapy even in the presence of a classic phenotype.

A predictive mRNA expression signature of response to an LSD1 inhibition therapy was defined by selecting top differentially expressed genes between classic and variant cell lines (Table 9). Based on adjusted p-values, DDC (adjusted p-value 4.37E-23), which encodes the enzyme L-dopa decarboxylase, and GRP (adjusted p-value 5.19E-14), which encodes bombesin-like immunoreactivity peptides rank as second and sixth most differentially expressed genes. The most differentially expressed gene is ASCL1 (adjusted p-value 2.6E-23). ASCL1 is a transcription factor required for proper development of pulmonary neuroendocrine cells, and is essential for the survival of a majority of lung cancers (Augustyn *et al.*<sup>112</sup>).

As discussed in Example 5 above, MYC amplification can predict resistance to LSD1 inhibition therapy.

Table 10 lists normalized read counts of DDC, GRP, and ASCL1 across the 19 cell lines of Table 6 described while Table 11 lists the corresponding z-scores.

The heat map of Figure 4 visually shows that sensitive cell lines can be distinguished from resistant cell lines based on mRNA expression levels of genes listed in Table 9, and based on expression levels of HOXA10 and copy number variations of MYC.

Ensembl Gene ID*	Gene	baseMean	log2Fold Change	pvalue
ENSG00000253293	<b>HOXA10</b>	2717.58	8.21	7.45E-023

Table 8. Principal component analysis for HOXA10 carried out from RNA-seq data for selected cell lines (\*<http://www.ensembl.org/>, Cunningham F. *et al.*<sup>106</sup>)

Ensembl Gene ID*	Gene	baseMean	log2Fold Change	pvalue
ENSG00000139352	ASCL1	43665.33	6.82	2.62E-023
ENSG00000132437	DDC	15817.8	6.42	4.37E-023
ENSG00000086548	CEACAM6	210.89	6.34	1.23E-017
ENSG00000188306	LRRIQ4	90.81	5.1	4.61E-016
ENSG00000131910	NR0B2	600.58	6.35	5.15E-015
ENSG00000134443	GRP	6711.45	6.52	5.19E-014
ENSG00000105388	CEACAM5	1788.17	6.22	9.23E-014
ENSG00000125285	SOX21	523.59	5.88	2.29E-013
ENSG00000167332	OR51E2	3047.56	6.39	3.37E-013
ENSG00000166562	SEC11C	36139.18	3.33	5.01E-013
ENSG00000164929	BAALC	1833.4	4.33	1.66E-012
ENSG00000141519	CCDC40	2309.83	2.26	2.07E-012
ENSG00000169213	RAB3B	28247.78	3.64	2.80E-012

Ensembl Gene ID*	Gene	baseMean	log2Fold Change	pvalue
ENSG00000091844	RGS17	2783.99	3.2	3.72E-012
ENSG00000164163	ABCE1	13643.12	-1.08	4.99E-012
ENSG00000157557	ETS2	11829.42	3.06	5.19E-012
ENSG00000197599	CCDC154	1198.98	4.61	7.21E-012
ENSG00000077327	SPAG6	767.39	5.34	7.85E-012
ENSG00000005421	PON1	334.17	5.15	1.53E-011
ENSG00000002933	TMEM176A	3224.04	5.38	7.65E-011
ENSG00000175262	C1orf127	596.15	5.04	1.19E-010
ENSG00000073792	IGF2BP2	2414.53	-5.17	1.28E-010
ENSG00000115461	IGFBP5	86866.7	4.41	1.38E-010
ENSG00000162981	FAM84A	4954.8	3.93	1.45E-010
ENSG00000125798	FOXA2	4530.46	5.12	1.71E-010

Table 9. Genes sorted according to pvalue obtained through principal component analysis carried out from RNA-seq data for selected cell lines (\*<http://www.ensembl.org/>, Cunningham F. et al.<sup>106</sup>).

Cell Line	ASCL1	DDC	GRP	HOXA10
NCI-H1417	42666.4	16161.1	10935.2	3327.72
NCI-H1876	34116.3	986.718	43.7461	2779.5
NCI-H69	19902.1	25773.6	3256.24	4271.2
NCI-H510A	79879.7	19456.3	27861	2730.12
NCI-H2227	4515.83	2005.02	645.86	2.59381
NCI-H2029	127171	39070.6	1800.43	10.0396
NCI-H146	59238.2	45308.8	426.015	2126.39
NCI-H187	71323.6	4363.62	130.681	2448.85
NCI-H2081	69670.9	29683.5	2.97459	3423.76
NCI-H345	81805.8	16935.7	30601.3	263.11
SHP-77	115523	71808.9	39002.6	4.72759
NCI-H748	122007	27938.7	12773.8	3940.53
DMS-114	59.1696	16.3227	12.242	1462.92
NCI-H1048	38.9626	90.2292	0	1168.88
NCI-H2171	1115.78	368.976	0	1248.61
NCI-H446	13.1805	32.0098	11.2976	2818.75
NCI-H82	577.05	486.304	9.30725	221.047
SBC5	4.51028	13.5308	0	617.908
NCI-H526	11.9576	38.2644	4.78305	4091.9

Table 10: Normalized read counts from mRNA expression levels.

Cell Line	ASCL1	DDC	GRP	HOXA10
NCI-H1417	0.63	0.69	1.09	0.67
NCI-H1876	0.57	-0.24	-0.34	0.6

Cell Line	ASCL1	DDC	GRP	HOXA10
NCI-H69	0.42	0.85	0.78	0.78
NCI-H510A	0.8	0.76	1.34	0.59
NCI-H2227	0.02	0	0.35	-2.31
NCI-H2029	0.93	0.99	0.62	-1.82
NCI-H146	0.72	1.04	0.25	0.48
NCI-H187	0.77	0.26	-0.06	0.54
NCI-H2081	0.77	0.9	-0.98	0.69
NCI-H345	0.81	0.71	1.36	-0.43
SHP-77	0.9	1.19	1.43	-2.11
NCI-H748	0.92	0.88	1.13	0.75
DMS-114	-1.16	-1.59	-0.66	0.32
NCI-H1048	-1.27	-1.04	-1.34	0.22
NCI-H2171	-0.36	-0.57	-1.34	0.25
NCI-H446	-1.55	-1.38	-0.68	0.6
NCI-H82	-0.54	-0.48	-0.73	-0.51
SBC5	-1.81	-1.65	-1.34	-0.06
NCI-H526	-1.58	-1.32	-0.88	0.76

Table 11: Z-scores generated by GenePattern from normalized mRNA read counts.

**Example 7. Neuroendocrine gene panel to predict response to LSD1 inhibition**

mRNA expression levels for a second set of genes according to Table 12 (NCAM1, NCAM2, NEUROD1, KRT8, ENO2, AVP, OXT, SYP, CHGA, CHGB, SOX21, BCL2) that

5 includes genes representative of a neuroendocrine phenotype and that are used as immunohistochemical markers for diagnosing lung neuroendocrine tumors are strongly downregulated in resistant cell lines DMS114, SBC5, and NCI-H1048, as illustrated in Figure 5. This is an agreement with our hypothesis that an LSD1 inhibition therapy stops cellular growth in tumors of neuroendocrine origin.

10 Tables 13A and 14B list normalized read counts of the genes of Table 12 across the 19 cell lines of Table 6 described.

Ensembl Gene ID*	Gene
ENSG00000149294	NCAM1
ENSG00000154654	NCAM2
ENSG00000162992	NEUROD1
ENSG00000170421	KRT8
ENSG00000111674	ENO2
ENSG00000101200	AVP
ENSG00000101405	OXT
ENSG00000102003	SYP

Ensembl Gene ID*	Gene
ENSG00000100604	CHGA
ENSG00000089199	CHGB
ENSG00000125285	SOX21
ENSG00000171791	BCL2

Table 12. Genes of the second neuroendocrine gene panel (\*<http://www.ensembl.org/>, Cunningham F. *et al.*<sup>106</sup>).

Cell Line	NCAM1	NCAM2	NEUROD1	KRT8	ENO2	AVP
NCI-H1417	52961.1	230.0	257.7	32261.1	32287.3	5.8
NCI-H1876	12131.4	111.0	143.4	36460.8	37021.4	33.2
NCI-H69	53702.4	16861.8	295.0	28560.6	28765.0	18.6
NCI-H510A	21010.6	197.4	255.2	67662.7	11901.4	1.7
NCI-H2227	42956.2	32469.4	1273.6	181.6	35558.6	2.6
NCI-H2029	37343.8	70.3	244.3	76401.1	22753.0	0.0
NCI-H146	39176.8	1929.1	173.4	50190.4	32430.6	5.5
NCI-H187	47022.6	8.5	31.3	61809.4	32195.9	2.8
NCI-H2081	37569.1	1279.1	2427.3	26842.7	32137.5	0.0
NCI-H345	62260.5	131.6	96.7	46256.4	32848.5	45.6
SHP-77	21787.1	990.4	0.0	35148.0	8851.6	0.0
NCI-H748	21844.8	892.7	12.1	1508.8	44468.6	0.9
DMS-114	95.9	512.1	18.4	377.5	3260.5	0.0
NCI-H1048	14740.2	760.8	0.0	12726.4	38304.4	0.0
NCI-H2171	16524.2	35.4	60402.8	26223.8	212034.0	0.0
NCI-H446	79657.4	3747.0	19164.5	45.2	36229.5	0.0
NCI-H82	20878.5	437.4	34283.3	27.9	22702.7	0.0
SBC-5	130.8	19026.6	9.0	640.5	160.1	0.0
NCI-H526	44561.3	0.0	23.9	38233.3	24912.5	0.0

Table 13A. Normalized read counts from mRNA expression levels.

Cell Line	OXT	SYP	CHGA	CHGB	SOX21	BCL2
NCI-H1417	NA	6220.2	44388.5	11152.1	20.4	6170.7
NCI-H1876	4.2	13216.2	7061.0	3968.7	1201.4	4126.7
NCI-H69	9.5	10950.9	16527.4	52724.6	20.9	10853.4
NCI-H510A	1.8	9116.9	22660.3	20808.2	79.1	27378.7
NCI-H2227	0.0	19962.0	11537.3	14927.4	2.6	1136.1
NCI-H2029	0.0	8905.1	16397.9	5776.1	786.4	8687.6
NCI-H146	16.9	14940.0	22829.6	9597.3	660.2	10340.5
NCI-H187	0.0	5696.0	23923.2	6804.0	264.2	14934.6
NCI-H2081	0.0	14334.6	79374.1	10934.6	44.6	2778.3
NCI-H345	0.0	9686.8	22971.1	7702.7	4953.5	39332.3
SHP-77	0.0	7861.2	47453.1	61511.4	480.6	7364.0
NCI-H748	2.7	19958.6	46176.5	7932.8	1408.9	11595.8
DMS-114	0.0	4299.0	1897.5	6161.8	10.2	185.7

Cell Line	OXT	SYP	CHGA	CHGB	SOX21	BCL2
NCI-H1048	0.0	260.4	16.4	6.2	4.1	8063.2
NCI-H2171	0.0	12335.6	9407.4	23159.9	0.0	1065.6
NCI-H446	0.0	7403.7	10702.6	5688.3	1.9	2398.9
NCI-H82	4.7	31714.5	19382.3	7303.9	4.7	148.9
SBC-5	0.0	3642.1	311.2	203.0	4.5	306.7
NCI-H526	0.0	12538.8	9920.1	9877.0	0.0	16511.1

Table 13B. Normalized read counts from mRNA expression levels.

**Example 8. Signature scores to predictive response to LSD1 inhibition**

Normalized expression levels (Norm\_read\_count) of ASCL1, DDC, GRP, and HOXA10 and MYC copy number variations (Copy\_number\_variation) were used to generate a gene 5 signature to predict response to an LSD1 inhibition therapy as follows:

A score was generated from the following equation, obtained by partial least square (PLS) analysis using the second principal component:

$$\begin{aligned}
 \text{Signature Score 1} = & \quad 0.0900693 \\
 & + \text{Norm\_read\_count(ASCL1)} \times 0.00000211296 \\
 & + \text{Norm\_read\_count(DDC)} \times 0.000000536658 \\
 & + \text{Norm\_read\_count(GRP)} \times 0.00000297345 \\
 & + \text{Norm\_read\_count(HOXA10)} \times 0.000234721 \\
 & - \text{Copy\_number\_variation(MYC)} \times 0.0537056
 \end{aligned}$$

A Signature Score 1 > 0.5 predicts response to an LSD1 inhibition therapy (Fisher's exact 15 test two-tailed p 0.0001, sensitivity 90%, specificity 100%) as depicted in Figure 6.

Alternatively, a score was generated from the following equation, obtained by partial least square analysis using the first principal component:

$$\begin{aligned}
 \text{Signature Score 2} = & \quad 0.483918 \\
 & + \text{Norm\_read\_count (ASCL1)} \times 0.00000188066 \\
 & + \text{Norm\_read\_count(DDC)} \times 0.00000188066 \\
 & + \text{Norm\_read\_count(GRP)} \times 0.00000352033 \\
 & - \text{Copy\_number\_variation(MYC)} \times 0.0407898
 \end{aligned}$$

A Signature Score 2 > 0.5 predicts response to an LSD1 inhibition therapy (Fisher's exact test two-tailed p 0.0055, sensitivity 90%, specificity 77.8%) as depicted in Figure 7.

25 Further, a score was generated from the following equation, obtained by partial least square analysis using the first principal component:

$$\begin{aligned}\text{Signature Score 3} = & 0.393569 \\ & + \text{Norm\_read\_count (ASCL1)} \times 0.00000182731 \\ & + \text{Norm\_read\_count (DDC)} \times 0.00000189664 \\ & + \text{Norm\_read\_count (GRP)} \times 0.00000342046\end{aligned}$$

5 A Signature Score 3 > 0.45 predicts response to an LSD1 inhibition therapy (Fisher's exact test two-tailed p 0.0055, sensitivity 90%, specificity 77.8%) as depicted in Figure 8.

A signature score above the reference level indicates a high likelihood of response to treatment with an LSD1 inhibitor, whereas a signature score below said level indicates a lower likelihood to respond to such treatment. A higher score is associated with higher mRNA 10 expression of ASCL1, DDC, GRP, HOXA10, and with lower copy number variations in MYC.

#### Example 9. *In vivo* tumor growth inhibition

##### NCI-H510A Models:

7-8-week old athymic nude mice were injected with  $5 \times 10^6$  H510A cells resuspended in 100  $\mu\text{L}$  of 1:1 mixture of Matrigel® matrix (Corning Inc., Tewksbury/MA, C.S. Hughes *et al.*<sup>113</sup>) 15 and PBS. Tumors were staged at  $200\text{-}300 \text{ mm}^3$  animals and distributed into dosing groups. (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine was administered at a dose of 40  $\mu\text{g}$  per kg (upk) five days on/two days off until end of study. Tumor volume was measure biweekly using a digital caliber. The study was concluded when mean tumor volume within control group reached  $2000 \text{ mm}^3$  or 28 days post-staging. Statistical analysis was performed 20 using unpaired t-test.

##### NCI-H526 and SHP-77 Models:

8-12-week old nu/nu mice were injected with  $1 \times 10^7$  H526 cells or  $5 \times 10^6$  SHP-77 resuspended in 100  $\mu\text{L}$  of 1:1 mixture of Matrigel® and PBS. Tumors were staged at  $100\text{-}150 \text{ mm}^3$  animals and distributed into dosing groups. (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-25 diamine was administered at a dose of 40 upk five days on/two days off until end of study. Tumor volume was measure biweekly using a digital caliber. The study was concluded when mean tumor volume within control group reached  $2000 \text{ mm}^3$  or 28 days post-staging. Statistical analysis was performed using unpaired t-test.

The *in vitro* activity of the LSD1 inhibitor (trans)-N1-((1R,2S)-2-30 phenylcyclopropyl)cyclohexane-1,4-diamine translated into *in vivo* growth inhibition in the H510A xenograft model as shown in Figure 9. Treatment of (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine in the "responsive signature" positive cell line H510A model resulted in a modest but measurable tumor growth inhibition of 34% compared to untreated controls after 21 days of dosing. These results suggest that the 15 gene response 35 signature as previously defined may predict *in vivo* sensitivity to (trans)-N1-((1R,2S)-2-

phenylcyclopropyl)cyclohexane-1,4-diamine. The *in vivo* activity of (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine has also been assessed in the “response signature positive” SHP-77 and “response signature negative” H526 xenografts to validate the predictability of the gene signature from *in vitro* results.

5 **Example 10. Expression patterns in SCLC patient samples**

Gene expression patterns in a set of SCLC patient samples were found to be similar to those observed in SCLC cell lines (Example 6, Figure 4), suggesting that use of LSD1 inhibitor response gene signature, particularly the use of the (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine response gene signature, may increase the 10 likelihood of identifying patients who will clinically benefit from LSD1 inhibitor based therapies, particularly from (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine based therapies.

Figure 10 provides a Heat Map showing mRNA expression (as z-scores) patterns in SCLC patient samples comprising the genes of Table 8, Table 9 and MYC. Higher z-scores 15 correlate with better sensitivity.

The dataset used corresponds to the dataset EGAD00001000223 obtained from European Genome-phenome Archive (EGA) of the The European Bioinformatics Institute, Part of the European Molecular Biology Laboratory (EMBL-EBI, Hinxton/UK, <https://www.ebi.ac.uk/ega/datasets/EGAD00001000223>). The patient ID (SAMxxxxxx) 20 corresponds to the ID used in this dataset.

---

<sup>1</sup> Shi *et al.* (2004) Cell 119:941

<sup>2</sup> WO 2011/131697 A1

<sup>3</sup> WO 2012/135113 A2

<sup>4</sup> WO 2013/057322 A1

<sup>5</sup> WO 2010/143582

<sup>6</sup> WO 2011/131576

<sup>7</sup> WO 2013/022047

<sup>8</sup> WO 2013/025805

<sup>9</sup> WO 2014/058071

<sup>10</sup> WO 2014/084298

<sup>11</sup> WO 2014/085613

<sup>12</sup> WO 2014/086790

<sup>13</sup> WO 2014/164867

<sup>14</sup> WO 2014/194280

<sup>15</sup> WO 2014/205213

<sup>16</sup> WO 2015/021128

<sup>17</sup> WO 2015/031564  
<sup>18</sup> WO 2015/089192  
<sup>19</sup> WO 2015/120281  
<sup>20</sup> WO 2015/123465  
<sup>21</sup> WO 2015/123437  
<sup>22</sup> WO 2015/123424  
<sup>23</sup> WO 2015/123408  
<sup>24</sup> WO 2015/134973  
<sup>25</sup> WO 2015/156417  
<sup>26</sup> WO 2016/004105  
<sup>27</sup> WO 2016/007722  
<sup>28</sup> WO 2016/007727  
<sup>29</sup> WO 2016/007731  
<sup>30</sup> WO 2016/007736  
<sup>31</sup> WO 2016/034946  
<sup>32</sup> WO 2016/037005  
<sup>33</sup> CN 105541806  
<sup>34</sup> WO 2016/123387  
<sup>35</sup> WO 2016/130952  
<sup>36</sup> CN 105924362  
<sup>37</sup> CN 105985265  
<sup>38</sup> WO 2016/161282  
<sup>39</sup> CN 106045862  
<sup>40</sup> CN 106045881  
<sup>41</sup> WO 2016/172496  
<sup>42</sup> WO 2016/177656  
<sup>43</sup> WO 2017/004519  
<sup>44</sup> WO 2017/027678  
<sup>45</sup> WO 2010/138588 A2  
<sup>46</sup> US 2007/0027135 A1  
<sup>47</sup> WO 2005/049594 A1  
<sup>48</sup> US 2006/0229289 A1  
<sup>49</sup> WO 2011/091213 A2  
<sup>50</sup> WO 2009/040517 A2  
<sup>51</sup> DD 159877 A1  
<sup>52</sup> WO 2006/000420 A1  
<sup>53</sup> WO 2012/129353 A1  
<sup>54</sup> ES 544159 A1  
<sup>55</sup> WO 2007/015632 A1  
<sup>56</sup> Rosenberg B. *et al.* Nature (1969) 222(5191):385-6  
<sup>57</sup> WO 2013/120104 A2  
<sup>58</sup> WO 2014/134583 A2  
<sup>59</sup> EP 253738 A1  
<sup>60</sup> DE 2510866 A1  
<sup>61</sup> Daigle S.R. *et al.* Cancer Cell (2011) 20(1):53-65  
<sup>62</sup> WO 2012/118812 A2  
<sup>63</sup> WO 2012/075381 A2  
<sup>64</sup> WO 2012/142504 A1  
<sup>65</sup> CH 514578 A

<sup>66</sup> WO 2013/178821 A1  
<sup>67</sup> US 2,802,005  
<sup>68</sup> WO 2006/028958 A2  
<sup>69</sup> GB 2136425  
<sup>70</sup> WO 2011/140324 A1  
<sup>71</sup> WO 2011/054843 A1  
<sup>72</sup> WO 2011/140325 A1  
<sup>73</sup> WO 2012/052390 A1  
<sup>74</sup> US 6,121,451 A  
<sup>75</sup> WO 2011/143651 A1  
<sup>76</sup> WO 99/35146 A1  
<sup>77</sup> WO 2010/033481 A1  
<sup>78</sup> WO 2006/105262 A1  
<sup>79</sup> WO 2013/016081 A1  
<sup>80</sup> US 2,331,725  
<sup>81</sup> WO 2002/081435 A1  
<sup>82</sup> WO 2008/063525 A1  
<sup>83</sup> WO 2012/116170 A1  
<sup>84</sup> US 2005/0282803  
<sup>85</sup> WO 2004/106328 A1  
<sup>86</sup> US 5,712,274 A  
<sup>87</sup> EP 253739 A1  
<sup>88</sup> WO 2002/022577 A2  
<sup>89</sup> EP 432677 A1  
<sup>90</sup> US 2007/0265272 A1  
<sup>91</sup> US 2005/0215610 A1  
<sup>92</sup> WO 93/07148 A1  
<sup>93</sup> Yu *et al.*, *Nature Communications* (2012) 3(1288):1-11  
<sup>94</sup> JP 10152462 A  
<sup>95</sup> WO 2010/147917 A1  
<sup>96</sup> DE 3231255 A1  
<sup>97</sup> EP 321122 A2  
<sup>98</sup> WO 2006/023778 A2  
<sup>99</sup> BE 624076  
<sup>100</sup> S. P. Parker, Ed., *McGraw-Hill Dictionary of Chemical Terms* (1984) McGraw-Hill Book Company, New York  
<sup>101</sup> Eliel, E. and Wilen, S., "Stereochemistry of Organic Compounds", John Wiley & Sons, Inc., New York, 1994  
<sup>102</sup> Cahn *et al.* *Angew. Chem. Inter. Edit.* 1966, 5, 385; errata 511  
<sup>103</sup> Ansel's *Pharmaceutical Dosage Forms and Drug Delivery Systems* (2004) Lippincott, Williams & Wilkins, Philadelphia  
<sup>104</sup> Rowe R.C, *Handbook of Pharmaceutical Excipients* (2005) Pharmaceutical Press, Chicago  
<sup>105</sup> Remington: *The Science and Practice of Pharmacy* (2000) Lippincott, Williams & Wilkins, Philadelphia  
<sup>106</sup> Cunningham F. *et al.*, *Nucl. Acids Res.* (2015) 43(D1): D662-D669  
<sup>107</sup> Mortazavi *et al.* *Nat Methods* (2008) 5(7):621-8  
<sup>108</sup> Selzer *et al.*, *Genes Chromosomes Cancer* (2005) 44(3):305-319  
<sup>109</sup> Reich M. *et al.*, *Nature Genetics* (2006) 38(5): 500-501

<sup>110</sup> Desmond *et al.*, Cancer Res (1985) 45(6):2913-2923

<sup>111</sup> Shoemaker R.H., Nature Reviews Cancer (2016) 6:813-823

<sup>112</sup> Augustyn *et al.*, Proc Natl Acad Sci U S A (2014) 111(41):14788-93

<sup>113</sup> Hughes *et al.*, Proteomics (2010) 10(9):1886-90

## Claims

1. A therapeutic combination comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof, and one or more active pharmaceutical ingredients selected from BCL2 inhibitors, BET inhibitors, EZH2 inhibitors, DOT1L inhibitors, Chk inhibitors, DNA alkylating agents, HDAC inhibitors, topoisomerase inhibitors, anti-mitotic agents, Aurora kinase inhibitors and pharmaceutically acceptable salts thereof.

2. A therapeutic combination comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof, and one or more active pharmaceutical ingredients selected from the list of ABT-199, ABT-263, ABT-737, ABT-888, ACY-1215, Belinostat, Bendamustine, BGJ398, BMS-906024, Carboplatin, CGK 733, Cisplatin, CPI-169, CPI-203, Docetaxel, Doxorubicin, EPZ-004777, EPZ005687, EPZ-5676, EPZ-6438, Erlotinib, Etoposide, FLI 06, Fluorouracil, GDC-0449, Gemcitabine, GSK126, GSK1324726A, GSK343, GSK-J1, GSK1210151A, Irinotecan, (+)-JQ1, Lapatinib, LDE225, LY2603618, LY-3039478, Menadione, Methotrexate, MK-0752, MLN8237, MS 436, Nutlin-3A, Obatoclax, OTX015, Paclitaxel, Panobinostat, Pemetrexed, PF-04217903, PF-3084014, SAHA, SGC 0946, SNDX-275, Taladegib, Temozolomide, Topotecan, TW-37, Vincristine and pharmaceutically acceptable salts thereof.

3. The therapeutic combination according to claim 1 or 2 comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof and one BCL2 inhibitor or a pharmaceutically acceptable salt thereof.

4. The therapeutic combination according to claim 1 or 2 comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof and one BCL2 inhibitor selected from the list of ABT-199, ABT-263, ABT-737, Obatoclax, TW-37 and a pharmaceutically acceptable salt thereof.

5. The therapeutic combination according to claim 1 or 2 comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof and one BET inhibitor or a pharmaceutically acceptable salt thereof.

6. The therapeutic combination according to claim 1 or 2 comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof and one BET inhibitor selected from the list of CPI-203, GSK1324726A, GSK1210151A, (+)-JQ1, MS 436, OTX015 and a pharmaceutically acceptable salt thereof.

7. The therapeutic combination according to claim 1 or 2 comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof and one EZH2 inhibitor or a pharmaceutically acceptable salt thereof.

8. The therapeutic combination according to claim 1 or 2 comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof and one EZH2 inhibitor selected from the list of CPI-169, EPZ005687, EPZ-6438, GSK126, GSK343 and a pharmaceutically acceptable salt thereof.

9. The therapeutic combination according to claim 1 or 2 comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof and one DOT1L inhibitor or a pharmaceutically acceptable salt thereof.

10. The therapeutic combination according to claim 1 or 2 comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof and one DOT1L inhibitor selected from the list of EPZ-004777, EPZ-5676, SGC 0946 and a pharmaceutically acceptable salt thereof.

11. The therapeutic combination according to claim 1 or 2 comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof and one Chk inhibitor or a pharmaceutically acceptable salt thereof.

12. The therapeutic combination according to claim 1 or 2 comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof and one Chk inhibitor selected from LY2603618 and a pharmaceutically acceptable salt thereof.

13. The therapeutic combination according to claim 1 or 2 comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof and one DNA alkylating agent or a pharmaceutically acceptable salt thereof.

14. The therapeutic combination according to claim 1 or 2 comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof and one DNA alkylating agent selected from the list of Bendamustine, Carboplatin, Cisplatin, Temozolomide and a pharmaceutically acceptable salt thereof.

15. The therapeutic combination according to claim 1 or 2 comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof and one HDAC inhibitor or a pharmaceutically acceptable salt thereof.

16. The therapeutic combination according to claim 1 or 2 comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof and one HDAC inhibitor

selected from the list of ACY-1215, Belinostat, Panobinostat, SAHA, SNDX-275 and a pharmaceutically acceptable salt thereof.

17. The therapeutic combination according to claim 1 or 2 comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof and one topoisomerase inhibitor or a pharmaceutically acceptable salt thereof.

18. The therapeutic combination according to claim 1 or 2 comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof and one topoisomerase inhibitor selected from the list of Etoposide, Irinotecan, Topotecan and a pharmaceutically acceptable salt thereof.

19. The therapeutic combination according to claim 1 or 2 comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof and one Aurora kinase inhibitor or a pharmaceutically acceptable salt thereof.

20. The therapeutic combination according to claim 1 or 2 comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof and one Aurora kinase inhibitor selected from the list of MLN8237 and a pharmaceutically acceptable salt thereof.

21. The therapeutic combination according to claim 1 or 2 comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof and one anti-mitotic agent or a pharmaceutically acceptable salt thereof.

22. The therapeutic combination according to claim 1 or 2 comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof and one anti-mitotic agent selected from the list of Docetaxel, Paclitaxel, Vincristine and a pharmaceutically acceptable salt thereof.

23. The therapeutic combination according to claim 1 or 2 comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof, a topoisomerase inhibitor or a pharmaceutically acceptable salt thereof, and a DNA alkylating agent or a pharmaceutically acceptable salt thereof.

24. The therapeutic combination according to claim 1 or 2 comprising an LSD1 inhibitor or a pharmaceutically acceptable salt thereof, Etoposide or a pharmaceutically acceptable salt thereof, and Carboplatin or a pharmaceutically acceptable salt thereof.

25. The therapeutic combination according to any of claims 1 to 24, wherein the LSD1 inhibitor is selected from the list of: 4-[[4-[[[(1R,2S)-2-phenylcyclopropyl]amino]methyl]-1-piperidinyl]methyl]-benzoic acid

(*trans*)-N1-((1*R*,2*S*)-2-phenylcyclopropyl)cyclohexane-1,4-diamine,  
(*R*)-1-((*trans*)-2-phenylcyclopropyl)amino)cyclohexyl)pyrrolidin-3-amine,  
4-(aminomethyl)-N-((*trans*)-2-phenylcyclopropyl)cyclohexanamine,  
N1-((*trans*)-2-phenylcyclopropyl)cyclohexane-1,3-diamine,  
N1-((*trans*)-2-phenylcyclopropyl)cyclobutane-1,3-diamine,  
N1-((*trans*)-2-phenylcyclopropyl)-2,3-dihydro-1*H*-indene-1,3-diamine,  
N1-methyl-N4-((*trans*)-2-phenylcyclopropyl)cyclohexane-1,4-diamine,  
N1-((*trans*)-2-(4-bromophenyl)cyclopropyl)cyclohexane-1,4-diamine,  
N1-(2-(*o*-tolyl)cyclopropyl)cyclohexane-1,4-diamine,  
N1-(2-(4-methoxyphenyl)cyclopropyl)cyclohexane-1,4-diamine,  
N1-(2-(2-fluorophenyl)cyclopropyl)cyclohexane-1,4-diamine,  
N1-(2-(naphthalen-2-yl)cyclopropyl)cyclohexane-1,4-diamine,  
N-(4'-((*trans*)-2-((4-aminocyclohexyl)amino)cyclopropyl)-[1,1'-biphenyl]-3-yl)-2-cyanobenzenesulfonamide,  
N1-((*trans*)-2-(4-(pyridin-3-ylmethoxy)phenyl)cyclopropyl)cyclohexane-1,4-diamine,  
and a pharmaceutically acceptable salt thereof.

26. The therapeutic combination according to any of claims 1 to 25, wherein the LSD1 inhibitor is (*trans*)-N1-((1*R*,2*S*)-2-phenylcyclopropyl)cyclohexane-1,4-diamine or a pharmaceutically acceptable salt thereof.

27. A pharmaceutical composition comprising a therapeutic combination according to any of claims 1 to 26 and one or more pharmaceutically acceptable excipients.

28. An article of manufacture comprising a therapeutic combination according to any of claims 1 to 26 useful in the treatment of a neoplastic disease.

29. A therapeutic combination according to any of claims 1 to 26 for use as therapeutically active substance.

30. A therapeutic combination according to any of claims 1 to 26 for use in the treatment of a neoplastic disease.

31. A method for the treatment of a neoplastic disease, which method comprises administering an effective amount of a therapeutic combination according to any of claims 1 to 26 to a human being or animal.

32. A method for the treatment of a neoplastic disease, which method comprises sensitizing through administration of an LSD1 inhibitor followed by administering an effective amount of a therapeutic combination according to any of claims 1 to 26 to a human being or animal.

33. A method for the treatment of a neoplastic disease, which method comprises sensitizing through administration of (trans)-N1-((1R,2S)-2-phenylcyclopropyl)cyclohexane-1,4-diamine, or a pharmaceutically acceptable salt thereof, followed by administering an effective amount of a therapeutic combination according to any of claims 1 to 26 to a human being or animal.

34. A use of a therapeutic combination according to any of claims 1 to 26 for the treatment of a neoplastic disease.

35. A use of a therapeutic combination according to any of claims 1 to 26 for the preparation of medicaments useful in the treatment of a neoplastic disease.

36. The article of manufacture of claim 28, the therapeutic combinations for uses according to claims 29 or 30, the methods of claims 31 to 33 or the uses of claims 34 or 35, wherein the neoplastic disease is a cancer.

37. The article of manufacture of claim 28, the therapeutic combinations for uses according to claims 29 or 30, the methods of claims 31 to 33 or the uses of claims 34 or 35, wherein the neoplastic disease is breast cancer, prostate cancer, cervical cancer, ovarian cancer, gastric cancer, colorectal cancer, pancreatic cancer, liver cancer, brain cancer, neuroendocrine cancer, lung cancer, kidney cancer, hematological malignancies, melanoma and sarcomas.

38. The article of manufacture of claim 28, the therapeutic combinations for uses according to claims 29 or 30, the methods of claims 31 to 33 or the uses of claims 34 or 35, wherein the neoplastic disease is a solid tumor.

39. The article of manufacture of claim 28, the therapeutic combinations for uses according to claims 29 or 30, the methods of claims 31 to 33 or the uses of claims 34 or 35, wherein the neoplastic disease is small cell lung cancer (SCLC).

40. The invention as hereinbefore described.

\*\*\*\*\*

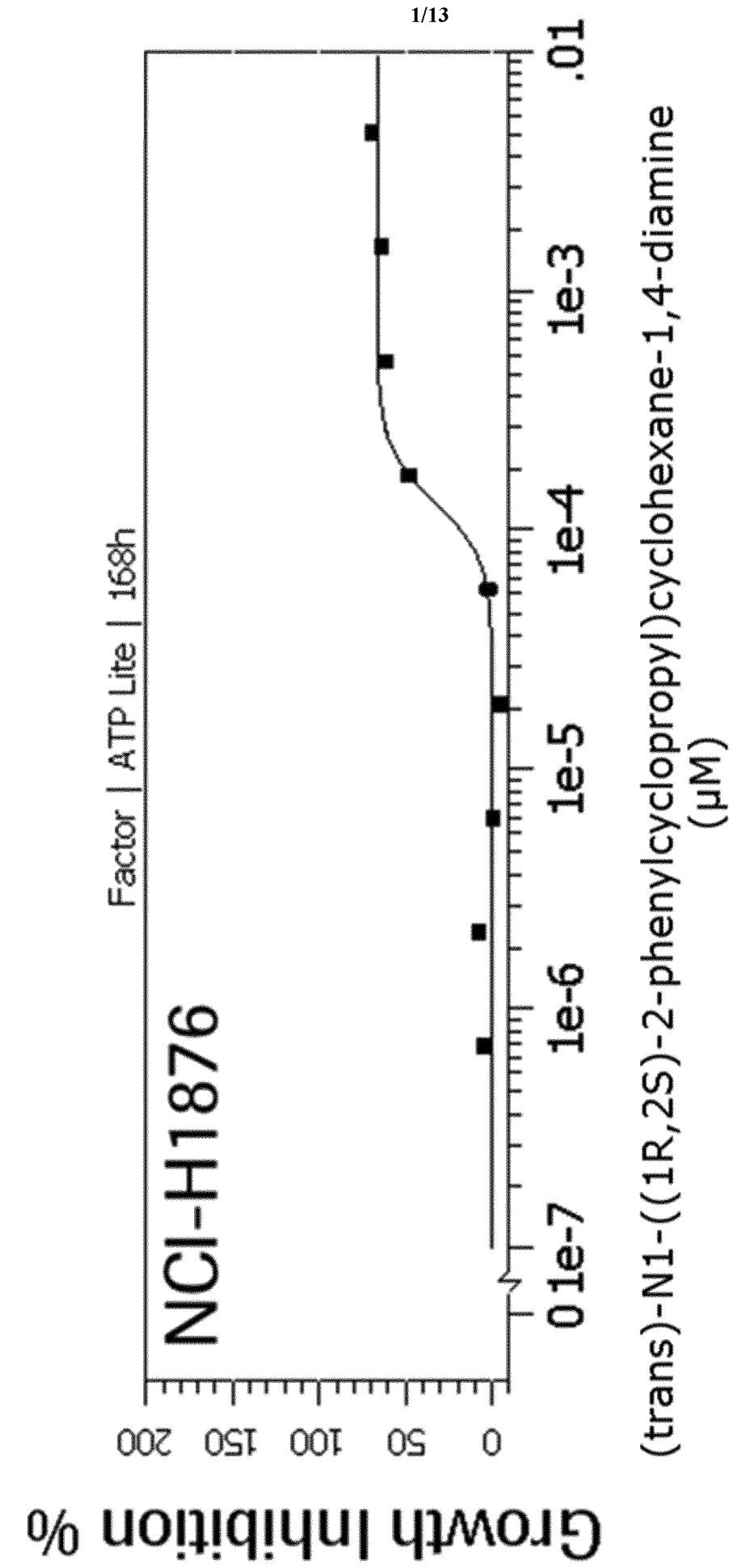


Figure 1A.

Figure 1B

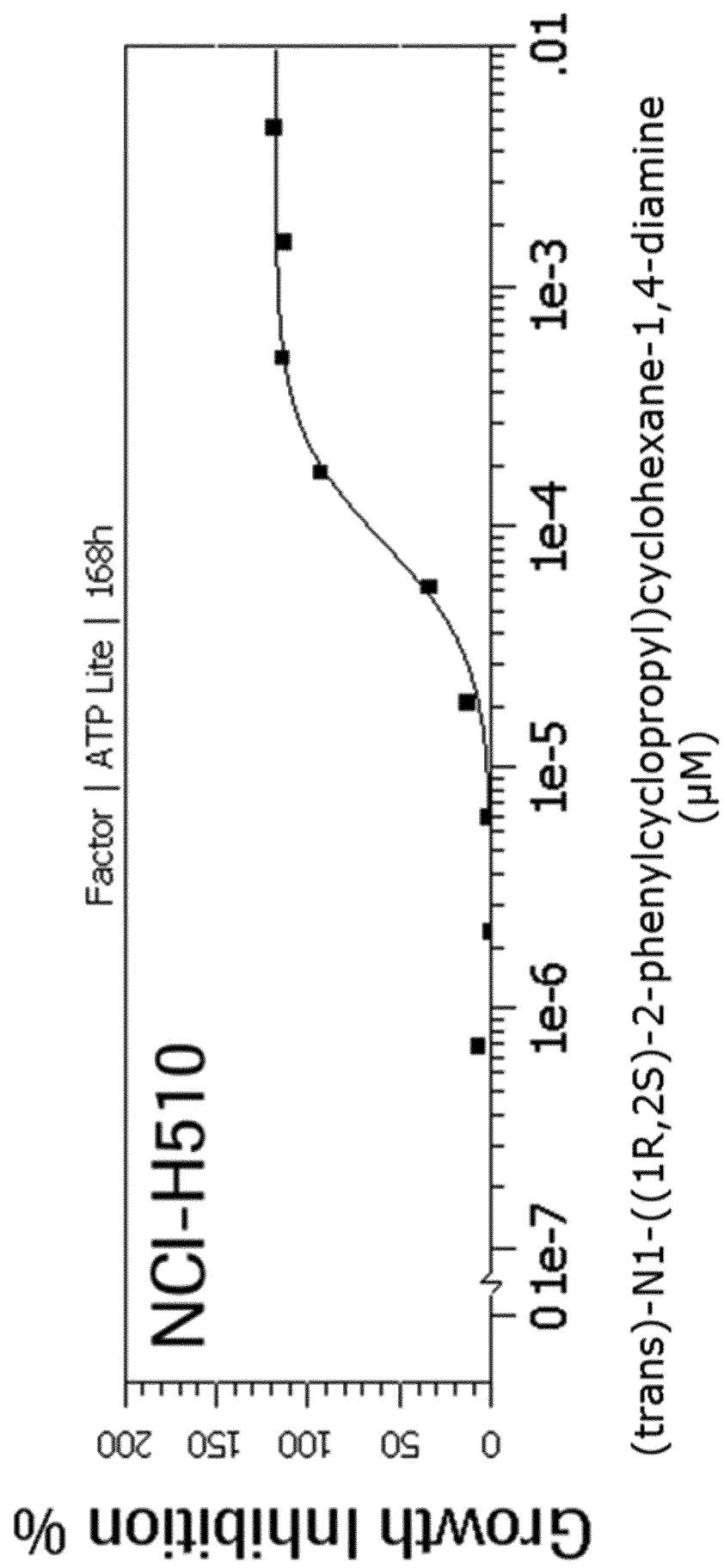


Figure 2A.

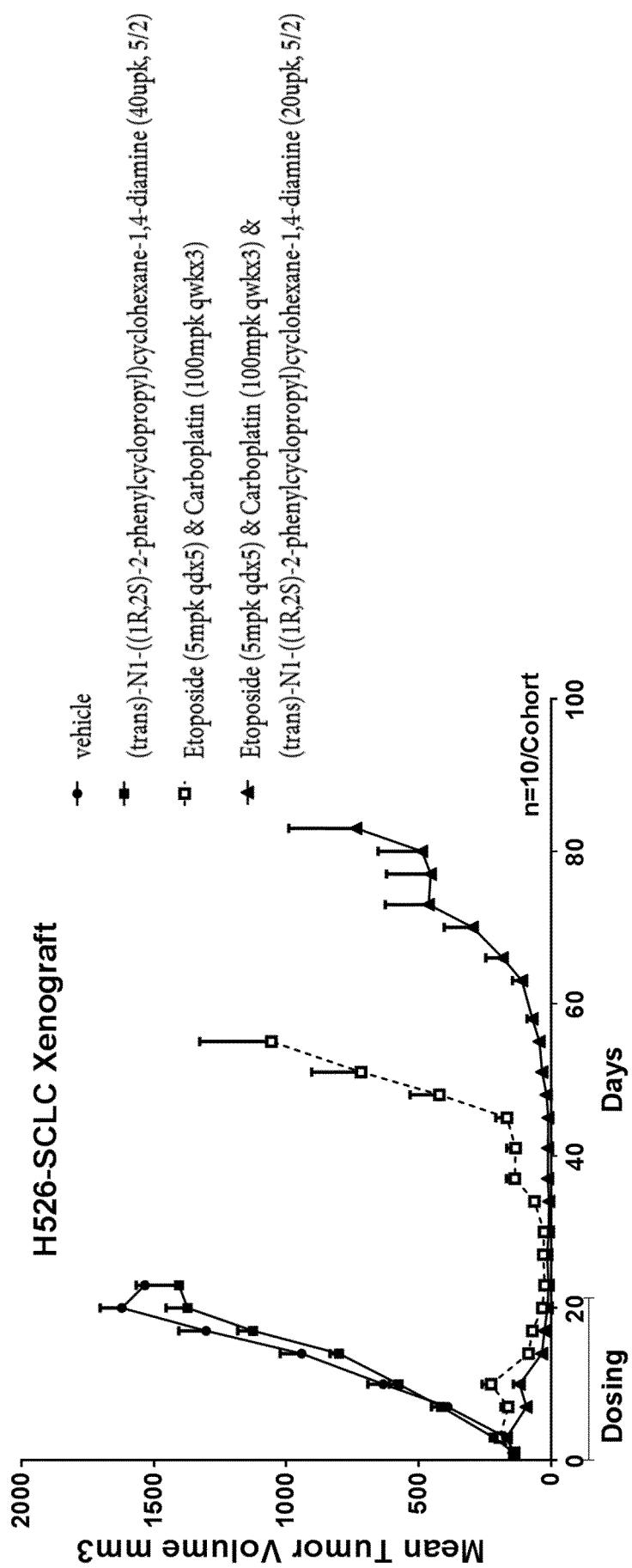
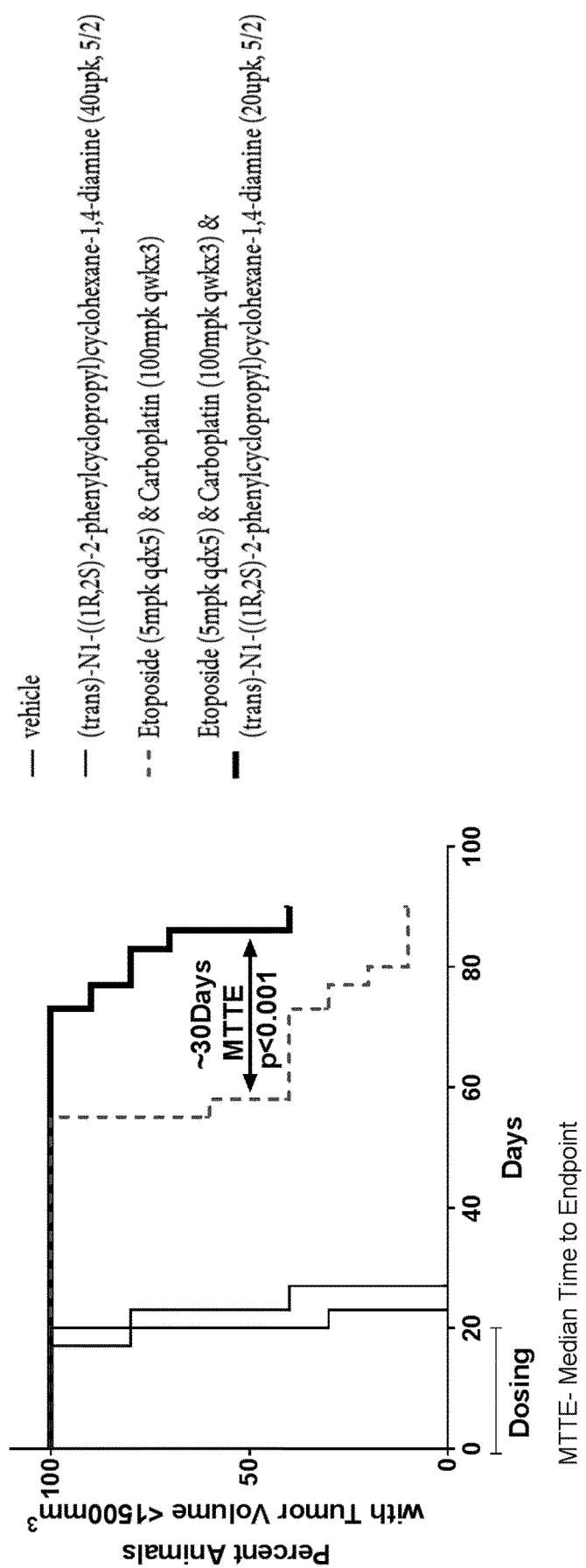


Figure 2B.



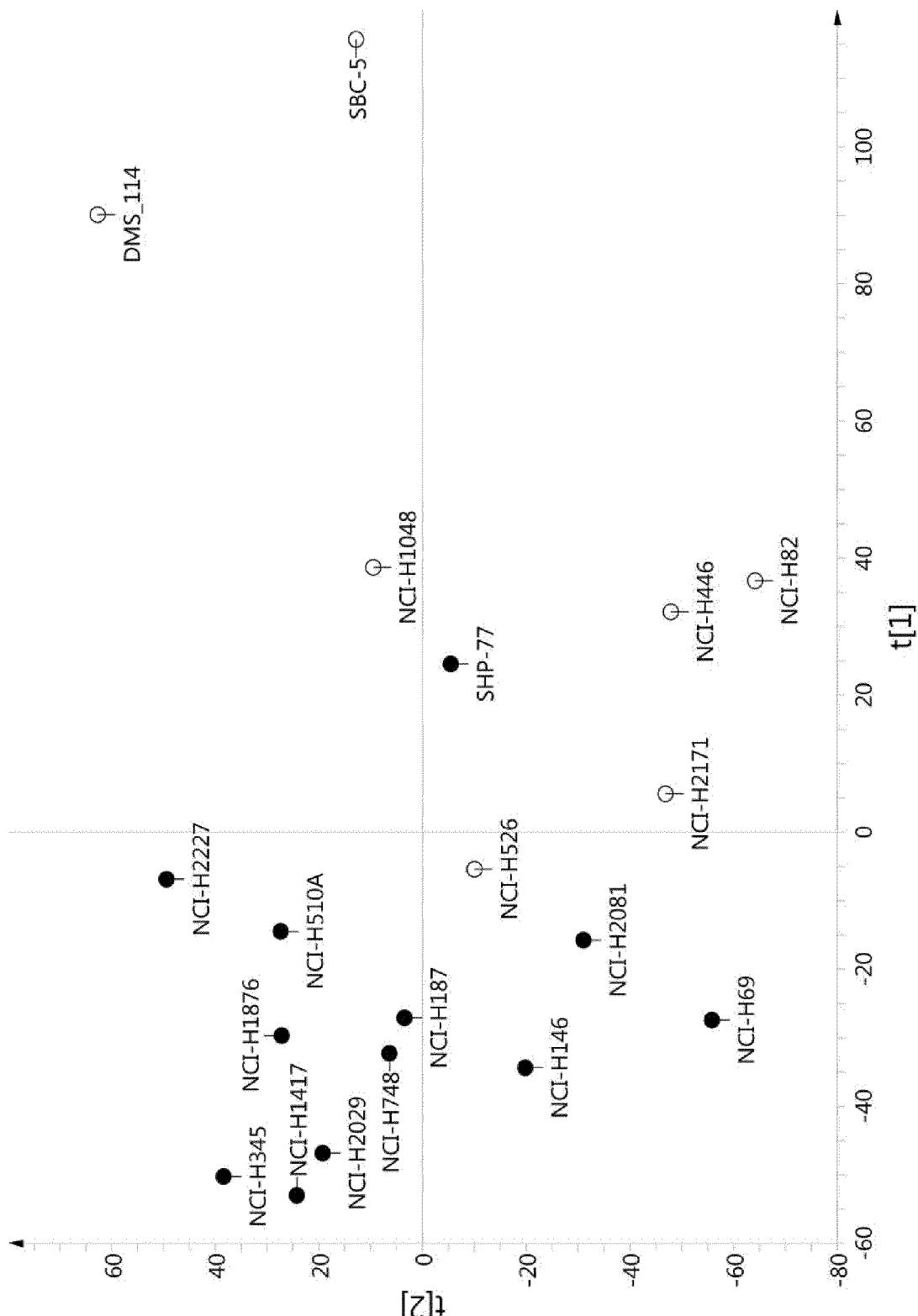
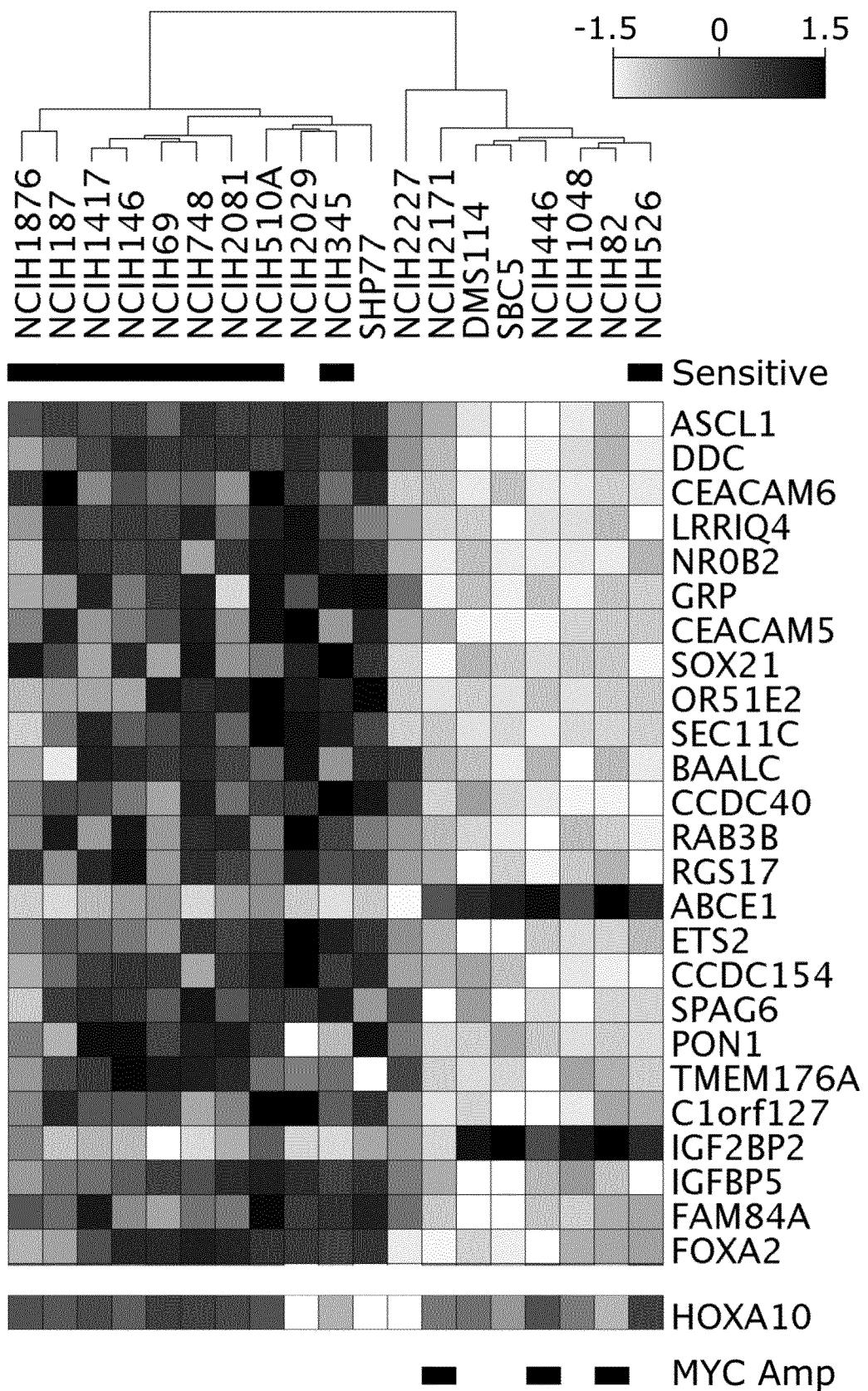
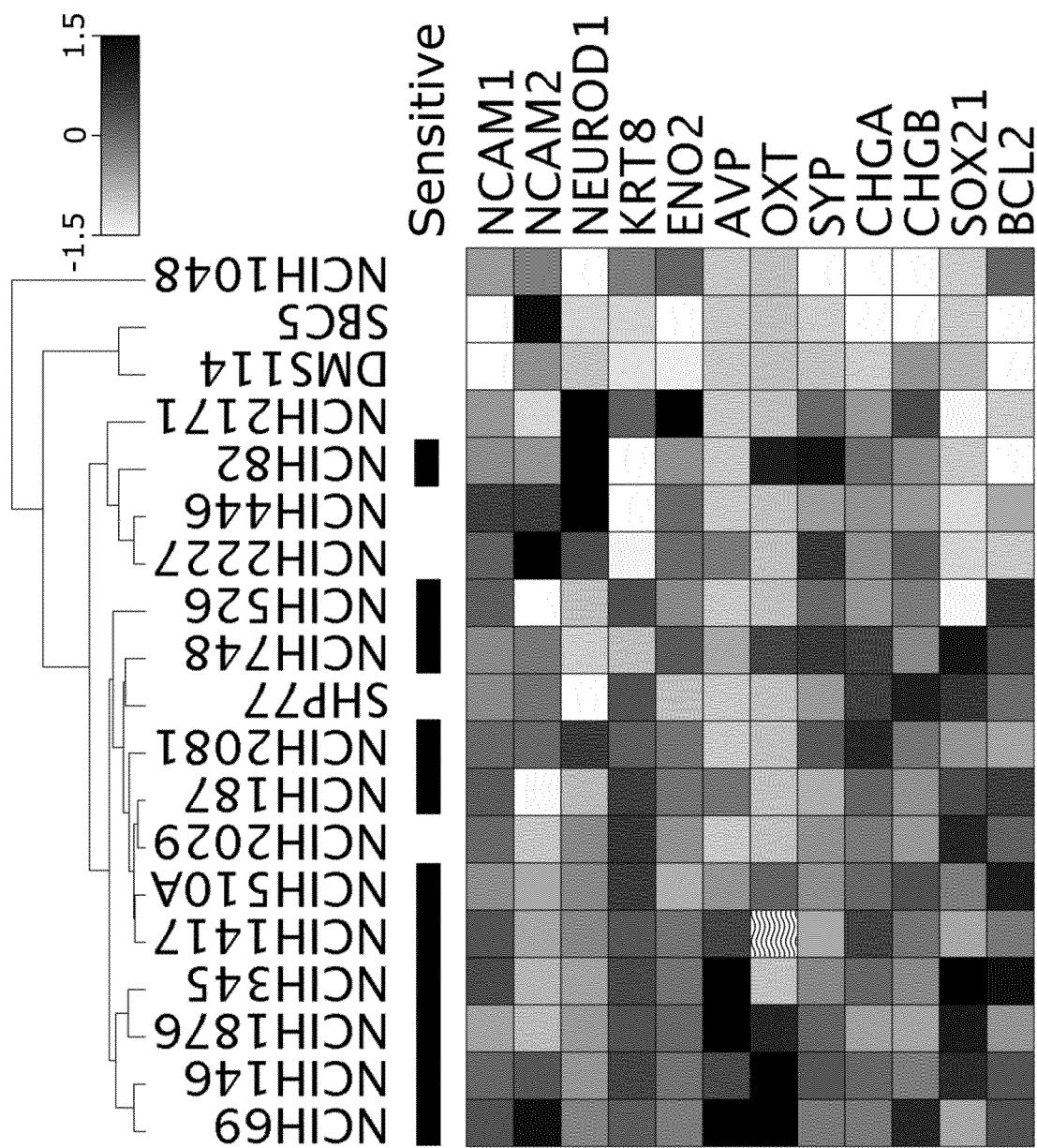


Figure 4.



Case 33471

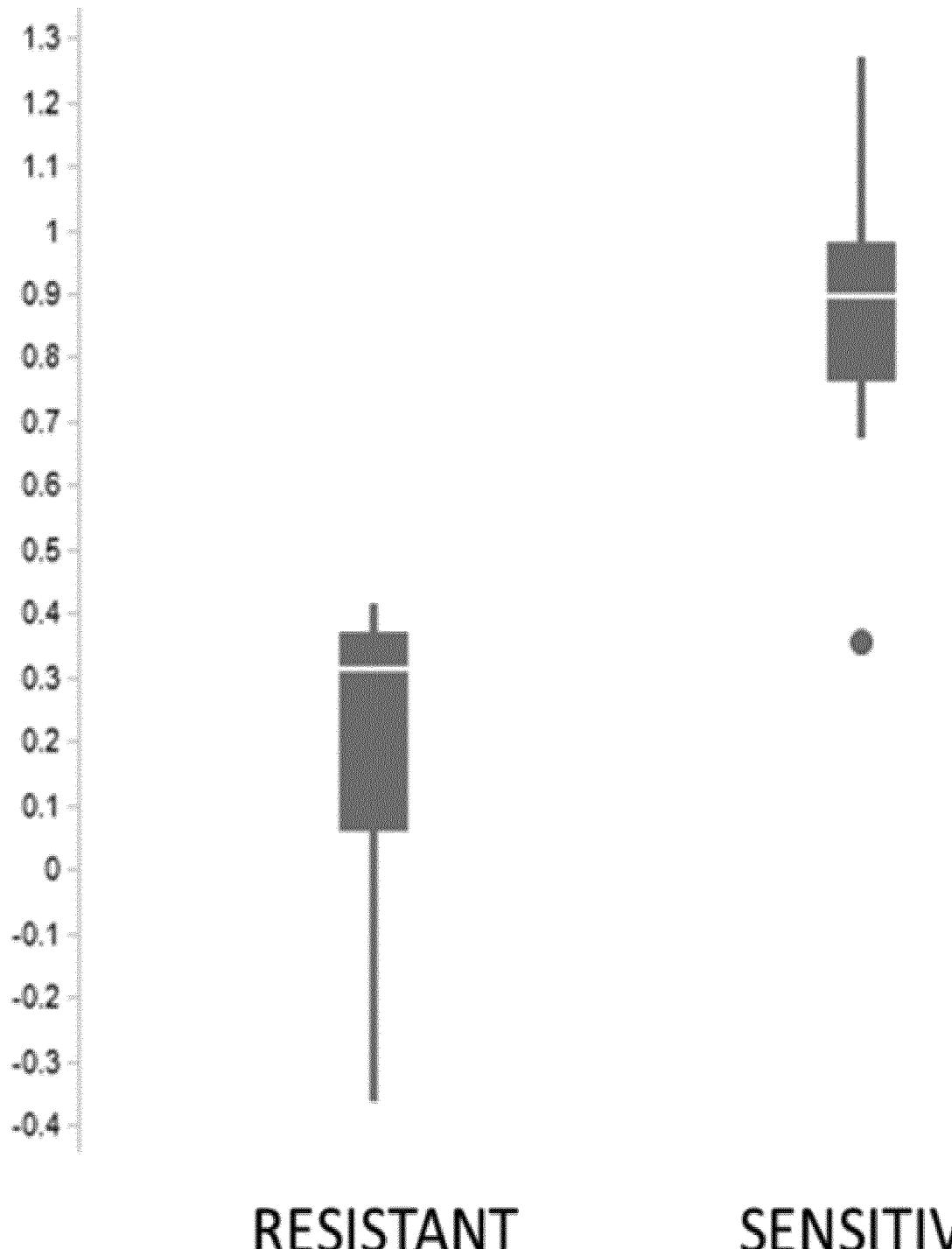
SUBSTITUTE SHEET (RULE 26)



Case 33471

Figur 6.

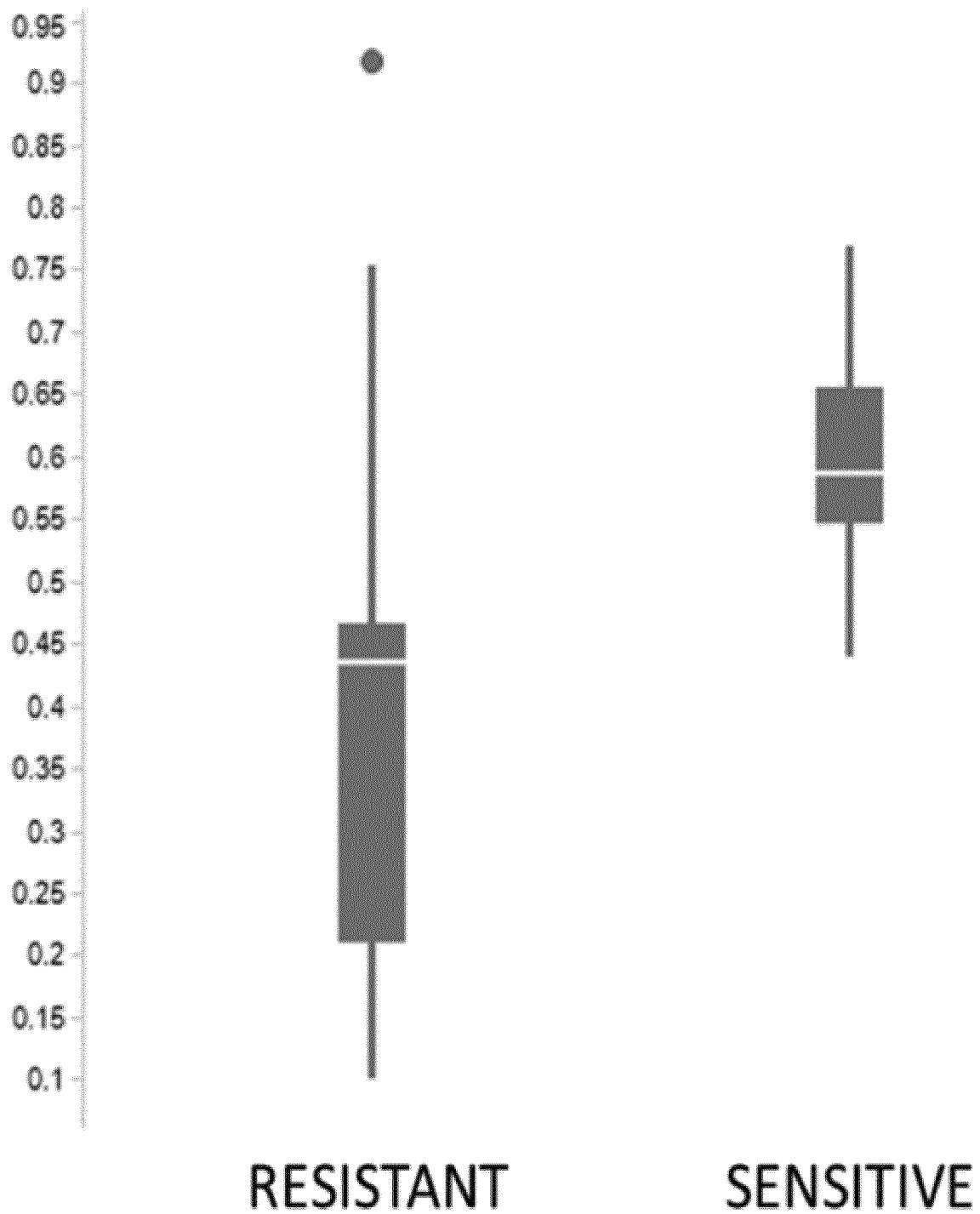
**score\_1**



**RESISTANT**

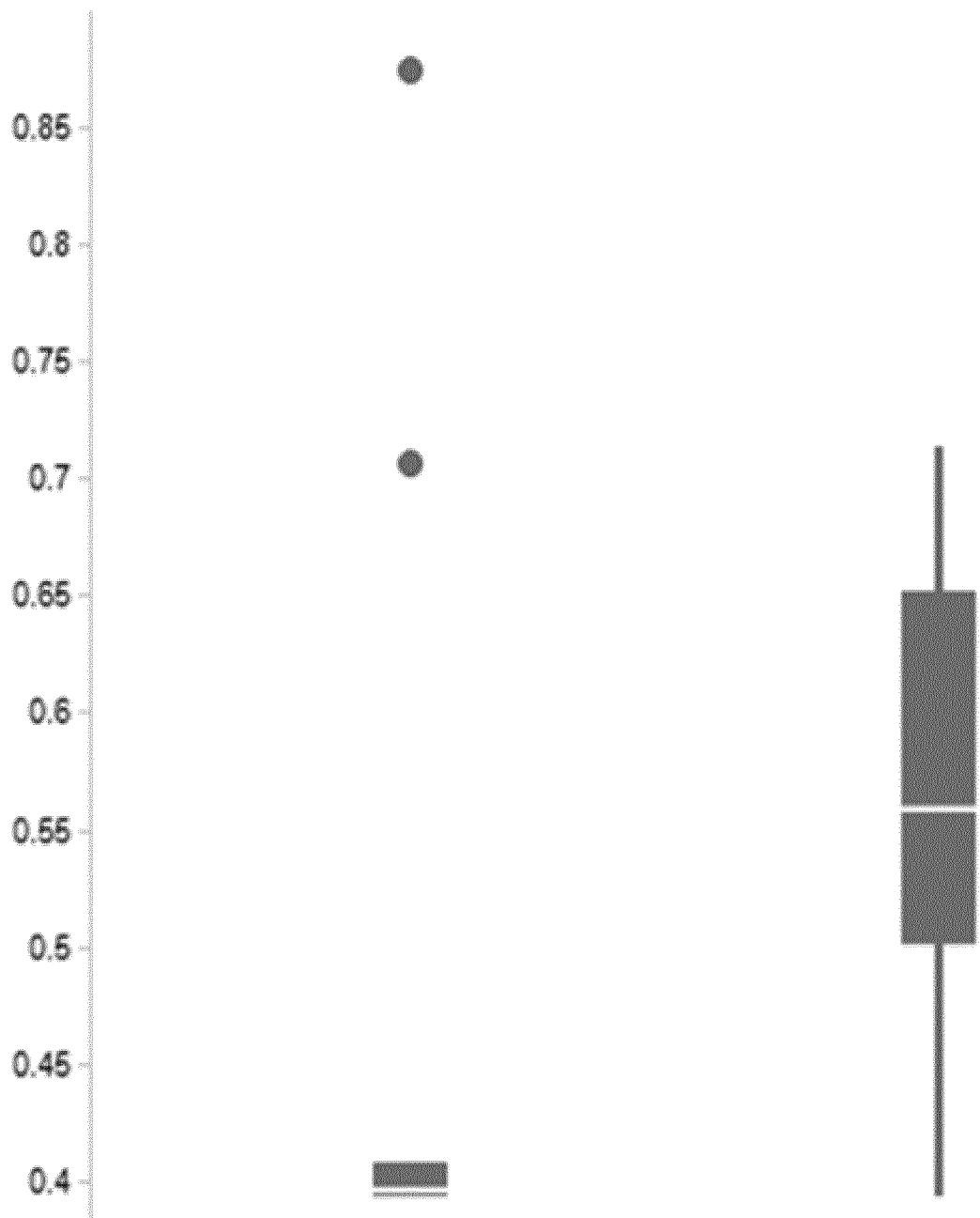
**SENSITIVE**

Figur 7.

**score\_2****RESISTANT****SENSITIVE**

Figur 8.

score\_3



RESISTANT

SENSITIVE

Figure 9.

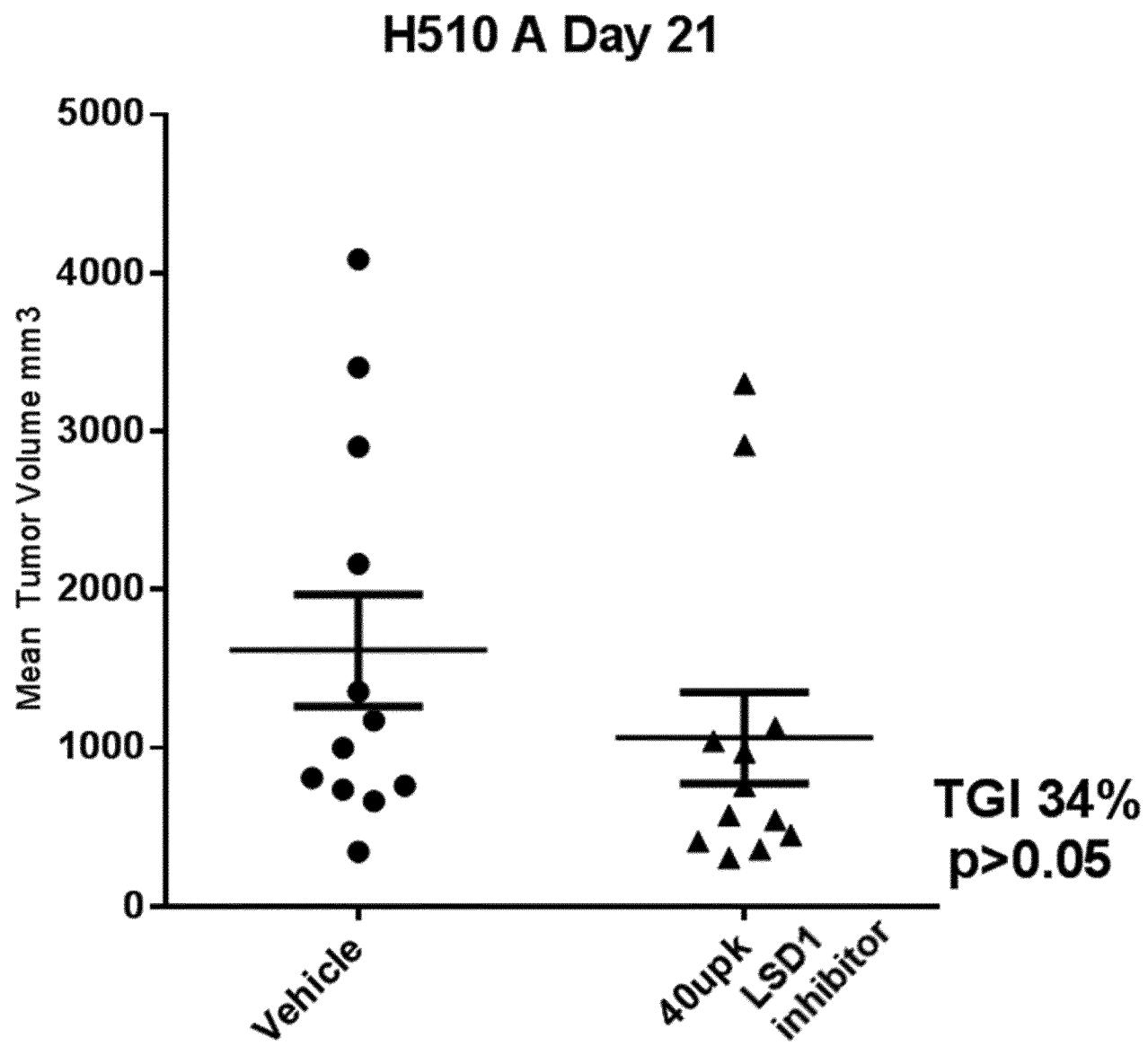
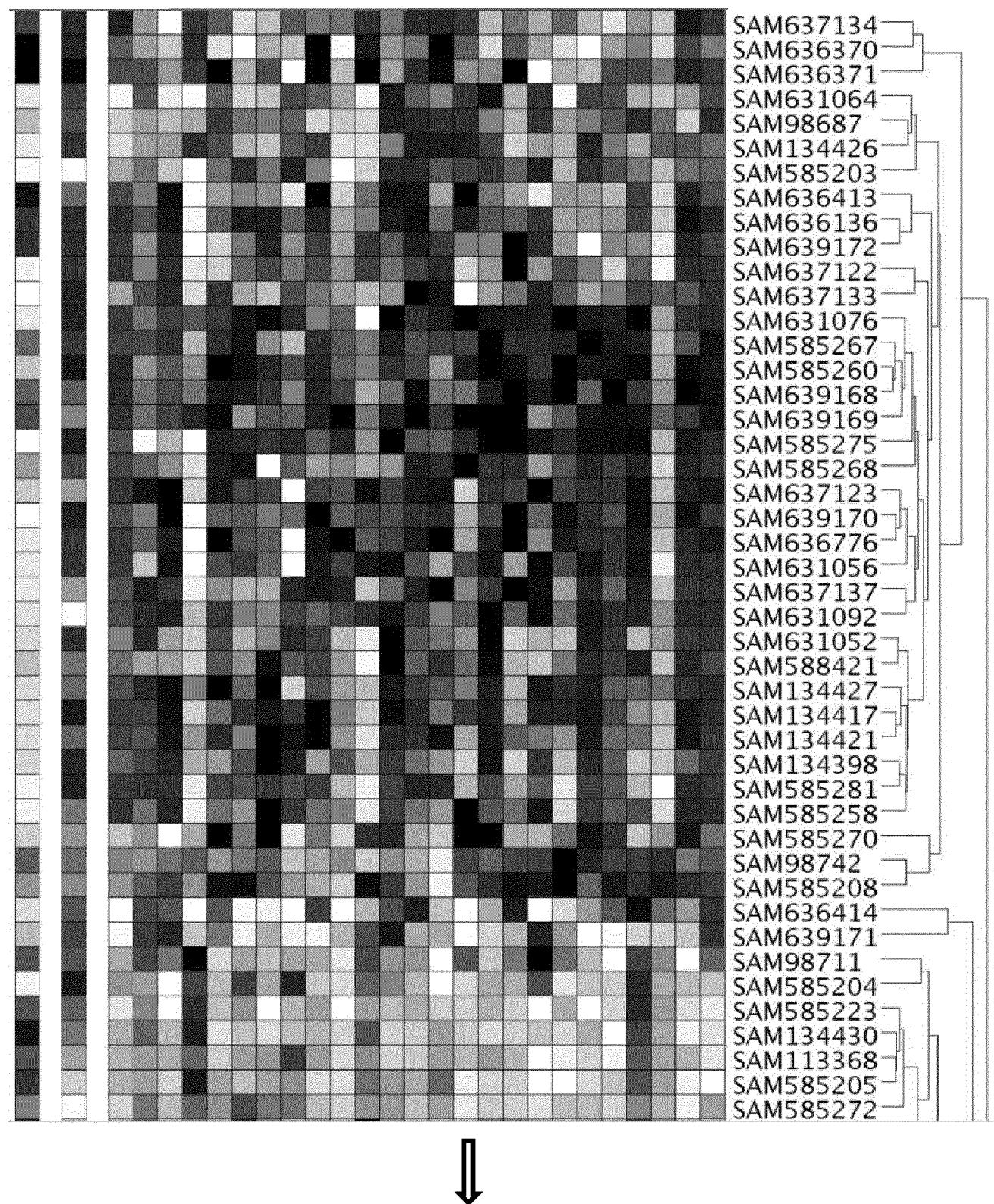


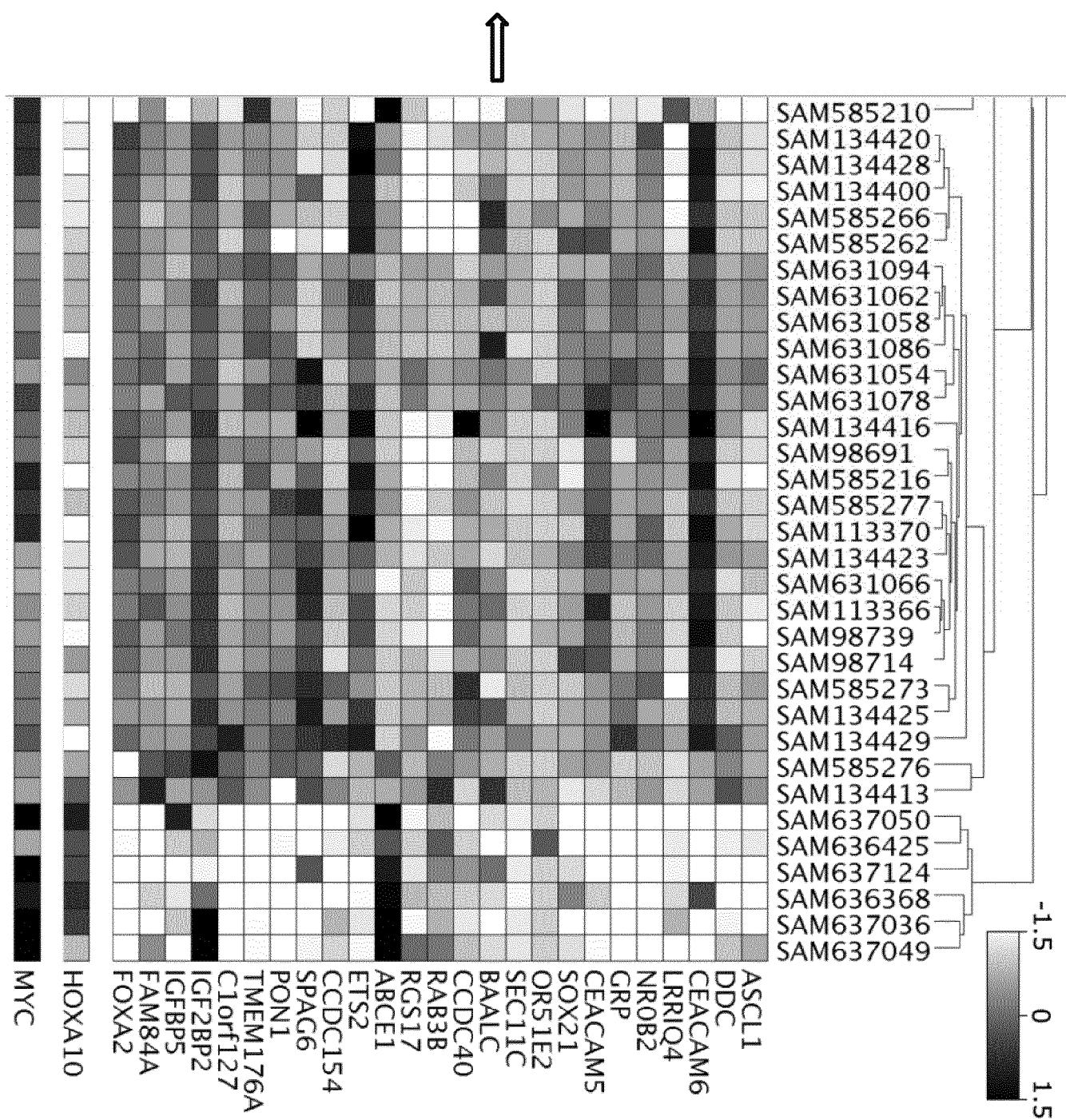
Figure 10-part 11



Case 33471

SUBSTITUTE SHEET (RULE 26)

Figure 10-part 2



# INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2017/055784

A. CLASSIFICATION OF SUBJECT MATTER				
INV.	A61K31/12	A61K31/135	A61K31/19	A61K31/282
	A61K31/4045	A61K31/4745	A61K31/475	A61K31/495
	A61K31/555	A61K31/704	A61K31/7068	A61P35/00

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, WPI Data, BIOSIS, EMBASE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LI AO ET AL: "Lysine-specific demethylase 1 inhibitors protect cochlear spiral ganglion neurons against cisplatin-induced damage", NEUROREPORT, LIPPINCOTT WILLIAMS & WILKINS, UK, vol. 26, no. 9, 1 January 2015 (2015-01-01), pages 539-547, XP009194296, ISSN: 0959-4965 Y page 540 - left-hand column ----- -/-	1,2,13, 14,23, 28,29, 36-40
Y		25,26,33

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	Date of mailing of the international search report
9 May 2017	19/06/2017

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

Albayrak, Timur

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2017/055784

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SINGH M M ET AL: "Inhibition of LSD1 sensitizes glioblastoma cells to histone deacetylase inhibitors", NEURO-ONCOLOGY : OFFICIAL JOURNAL OF THE WORLD FEDERATION OF NEURO-ONCOLOGY, OXFORD : OXFORD UNIV. PRESS, GB, vol. 13, no. 8, 1 August 2011 (2011-08-01), pages 894-903, XP002737873, ISSN: 1523-5866, DOI: 10.1093/NEUONC/NOR049 [retrieved on 2011-06-08] the whole document -----	1,2,15, 16, 27-30, 32,34-40
Y	-----	25,26,33
Y	WO 2013/057322 A1 (ORYZON GENOMICS SA [ES]) 25 April 2013 (2013-04-25) cited in the application claim 80 -----	25,26,33
X	CN 105 233 292 A (BEIJING INST GENOMICS CAS) 13 January 2016 (2016-01-13) -----	1,2,21, 22, 27-32, 34-40
Y	claims 1-8 -----	25,26,33
X	WO 2016/025635 A2 (EPIZYME INC [US]; CELGENE CORP [US]) 18 February 2016 (2016-02-18) -----	1,2,9, 10, 27-32, 34-40
Y	Claim 1+5: Tranylcypromine in combination with compounds A2 or D16. Page 11: compound A2 = pinometostat or "EPZ-5657" and compound D16 = EPZ-4777. Both compounds are DOT1L inhibitors. claim 19: treatment of cancer -----	25,26,33
X	WO 2015/134973 A1 (UNIV JOHNS HOPKINS [US]; INTONATION RES LAB [IN]) 11 September 2015 (2015-09-11) cited in the application -----	1,2,13, 14,17, 18, 21-24, 27-32, 34-40
Y	claim 27 p38 line 15: paclitaxel (taxol), docetaxel; p39 line 20: vinblastine, vincristine, vinorelbine; p40 line 11: cisplatin, carboplatin; p45: irinotecan, topotecan; p43: 5-FU, gemcitabine, methotrexate; p42 lines 28,29: etoposide, teniposide; all for combination with the LSD1 inhibitors Cancer is the disease to be treated (claims) -----	25,26,33
		-/-

## INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/055784

## C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SINGH MELISSA M ET AL: "Preclinical activity of combined HDAC and KDM1A inhibition in glioblastoma.", NEURO-ONCOLOGY NOV 2015, vol. 17, no. 11, November 2015 (2015-11), pages 1463-1473, XP002769953, ISSN: 1523-5866 the whole document -----	1,2,15, 16, 27-30, 32,34-40
Y		25,26,33

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/EP2017/055784
---

Patent document cited in search report	Publication date	Patent family member(s)			Publication date
WO 2013057322	A1 25-04-2013	AU 2012324805 A1 CA 2849564 A1 CN 103958474 A CO 6960552 A2 CR 20140166 A EP 2776394 A1 HK 1200170 A1 HK 1200457 A1 JP 6046154 B2 JP 2015502335 A JP 2017075155 A KR 20140081883 A NZ 622656 A PE 16922014 A1 RU 2014119976 A SG 11201401066P A US 2014256729 A1 US 2016368857 A1 WO 2013057322 A1			03-04-2014 25-04-2013 30-07-2014 30-05-2014 19-06-2014 17-09-2014 31-07-2015 07-08-2015 14-12-2016 22-01-2015 20-04-2017 01-07-2014 29-04-2016 08-11-2014 27-11-2015 30-10-2014 11-09-2014 22-12-2016 25-04-2013
CN 105233292	A 13-01-2016	CN 105233292 A WO 2017067454 A1			13-01-2016 27-04-2017
WO 2016025635	A2 18-02-2016	AU 2015301746 A1 CA 2956962 A1 WO 2016025635 A2			16-02-2017 18-02-2016 18-02-2016
WO 2015134973	A1 11-09-2015	AU 2015226881 A1 CA 2941716 A1 CN 106458856 A EP 3114109 A1 JP 2017508798 A US 2017029366 A1 WO 2015134973 A1			29-09-2016 11-09-2015 22-02-2017 11-01-2017 30-03-2017 02-02-2017 11-09-2015