Provided methods for treating pancreatic cancer in a patient by co-administering combinations of an anti-ErbB3 antibody and one or more additional therapeutic agents. Further disclosed are the combinations of therapies which include: the anti-ErbB3 antibody is coadministered with irinotecan, the anti-ErbB3 antibody is co-administered with paclitaxel (e.g., nab-paclitaxel), and the anti-ErbB3 antibody is coadministered with erlotinib and gemcitabine.
METHODS FOR TREATING PANCREATIC CANCER USING COMBINATION THERAPIES COMPRISING AN ANTI-ERBB3 ANTIBODY

Background

Despite improvements in cancer treatments, there remains a critical need to further improve therapies so as to prolong patients’ lives while maintaining quality of life, particularly in the case of advanced cancers such as pancreatic cancers that often are, or become, resistant to current therapeutic modalities.

The ErbB 3 receptor is 148 kD transmembrane receptor that belongs to the ErbB/EGFR tyrosine kinase family; it is the only family member known to lack intrinsic kinase activity. The ErbB receptors form homo- and heterodimeric complexes with other ErbB receptors that impact the physiology of cells and organs by mediating ligand-dependent (or rarely ligand independent) activation of multiple signal transduction pathways. Upon binding one of its physiological ligands (e.g., heregulin), ErbB3 heterodimerizes with another ErbB family member, typically ErbB2 (HER2). ErbB3/ErbB2 dimerization results in phosphorylation of ErbB3 on tyrosine residues of the intracellular cytoplasmic region of the protein. ErbB3-containing heterodimers in tumor cells have been shown to be the most mitogenic and oncogenic receptor complexes of ErbB family members, and they strongly activate intracellular signaling pathways involved in tumorigenesis, such as those promoting cell survival, growth, and migration.

Incidence of pancreatic cancer has markedly increased during the past several decades. It now ranks as the fourth leading cause of cancer death in the United States. Pancreatic cancer’s high mortality rate is due to a dearth of effective therapies and a complete absence of reliably durable therapies. Because of the location of the pancreas, pancreatic cancer is typically not diagnosed until a tumor has become large enough to produce systemic symptoms. This, coupled with the absence of good screening tools and a limited understanding of risk factors, results in patients usually having advanced disease, often advanced metastatic disease, at the time of diagnosis. Metastatic pancreatic cancer has a dismal prognosis and is almost uniformly fatal, with an overall survival rate of less than 4% at 5 years.

There are few approved treatment options for advanced or metastatic pancreatic cancers, particularly for those of exocrine origin. Single-agent gemcitabine is the current standard of care in first-line treatment of advanced and metastatic pancreatic adenocarcinoma. In clinical trials, single-agent gemcitabine has consistently demonstrated a median prolongation of survival of 5 to 6 months and a 1-year survival rate of about 20%. Single agent gemcitabine was also approved as second line treatment for patients previously treated with but no longer responsive to 5-Fluorouracil, with a median overall prolongation of survival of 3.9 months.
Based upon what is known of the biology of pancreatic cancer, a variety of targeted agents have been evaluated, but only erlotinib, a protein tyrosine kinase inhibitor targeted to EGFR, has been approved for first-line use in advanced pancreatic cancer, and the approval is only for use in combination with gemcitabine. The co-administration of erlotinib with gemcitabine resulted in a statistically significant benefit in survival, and improvements in median survival (6.4 months vs. 5.9 months), and 1-year survival rate (24% vs. 17%) compared to gemcitabine alone. Clinical trials evaluating other targeted agents, including studies testing the antibodies bevacizumab and cetuximab, have been disappointingly negative. Thus, there is an urgent need for improvements in, and effective alternatives to, current therapies for pancreatic cancer. The disclosed invention addresses this need.

**Summary**

Monotherapy with an anti-ErbB3 antibody significantly suppresses tumor growth in a dose-dependent manner in *in vivo* pancreatic adenocarcinoma xenograft models. It has now been discovered that co-administration of an anti-ErbB3 antibody with one or more additional therapeutic agents, such as paclitaxel (e.g., nab-paclitaxel), irinotecan, or erlotinib (with or without concomitant gemcitabine), exhibits therapeutic synergy.

Accordingly, provided are methods of treating pancreatic cancer in a patient by co-administering therapeutically synergistic combinations of an anti-ErbB3 antibody and one or more additional therapeutic agents. These methods include a method of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents, wherein the one of the one or more additional therapeutic agents comprise an EGFR inhibitor. In some embodiments the one or more additional therapeutic agents is an EGFR inhibitor that is selected from, gefitinib, erlotinib, afatinib and lapatinib. In some embodiments the one or more additional therapeutic agents is an EGFR inhibitor that is selected from MM-151, Sym004, cetuximab, panitumumab, zalutumumab, nimotuzumab, and matuzumab. In further embodiments the one or more additional therapeutic agents further comprise a nucleoside metabolic inhibitor (e.g., formulated for intravenous administration) such a gemcitabine and the EGFR inhibitor (e.g., formulated for oral administration) is optionally erlotinib.

Also provided are methods of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents wherein the one or more additional therapeutic agents comprise 1) a nucleoside metabolic inhibitor such as gemcitabine, or 2) a microtubule stabilizing agent (e.g., formulated for intravenous administration) such as paclitaxel injection, nab-paclitaxel and docetaxel. Such co-administrations beneficially have an additive or superadditive effect on suppressing pancreatic tumor
growth, which effect on suppressing pancreatic tumor growth is measured, e.g., in a mouse xenograft model using BxPC-3 or COLO-357 cells.

Also provided are methods of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents wherein the one or more additional therapeutic agents comprise a topoisomerase 1 inhibitor and optionally wherein the topoisomerase 1 inhibitor is formulated for intravenous administration, such inhibitors are e.g., camptothecins selected from the group consisting of 9-aminocamptothecin, 7-ethylcamptothecin, 10-hydroxycamptothecin, 9-nitrocamptothecin, 10,11-methylenedioxy camptothecin, 9-amino-10,11-methylenedioxy camptothecin, 9-chloro-10,11-methylenedioxy camptothecin, topotecan, lurtotecan, siltexan, and irinotecan and when the camptothecin is irinotecan or topotecan the irinotecan or topotecan may be liposomally encapsulated irinotecan or liposomally encapsulated topotecan. When the one or more additional therapeutic agents is liposomally encapsulated irinotecan or liposomally encapsulated topotecan , the liposomally encapsulated irinotecan or liposomally encapsulated topotecan may each advantageously be contained in liposomes in the form of a sucrose octasulfate salt.

Also provided are methods of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents, wherein the one or more additional therapeutic agents is chosen from the group consisting of a bispecific anti-ErbB2/anti-ErbB3 antibody, an anti-IGF-1R/anti-ErbB3 antibody, an anti EGFR/anti-ErbB3 antibody, or a mixture of anti-EGFR and anti-ErbB3 antibodies.

Further provided are methods of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents, wherein i) the antibody is an antibody having the heavy chain sequence set forth in SEQ ID NO:2 and the light chain sequence set forth in SEQ ID NO:4, and ii) the one or more additional therapeutic agents comprises eribulin.

In each of the preceding methods the ErbB3 inhibitor may be an anti-ErbB3 antibody, e.g., an anti-ErbB3 antibody comprising CDRH1, CDRH2, and CDRH3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 5 (CDRH1) SEQ ID NO: 6 (CDRH2) and SEQ ID NO: 7 (CDRH3), and further comprises CDRL1, CDRL2, and CDRL3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 8 (CDRL1) SEQ ID NO: 9 (CDRL2) and SEQ ID NO: 10 (CDRL3), or one comprising VH and/or VL regions comprising the amino acid sequences set forth in SEQ ID NO:s 2 and 4, respectively. Anti-ErbB3 antibodies may further be selected from GE-huMab-HER3, MEDI3379, 8B8 (ATCC HB-12070), 1B4C3, 2D1D12, AMG888 and AV-203.
Further provided is a composition for the treatment of pancreatic cancer, or for the manufacture of a medicament for the treatment of pancreatic cancer, in a patient, said treatment comprising co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents, wherein the one of the one or more additional therapeutic agents comprise

1) an orally available EGFR inhibitor, e.g., gefitinib, erlotinib, afatinib or lapatinib (frequently erlotinib), or a parenterally available EGFR inhibitor, e.g., MM-151, Sym004, cetuximab, panitumumab, zalutumumab, nimotuzumab, or matuzumab. In such combinations the one or more additional therapeutic agents may comprise a nucleoside metabolic inhibitor, e.g., gemcitabine; 2) a nucleoside metabolic inhibitor, e.g., gemcitabine; 3) a microtubule stabilizing agent, e.g., a taxane such as eribulin, paclitaxel injection, nab-paclitaxel or docetaxel (frequently nab-paclitaxel) - preferably co-administration of the anti-ErbB3 antibody and the taxane has an additive or superadditive effect on suppressing pancreatic tumor growth, as compared to administration of the anti-ErbB3 antibody alone or the taxane alone, wherein the effect on suppressing pancreatic tumor growth is measured in a mouse xenograft model using BxPC-3 or COLO-357 cells; 4) a topoisomerase 1 inhibitor, e.g., a camptothecin such as 9-aminocamptothecin, 7-ethycamptothecin, 10-hydroxycampothecin, 9-nitrocampothecin, 10,11-methylenedioxycamptothecin, 9-amino-10,11-methylenedioxycamptothecin, 9-chloro-10,11-methylenedioxycamptothecin, lurtotecan, silatecan, or (frequently) topotecan or irinotecan, e.g., liposomally encapsulated irinotecan or liposomally encapsulated topotecan, each encapsulated, e.g., in the form of a sucrose octasulfate salt. In one embodiment, the combination treatments are useful for inhibiting the spread of cancer cells from the pancreas to other tissues.

In each of the preceding methods and compositions the co-administration of the anti-ErbB3 antibody and the additional chemotherapeutic agent or agents preferably has an additive or superadditive effect on suppressing pancreatic tumor growth, as compared to administration of the anti-ErbB3 antibody alone or the one or more additional chemotherapeutic agents alone, wherein the effect on suppressing pancreatic tumor growth is measured in a mouse xenograft model using BxPC-3 or COLO-357 cells. In certain embodiments of these methods, at least one of the one or more additional therapeutic agents is administered at a dosage that is a reduced dosage that provides less of the at least one additional therapeutic agent than is provided by a dosage recommended by the manufacturer of the at least one additional therapeutic agent for administration for the treatment of cancer in a patient who is not receiving concurrent anti-ErbB3 antibody therapy, e.g., the reduced dosage is a dosage that is about half the dosage recommended by the manufacturer.

In each of the methods and compositions disclosed herein, the anti-ErbB3 antibody is advantageously formulated for intravenous administration. In each, the patient may have recurrent or persistent pancreatic cancer following primary chemotherapy and may have failed prior therapy with a
platinum-based therapeutic agent or have failed prior treatment with, or become resistant to treatment with one or more of a) a nucleoside analog therapeutic agent, b) a platinum-based therapeutic agent, c) a therapeutic agent, that is a topoisomerase 1 inhibitor and d) a therapeutic agent that is a tyrosine kinase inhibitor. In each of the additional therapeutic agent or agents may be administered following the administration of the anti-ErbB3 antibody; optionally, the topoisomerase 1 inhibitor may be administered before the administration of the anti-ErbB3 antibody or the topoisomerase 1 inhibitor and the anti-ErbB3 antibody are administered simultaneously. When a microtubule stabilizing agent is co-administered it may be administered before, after or concurrently with an anti-ErbB3 antibody. When EGFR inhibitor and nucleoside metabolic inhibitor are co-administered they may be administered before, after or concurrently with an anti-ErbB3 antibody.

In any of the foregoing methods and compositions the one or more additional therapeutic agents comprise two or more additional therapeutic agents, one of which is optionally gemcitabine. In the foregoing methods, the two or more additional therapeutic agents may be a combination of folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin (FOLFOX), or a combination of folinic acid, 5-fluorouracil, and oxaliplatin (FOLFOX), or a combination of folinic acid, 5-fluorouracil, and irinotecan (FOLFIRI).

In any of the foregoing methods and compositions the anti-ErbB3 antibody may be formulated for intravenous administration and 1) is selected from the group comprising GE-huMab-HER3, MEDI3379, AMG888, AV-203, 8B8, 1B4C3 and 2D1D12, or 2) is selected from an antibody comprising VH and/or VL regions comprising the amino acid sequences set forth in SEQ ID NOs: 2 and 4, respectively, or 3) comprises CDRH1, CDRH2, and CDRH3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 5 (CDRH1) SEQ ID NO: 6 (CDRH2) and SEQ ID NO: 7 (CDRH3), and further comprises CDRL1, CDRL2, and CDRL3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 8 (CDRL1) SEQ ID NO: 9 (CDRL2) and SEQ ID NO: 10 (CDRL3).

Furthermore, in any of the foregoing methods the pancreatic cancer may be an exocrine pancreatic cancer selected from the group consisting of acinar cell carcinoma, adenocarcinoma, adenosquamous carcinoma, giant cell tumor, intraductal papillary-mucinous neoplasm (IPMN), mucinous cystadenocarcinoma, pancreatoblastoma, serous cystadenocarcinoma, and solid and pseudopapillary tumors; or an adenocarcinoma that is a pancreatic ductal carcinoma; or an endocrine pancreatic cancer selected from the group consisting of: Gastrinoma (Zollinger-Ellison Syndrome), Insulinoma, Nonfunctional Islet Cell Tumor, Somatostatinaoma, and Vasoactive Intestinal Peptide-Releasing Tumor (VIPoma or Verner-Morrison Syndrome) - any of which may comprise a KRAS gene comprising a KRAS mutation such as KRAS G12S and may also or alternately comprise a BRAF mutation (e.g., BRAF V600E), in which case one of the one or more additional therapeutic agents is optionally a BRAF kinase inhibitor, frequently vemurafenib.
In any of the foregoing methods and compositions, the one or more additional therapeutic agents may comprise an mTOR inhibitor selected from the group consisting of temsirolimus, everolimus, sirolimus, and ridaforolimus, most commonly everolimus.

In any of the preceding methods and compositions, the treatment produces at least one therapeutic effect selected from the group consisting of: reduction of the rate of tumor growth, reduction in size of tumor, reduction of tumor mitotic index, reduction in number of metastatic lesions over time, complete response, partial response, stable disease, increase in overall response rate, or a pathologic complete response.

In any of the foregoing compositions, the ErbB3 inhibitor may be an anti-ErbB3 antibody, e.g., an anti-ErbB3 antibody comprising CDRH1, CDRH2, and CDRH3 sequences comprising VH and/or VL regions comprising the amino acid sequences set forth in SEQ ID NOs: 2 and 4, respectively, or comprising the amino acid sequences set forth in SEQ ID NO: 5 (CDRH1) SEQ ID NO: 6 (CDRH2) and SEQ ID NO: 7 (CDRH3), SEQ ID NO: 8 (CDRL1) SEQ ID NO: 9 (CDRL2) and SEQ ID NO: 10 (CDRL3). Alternately, the anti-ErbB3 antibody may be selected from 8B8, 1B4C3, 2D1D12, AMG888 and AV-203. Preferably co-administration of the anti-ErbB3 antibody and the additional chemotherapeutic agent or agents has an additive or superadditive effect on suppressing pancreatic tumor growth, as compared to administration of the anti-ErbB3 antibody alone or the one or more additional chemotherapeutic agents alone, wherein the effect on suppressing pancreatic tumor growth is measured in a mouse xenograft model using BxPC-3 or COLO-357 cells. In certain embodiments, at least one of the one or more additional therapeutic agents is administered at a dosage that is a reduced dosage that provides less of the at least one additional therapeutic agent than is provided by a dosage recommended by the manufacturer of the at least one additional therapeutic agent for administration for the treatment of pancreatic cancer in a patient who is not receiving concurrent anti-ErbB3 antibody therapy, optionally the reduced dose is a dose that is about half the dosage recommended by the manufacturer.

In any of the preceding methods and compositions, the effective amount optionally 1) achieves a synergistic effect in reducing tumor volume in the patient; or 2) achieves tumor stasis in the patient.

Brief Description of the Drawings

Figure 1 shows suboptimal and optimal doses of MM-121 (Figure 1A) and irinotecan hydrochloride (CPT-11) (Figure 1B) for inhibiting tumor growth in a BxPC3 xenograft model.

Figure 2 shows tumor regression in a BxPC3 xenograft model after treatment with either CPT-11 or MM-398 in combination with the suboptimal (150 μg Q3D - Figure 2A) or optimal (600μg Q3D - Figure 2B) dose of MM-121.
**Figure 3** shows tumor growth inhibition in a COLO-357 xenograft model after treatment with varying doses of MM-121.

**Figure 4** shows tumor growth inhibition in a COLO-357 xenograft model after treatment with a suboptimal dose of MM-121 (300 μg Q3D) in combination with nab-paclitaxel (**Figure 4A**) or the same dose of MM-121 in combination with nab-paclitaxel with and without gemcitabine (**Figure 4B**).

**Figure 5** shows tumor growth inhibition in a COLO-357 xenograft model after treatment with MM-121 at 300 μg Q3D, erlotinib, and gemcitabine, either alone or in two-way or three-way combinations (**Figure 5A**). **Figures 5B-E** depict each distinct dose combination shown in **Figure 5A**.

**Figure 6** shows tumor growth inhibition in a pancreatic primary tumor explant model after three-way combination treatment with MM-121, gemcitabine, and erlotinib.

**Figure 7** shows the effect of MM-121 in combination with nab-paclitaxel and MM-398 in bioluminescent orthotopic pancreatic model using luciferase-labeled BxPC3 cells (BxPC3-Luc-2).

**Figure 8** is a graph showing the effect of MM-121 on tumor cell migration to the lung (Figure 8A) or the liver (Figure 8B) in a pancreatic cancer orthotopic model.

**Detailed Description**

Methods of combination therapy and combination compositions for treating pancreatic cancer in a patient are provided. In these methods, the cancer patient is treated with both an anti-ErbB3 antibody and one or more additional therapeutic agents selected, e.g., from irinotecan, paclitaxel, nab-paclitaxel, erlotinib, gemcitabine, everolimus, and afatinib.

**Definitions:**

The terms "combination therapy," "co-administration," "co-administered" or "concurrent administration" (or minor variations of these terms) include simultaneous administration of at least two therapeutic agents to a patient or their sequential administration within a time period during which the first administered therapeutic agent is still present in the patient when the second administered therapeutic agent is administered.

The term "monotherapy" refers to administering a single drug to treat a disease or disorder in the absence of co-administration of any other therapeutic agent that is being administered to treat the same disease or disorder.

"Additional therapeutic agent" is used herein to indicate any drug that is useful for the treatment of a malignant pancreatic tumor other than a drug that inhibits heregulin binding to ErbB2/ErbB3 heterodimer.
"Antibody" describes a polypeptide comprising at least one antibody-derived antigen binding site (e.g., VH/VL region or Fv, or complementarity determining region - CDR) that specifically binds to a specific antigen, e.g., ErbB3. "Antibodies" include whole antibodies and any antigen binding fragment, e.g., Fab or Fv, or a single chain fragment (e.g., scFv), as well as bispecific antibodies and similar engineered variants, human antibodies, humanized antibodies, chimeric antibodies Fabs, Fab'2s, ScFvs, SMIPs, Affibodies®, nanobodies, or a domain antibodies, and may be of any of the following isotypes: IgGl, IgG2, IgG3, IgG4, IgM, IgAl, IgA2, IgAsec, IgD, and IgE. The antibody may be a naturally occurring antibody or may be an antibody that has been altered (e.g., by mutation, deletion, substitution, conjugation to a non-antibody moiety). For example, an antibody may include one or more variant amino acids (compared to a naturally occurring antibody) which change a property (e.g., a functional property) of the antibody. For example, numerous such alterations are known in the art which affect, e.g., half-life, effector function, and/or immune responses to the antibody in a patient. The term "antibody" thus includes whole antibodies and any antigen binding fragment (i.e., "antigen-binding portion," e.g., Fabs) or single chains thereof (e.g., scFvs) as well as bispecific antibodies and similar engineered variants, provided that they retain the binding specificity of an antibody.

An "anti-ErbB3 antibody" is an antibody that immunospecifically binds to the ectodomain of ErbB3. Such binding to ErbB3 typically exhibits a binding affinity equal or greater than that indicated by a $K_d$ of 50 nM (i.e., a binding affinity corresponding to a $K_d$ value of 50 nM, or a higher binding affinity as indicated by a lower $K_d$ value such as 50 pM), e.g., as measured by a surface plasmon resonance assay or a cell binding assay.

The terms "ErbB2," "HER2," and "HER2 receptor," as used interchangeably herein, refer to the protein product of the human neu oncogene, also referred to as the ErbB2 oncogene or the HER2 oncogene.

"Dosage" refers to parameters for administering a drug in defined quantities per unit time (e.g., per hour, per day, per week, per month, etc.) to a patient. Such parameters include, e.g., the size of each dose. Such parameters also include the configuration of each dose, which may be administered as one or more units, e.g., taken at a single administration, e.g., orally (e.g., as one, two, three or more pills, capsules, etc.) or injected (e.g., as a bolus). Dosage sizes may also relate to doses that are administered continuously (e.g., as an intravenous infusion over a period of minutes or hours). Such parameters further include frequency of administration of separate doses, which frequency may change over time.

"Dose" refers to an amount of a drug given in a single administration.

"Effective treatment" refers to treatment producing a beneficial outcome, e.g., amelioration of at least one symptom of a disease or disorder. A beneficial outcome can take the form of an improvement over baseline, which is generally an improvement over measurements, observations, or reported
symptoms made, e.g., prior to, simultaneously with, or immediately following initiation of therapy. A beneficial outcome can also take the form of arresting, slowing, retarding, or stabilizing the progression of disease, e.g., as indicated by changes in a biomarker. Effective treatment may also refer to improvement or alleviation of one or more symptoms of pancreatic cancer; e.g., such treatment may reduce pain, increase patient mobility, reduce tumor size and/or number, increase longevity, reduce the rate of development of metastatic lesions, slow or reverse tumor growth, prevent or delay tumor recurrence, or inhibit, retard, slow or stop cancer cell infiltration into organs or tissues outside the pancreas.

"Effective amount" refers to an amount (administered in one or more doses) of an antibody, protein or additional therapeutic agent, which amount is sufficient to provide effective treatment.

The term "platinum-based therapeutic agent" refers to organoplatinum compounds (or treatment therewith), including for example oxaliplatin, carboplatin and cisplatin.

The disclosures if the following subsections should not be construed as limiting.

1. **Anti-ErbB3 Antibody:** An anti-ErbB3 antibody (e.g., MM-121) is to be administered to a patient in a disclosed combination. MM-121 is a fully human anti-ErbB3 antibody currently undergoing Phase II clinical trials. MM-121 (also referred to as "Ab #6") and related human anti-ErbB3 antibodies are described in detail in U.S. patent No. 7,846,440, U.S. Patent Publication Nos. US 20100056761, and US 20100266584, and PCT Publication No. WO 2008/100624. Other anti-ErbB3 antibodies that may be used in a disclosed combination include any of the other anti-ErbB3 antibodies described in U.S patent No. 7,846,440, such as Ab #3 (SEQ ID NOs: 14-21), Ab #14 (SEQ ID NOs:22-29), Ab #17 (SEQ ID NOs:30-37) or Ab #19 (SEQ ID NOs:38-45) or an antibody that competes with Ab #3, Ab #14, Ab #17 or Ab #19 for binding to ErbB3.

Additional examples of anti-ErbB3 antibodies that may be administered in accordance with the methods disclosed herein include antibodies disclosed in US patents and patent publications Nos. 7,285,649, 8,362,215, and 20100255010, as well as antibodies 1B4C3 (cat # sc-23865, Santa Cruz Biotechnology) and 2D1D12 (U3 Pharma AG), both of which are described in, e.g., US Publication No. 20040197332 and are produced by hybridoma cell lines DSM ACC 2527 or DSM ACC 2517 (deposited at DSMZ) anti-ErbB3 antibodies disclosed in U.S. Patent No. 7,705,130 including but not limited to the anti-ErbB3 antibody referred to as AMG888 (U3-1287 —U3 Pharma AG and Amgen), described in, e.g., U.S. patent No. 7,705,130; the anti-ErbB3 antibody referred to as AV-203 (Aveo Pharmaceuticals) which is described in US patent publication No. 20110256154, and the monoclonal antibodies (including humanized versions thereof), such as 8B8 (ATCC® HB-12070™), described in U.S. patent No. 5,968,511. Additional examples include MEDI3379 (Medimmune), and GE-huMab-HER3 (Genentech), which is a glycoengineered anti-ErbB3 antibody. Other such examples include anti-ErbB3 antibodies that are multi-specific antibodies and comprise at least one anti-ErbB3 antibody (e.g., one of the aforementioned anti-ErbB3 antibodies) linked to at least a second therapeutic antibody or to an
additional therapeutic agent. Examples of such antibodies include MM-141 and MM-111, described, e.g., in copending U.S. patent publication No. US 2011-0059076. Other suitable anti-ErbB3 antibodies also include pan-HER antibody compositions such as those disclosed, e.g., in PCT publication No. WO/2012/059857 (Symphogen) which describes antibody compositions targeting multiple ErbB family receptors. Yet other suitable anti-ErbB3 antibodies comprise either: 1) variable heavy (VH) and/or variable light (VL) regions encoded by the nucleic acid sequences set forth in SEQ ID NOs: 1 and 3, respectively, or 2) VH and/or VL regions comprising the amino acid sequences set forth in SEQ ID NOs: 2 and 4, respectively, or 3) CDRH1, CDRH2, and CDRH3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 5 (CDRH1) SEQ ID NO: 6 (CDRH2) and SEQ ID NO: 7 (CDRH3), and/or CDRL1, CDRL2, and CDRL3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 8 (CDRL1) SEQ ID NO: 9 (CDRL2) and SEQ ID NO: 10 (CDRL3) as well as an antibody that binds to human ErbB3 and has at least 90% variable region sequence identity with the above-mentioned antibodies 1), 2), or 3). In one embodiment, the antibody has heavy and light chains comprising the amino acid sequences set forth in SEQ ID NOs 12 and 13, respectively. In another embodiment, the antibody competes for binding with and/or binds to the same epitope on human ErbB3 as any one of the above-mentioned antibodies. When the antibody is MM-121, the epitope typically comprises residues 92-104 of human ErbB3 (SEQ ID NO: 11). In other embodiments, the antibody is a fully human monoclonal antibody that binds to ErbB3 and, in living cells and either a) inhibits ErbB2/ErbB3 complex formation or b) prevents intracellular phosphorylation of ErbB3-induced by any of the forms of each of the following: heregulin, EGF, TGFα, betacellulin, heparin-binding epidermal growth factor, biregulin, epigen, epiregulin, and amphiregulin, or does both a) and b).

Anti-ErbB3 antibodies described above, can be generated, e.g., in prokaryotic or eukaryotic cells, using methods well known in the art, e.g., in a cell line capable of glycosylating proteins, such as CHO cells.

II. Additional therapeutic agents:

Chemotherapy with one or more of 5-fluorouracil (5-FU) and gemcitabine has been shown to prolong survival in advanced pancreatic cancer. Many novel small molecules are being widely and actively researched as chemotherapeutic agents. These compounds include fluoropyrimidines, nucleoside analogues, platinum-based therapeutic agents, topoisomerase 1 inhibitors, antimicrotubule agents, BRAF inhibitors, proteasome inhibitors, vitamin D analogues, folic acid (leucovorin or levoleucovorin), arachidonic acid pathway inhibitors, histone deacetylase inhibitors, farnesyltransferase inhibitors and epidermal growth factor receptor tyrosine kinase inhibitors. A combination therapy including folic acid, 5-fluorouracil, and irinotecan (FOLFIRI), folic acid, 5-fluorouracil, irinotecan and oxaliplatin
(FOLFIRINOX), or, less commonly, a combination of folinic acid, 5-fluorouracil, and oxaliplatin (FOLFOX) are also used to treat pancreatic cancer.

Additional therapeutic agents suitable for combination with anti-ErbB3 antibodies may further include: 1) EGFR inhibitors including but not limited to monoclonal antibody EGFR inhibitors (e.g. MM-151, Sym004, cetuximab, panitumumab, zalutumumab, nimotuzumab, and matuzumab), small molecule tyrosine kinase inhibitors (e.g. afatinib, gefitinib, erlotinib, PKI-166, PD-158780, Tyrophostin AG 1478), dual inhibitors of EGFR and ErbB2 (e.g. afatinib and lapatinib), and pan-HER kinase inhibitors (e.g. CI-1033 (PD 183805), AC480, HM781-36B, AZD8931 and PF299804); 2) pyrimidine antimetabolites, e.g. the nucleoside metabolic inhibitor gemcitabine; 3) topoisomerase 1 inhibitor (e.g. irinotecan); 4) microtubule stabilizing agents (e.g. laulimalide, epothilone A, epothilone B, docodermolide, eleutherobin, sarcodictyn A, sarcodictyn B, cabazitaxel, paclitaxel, nab-paclitaxel or docetaxel); 5) BRAF inhibitors, (e.g. vemurafenib); 6) IGFIR inhibitors (e.g. dalotuzumab, XL228, BMS-754807 AMG-479, R1507, figitumumab, IMC-A12, and MM-141, a bispecific ErbB3/IGFIR inhibitor (further described in Lugovskoy et al., copending commonly assigned U.S. Patent Application Serial No. 61/558,192, filed 11/10/2011, and PCT application No. PCT/US2012/034244) and molecule IGFIR inhibitors include XL228 and BMS-754807); 7) phosphoinositide-3-kinase (PI3K) inhibitors (e.g. CAL101 and PX-866); 8) mitogen activated kinase kinase (MEK) inhibitors (e.g. XL518, CI-1040, PD035901, selumetinib, and GSK1 120212); and 9) mTOR inhibitors (e.g. everolimus, temsirolimus, sirolimus, or ridaforolimus). mTOR (mammalian target of rapamycin) is a serine/threonine protein kinase that regulates cell growth, proliferation, motility, survival, and protein synthesis and transcription. Rapamycin is now known as sirolimus, an mTOR inhibitor used as an immunosuppressant.

In certain combination therapy methods, one or more of the following therapeutic agents is co-administered to the patient with an anti-ErbB3 antibody.

**Gemcitabine** (Gemzar®) is indicated as first line therapy for pancreatic adenocarcinoma and is also used in various combinations to treat ovarian, breast and non-small-cell lung cancers. Gemcitabine HCl is 2'-deoxy-2',2'-difluorocytidine monohydrochloride (-isomer) (MW=299.66) and is administered parenterally, typically by i.v. infusion.

**Irinotecan** (Camptosar®) (irinotecan hydrochloride injection), also referred to as CPT-11, is administered parenterally, typically by i.v. infusion. CPT-11 is approved in the United States for treatment of metastatic colon or renal cancer. CPT-11 is also used to treat colorectal, gastric, lung, uterine cervical and ovarian cancers.

In one embodiment, CPT-11 is administered in a stable nanoliposomal formulation, e.g., the formulation referred to herein as "MM-398" (also known as PEP02). MM-398 may be provided as a sterile, injectable parenteral liquid for intravenous injection. MM-398 may be administered, for example,
at a dosage of 120mg/m². The required amount of MM-398 may be diluted, e.g., in 500mL of 5% dextrose injection USP and infused over a 90 minute period.

An MM-398 liposome is a unilamellar lipid bilayer vesicle of approximately 80-140 nm in diameter that encapsulates an aqueous space which contains irinotecan complexed in a gelated or precipitated state as a salt with sucrose octasulfate. The lipid membrane of the liposome is composed of phosphatidylcholine, cholesterol, and a polyethyleneglycol-derivated phosphatidyl-ethanolamine in the amount of approximately one polyethyleneglycol (PEG) molecule for 200 phospholipid molecules. MM-398 recently achieved primary efficacy endpoints in Phase II clinical trials in metastatic pancreatic cancer and in gastric cancer, and is being investigated in the context of metastatic colorectal cancer.

Paclitaxel is administered parenterally, typically by i.v. infusion, and is formulated with polyethoxylated castor oil as “Taxol® (paclitaxel) injection” or with human serum albumin as “Abraxane® (paclitaxel protein-bound particles for injectable suspension) (albumin bound)” also called nab-paclitaxel. Paclitaxel is used to treat, e.g., breast cancer, non-small cell lung cancer (in combination with cisplatin), and AIDS-related Kaposi’s sarcoma.

Erlotinib (Tarceva®) is orally administered and is used to treat, e.g., locally advanced or metastatic non-small cell lung cancer (NSCLC) and locally advanced, unresectable or metastatic pancreatic cancer (in combination with gemcitabine).

Afatinib (Tomtovik®) is an orally administered tyrosine kinase inhibitor that irreversibly inhibits HER2 and EGFR kinases. It is not yet marketed and is being tested in the context of non-small cell lung carcinoma, breast, prostate, head and neck cancers, and glioma.

Temsirolimus (Torisel®) is an mTOR inhibitor that is administered parenterally, typically by i.v. infusion and is used to treat advanced renal cell carcinoma.

Everolimus (Afinitor®), a 40-O-(2-hydroxyethyl) derivative of sirolimus, is an mTOR inhibitor that is administered orally and is used to treat progressive neuroendocrine tumors of pancreatic origin (PNET) in patients with unresectable, locally advanced or metastatic disease.

Vemurafenb (Ze!boraf®) is a BRAE enzyme inhibitor approved for the treatment of late-stage melanoma in patients whose cancer harbors a V600E BRAF mutation.

III. Combination Therapies

As herein provided, anti-ErbB3 antibodies (e.g., MM-121) are co-administered with one or more additional therapeutic agents (e.g. irinotecan, nab-paclitaxel, erlotinib, gemcitabine, everolimus, and/or afatinib), to provide effective treatment to human patients having a pancreatic cancer (e.g., pancreatic adenocarcinoma).

The anti-ErbB3 antibody and one or more additional therapeutic agents for combination therapy may be administered to the patient in any suitable form. Typically, each of the anti-ErbB3 antibody and
the one or more additional therapeutic agents is provided in the form of a pharmaceutical composition, which comprises the antibody or additional therapeutic agent in a physiologically acceptable carrier. In certain embodiments, the one or more additional therapeutic agents are formulated for oral or intravenous administration. In another embodiment, the anti-ErbB3 antibody is formulated for intravenous administration.

In particular embodiments, the anti-ErbB3 antibody is administered at a dose selected from: 2-50 mg/kg (body weight of the patient) administered once a week, or twice a week or once every three days, or once every two weeks, and 1-100 mg/kg administered once a week, or twice a week or once every three days, or once every two weeks. In various embodiments, the anti-ErbB3 antibody is administered at a dosage of 3.2 mg/kg, 6 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg or 40 mg/kg at a timing of once a week, or twice a week or once every three days, or once every two weeks. Additional dosage ranges for the anti-ErbB3 antibody include: 1-1000 mg/kg, 1-500 mg/kg, 1-400 mg/kg, 1-300 mg/kg and 1-200 mg/kg. Suitable dosage schedules include once every three days, once every five days, once every seven days (*i.e.*, once a week), once every 10 days, once every 14 days (*i.e.*, once every two weeks), once every 21 days (*i.e.*, once every three weeks), once every 28 days (*i.e.*, once every four weeks) and once a month.

IV. Patient Populations

In one embodiment, a human patient for treatment using the methods and compositions disclosed herein exhibits evidence of recurrent or persistent disease following primary chemotherapy.

In another embodiment, such a human patient has had and failed at least one prior platinum based chemotherapy regimen for management of primary or recurrent disease, *e.g.*, a chemotherapy regimen comprising carboplatin, cisplatin, or another organoplatinum compound.

In an additional embodiment, the human patient has failed prior treatment with gemcitabine or become resistant to gemcitabine.

As used herein the terms "resistant" and "refractory" refer to tumor cells that survive treatment with a therapeutic agent. Such cells may have responded to a therapeutic agent initially, but subsequently exhibited a reduction of responsiveness during treatment, or did not exhibit an adequate response to the therapeutic agent in that the cells continued to proliferate in the course of treatment with the agent. In one embodiment a resistant or refractory tumor is one where the treatment-free interval following completion of a course of therapy for a patient having the tumor is less than 6 months (*e.g.*, owing to recurrence of the cancer) or where there is tumor progression during the course of therapy.

In another embodiment, the pancreatic cancer undergoing treatment is advanced pancreatic cancer, which is a pancreatic tumor that exhibits either or both of distant metastasis or peripancreatic extension of the tumor.
The combination therapies and methods disclosed herein are useful for the treatment of pancreatic cancers, including pancreatic cancers that are refractory or resistant to other anti-cancer treatments. The methods can be used in the treatment of essentially any type of pancreatic cancer tumor that expresses ErbB3. Examples of types of pancreatic cancers to be treated include 1) exocrine pancreatic cancers, e.g., acinar cell carcinoma, adenocarcinoma, adenosquamous carcinoma, giant cell carcinoma of the pancreas, intraductal papillary-mucinous neoplasm (IPMN), mucinous cystadenocarcinoma, pancreaticoblastoma, and serous cystadenocarcinoma, and 2) endocrine pancreatic cancers, e.g., gastrinoma (Zollinger-Ellison Syndrome), insulinoma, nonfunctional islet cell tumor, somatostatinoma, vasoactive intestinal peptide-releasing tumor (VIPoma or Verner-Morrison Syndrome). In one embodiment, the pancreatic cancer is an adenocarcinoma (i.e., pancreatic ductal carcinoma).

In one embodiment, the pancreatic cancer comprises one or more KRAS mutations (e.g., a KRAS G12S mutation). "KRAS mutation" refers to oncogenic mutations found in certain cancers in KRAS, the human homolog of the v-Ki-ras2 Kirsten rat sarcoma viral oncogene. It has been reported that KRAS mutations are found in 73% of pancreatic tumors. In another embodiment, the pancreatic cancer comprises a BRAF mutation (e.g., a BRAF V600E mutation). "BRAF mutation" refers to oncogenic mutations in the BRAF (Serine/threonine-protein kinase B-Raf or "B-Raf") gene. When present, KRAS and BRAF mutations are typically found together in pancreatic tumors. Transgenomic, Inc., Omaha, Nebraska; Asuragen, Inc., Austin, Texas; EntroGen, Inc., Tarzana, California; and QIAGEN Gmbh, Hilden, Germany, are among the many companies that market both KRAS and BRAF testing kits.

Multiple laboratories now offer KRAS and BRAF mutation testing of tumor biopsy samples as a commercial service, e.g., GenPath, Elmwood Park, New Jersey and Clarient, Inc., Aliso Viejo, California.

V. Outcomes

As shown in the Examples herein, co-administration of an anti-ErbB3 antibody with one or more additional therapeutic agents (e.g. irinotecan, nab-paclitaxel, erlotinib, gemcitabine, everolimus, and/or afatinib) provides improved efficacy compared to treatment with the antibody alone or with the one or more additional therapeutic agents in the absence of antibody therapy. Preferably, a combination of an anti-ErbB3 antibody with one or more additional therapeutic agents exhibits therapeutic synergy.

"Therapeutic synergy" refers to a phenomenon where treatment of patients with a combination of therapeutic agents manifests a therapeutically superior outcome to the outcome achieved by each individual constituent of the combination used at its optimum dose (T. H. Corbett et al., 1982, Cancer Treatment Reports, 66, 1187). In this context a therapeutically superior outcome is one in which the patients either a) exhibit fewer incidences of adverse events while receiving a therapeutic benefit that is equal to or greater than that where individual constituents of the combination are each administered as monotherapy at the same dose as in the combination, or b) do not exhibit dose-limiting toxicities while
receiving a therapeutic benefit that is greater than that of treatment with each individual constituent of the combination when each constituent is administered individually at the same doses in the combination(s) as is administered as individual components. In xenograft models, a combination, used at its maximum tolerated dose, in which each of the constituents will be present at a dose generally not exceeding its individual maximum tolerated dose, manifests therapeutic synergy when decrease in tumor growth achieved by administration of the combination is greater than the value of the decrease in tumor growth of the best constituent when the constituent is administered alone.

Thus, in combination, the components of such combinations have an additive or superadditive effect on suppressing pancreatic tumor growth, as compared to monotherapy with the anti-ErbB3 antibody or treatment with the chemotherapeutic(s) in the absence of antibody therapy. By "additive" is meant a result that is greater in extent (e.g., in the degree of reduction of tumor mitotic index or of tumor growth or in the degree of tumor shrinkage or the frequency and/or duration of symptom-free or symptom-reduced periods) than the best separate result achieved by monotherapy with each individual component, while "superadditive" is used to indicate a result that exceeds in extent the sum of such separate results. In one embodiment, the additive effect is measured as slowing or stopping of pancreatic tumor growth. The additive effect can also be measured as, e.g., reduction in size of a pancreatic tumor, reduction of tumor mitotic index, reduction in number of metastatic lesions over time, increase in overall response rate, or increase in median or overall survival.

One non-limiting example of a measure by which effectiveness of a therapeutic treatment can be quantified is by calculating the log10 cell kill, which is determined according to the following equation:

\[
\text{log10 cell kill} = \frac{T \times C \times (\text{days})}{3.32 \times Td}
\]

in which \(T\) represents the delay in growth of the cells, which is the average time, in days, for the tumors of the treated group \(T\) and the tumors of the control group \(C\) to have reached a predetermined value (1 g, or 10 nL, for example), and \(Td\) represents the time, in days necessary for the volume of the tumor to double in the control animals. When applying this measure, a product is considered to be active if log10 cell kill is greater than or equal to 0.7 and a product is considered to be very active if log10 cell kill is greater than 2.8. Using this measure, a combination, used at its own maximum tolerated dose, in which each of the constituents is present at a dose generally less than or equal to its maximum tolerated dose, exhibits therapeutic synergy when the log10 cell kill is greater than the value of the log10 cell kill of the best constituent when it is administered alone. In an exemplary case, the log10 cell kill of the combination exceeds the value of the log10 cell kill of the best constituent of the combination by at least 0.1 log cell kill, at least 0.5 log cell kill, or at least 1.0 log cell kill.
VI. Kits and Unit Dosage Forms

Kits that include a pharmaceutical composition containing an anti-ErbB3 antibody, such as MM-121, and a pharmaceutically-acceptable carrier, in a therapeutically effective amount adapted for use in the preceding methods are provided. The kits can optionally also include instructions, e.g., comprising administration schedules, to allow a practitioner (e.g., a physician, nurse, or patient) to administer the compositions contained therein to a patient having a pancreatic cancer. In one embodiment, the kit further comprises irinotecan. In another embodiment, the kit further comprises paclitaxel (e.g., nab-paclitaxel). In another embodiment, the kit further comprises erlotinib and/or gemcitabine. In another embodiment the kit includes infusion devices such as needles, catheters, tubing, and the like. Optionally, the kits include multiple packages each containing a single dose amount of the antibody or of the chemotherapeutic (e.g., in a unit dosage form distributed by the manufacturer) for administration in accordance with the methods provided herein.

VII. Treatment of Cancer Types other than Pancreatic Cancer

ErbB3 is a critical activator of phosphoinositide 3-kinase (PI3K) signaling in cancers that arise from dependence on the epidermal growth factor receptor, e.g., pancreatic cancer, and reactivation of ErbB3 is a prominent method by which a cancer can become resistant to ErbB inhibitors. The methods and combination treatments described herein will thus be useful for treatment of types of cancer with a molecular pathology similar to that of pancreatic cancer in that they are EGFR-driven and, after anti-EGFR treatment, become resistant to such treatment through increased signaling in the PI3K pathway via ErbB3. Such cancer types include, but are not limited to, lung, colon, head and neck, and esophageal cancers.

The following examples are illustrative and should not be construed as limiting the scope of this disclosure in any way; many variations and equivalents will become apparent to those skilled in the art upon reading the present disclosure.

**Incorporation By Reference:** The disclosure of each and every US, International, or other patent or patent application or publication referred to herein is hereby incorporated herein by reference in its entirety.

**Examples**

**Example 1 Combination Treatment with MM-121 and irinotecan Inhibits Tumor Growth in Pancreatic Cancer**

The anti-tumor efficacy and tolerability of MM-121 and irinotecan (CPT-11 or in liposomal formulation (MM-398)), either alone (i.e., as a monotherapy) or in combination, in tumor-bearing mice was evaluated using human pancreatic adenocarcinoma BxPC-3 cells (ATCC # CRL-1687) implanted as xenografts in nu/nu nude mice. BxPC-3 cells were derived from a human metastatic tumor and expressed
high levels of HRG and EGFR. In these xenograft studies, nu/nu nude mice were obtained from Charles River Laboratories International. The mice were housed in Tecniplast® Individually Ventilated polycarbonate (Makrolon®) Cages (IVC) set in climate-controlled rooms and had free access to food and acidified water. 8 x 10^6 cells were mixed 1:1 in reduced growth factor Matrigel™ (BD Biosciences, Cat # 354230) and implanted by subcutaneous injection into the left flank of female, 4-5 week old nu/nu mice. Tumors were allowed to reach 150 mm³ in size before randomization.

Dose Escalation Study A dose escalation study was performed to determine suboptimal and optimal doses of MM-121 and CPT-11 in preparation for combination therapy using the BxPC-3 xenograft model.

Xenograft-bearing mice were randomized into 10 groups of 5 mice, containing mice with a similar size distribution of tumors. Four groups were treated with escalating intraperitoneal (i.p.) doses of MM-121 (75, 150, 300 or 600 µg, Q3D per group), 3 groups were treated with escalating doses of irinotecan (CPT-11) (6.25, 12.5, 25 or 50 mg/kg, Q7D, per group), one control group was treated with PBS, Q3D, and another control group was treated with 5% DMSO in PBS (CPT-11 vehicle), Q7D.

Treatment continued for 3 weeks. Tumors were measured twice weekly, and tumor volume was calculated as π/6 x length x width^2, where the width is the shorter measurement.

Dose responses for inhibition of tumor growth were observed for MM-121 (Figure 1A) and CPT-11 (Figure 1B). The "suboptimal" doses for evaluation in combination therapy in BxPC-3 xenografts were identified as 150 µg Q3D for MM-121 and 12.5 to 25 mg/kg for CPT-11 Q7D. Meanwhile, the "optimal" doses for evaluation in BxPC-3 xenografts were identified as 600µg Q3D for MM-121 and 50 mg/kg for CPT-11.

Combination therapy study A combination therapy study was performed to demonstrate the effects of various combinations of MM-121, irinotecan (CPT-11), and liposomal irinotecan (MM-398).

Mice were randomized as above into 9 groups of 5 mice each. Five groups were treated with i.p. doses of a single agent alone, as follows: (1) MM-121 (150 µg Q3D), (2) MM-121 (600 µg Q3D), (3) CPT-11 (25 mg/kg Q7D), (4) MM-398 (10 mg/kg Q3D), or (5) PBS (Q3D) alone (Control). Four groups were treated with a combination therapy of (1) MM-121 and CPT-11 or (2) MM-121 and MM-398 with the doses described above. Treatment continued for 4 weeks. Tumors were measured twice weekly and tumor volume calculated.

As shown in Figure 2A (MM-121 dose; 150 µg Q3D) and Figure 2B (MM-121 optimal dose; 600µg Q3D), MM-121 as a single agent significantly suppressed tumor growth in a dose-dependent manner. Moreover, while CPT-11 and MM-398 alone each inhibited tumor growth in vivo, combination treatments with MM-121 and CPT-11 or MM-121 and MM-398 exhibited an additive effect on tumor growth inhibition, as compared to tumor growth inhibition observed with each of the individual agents.
Furthermore, treatment with either CPT-11 or MM-398 in combination with the optimal dose of MM-121 (60\(\text{mg} \text{ Q3D}\)) resulted in pronounced tumor regression.

**Example 2 Combination Treatment with MM-121 and nab-paclitaxel Inhibits Tumor Growth in Pancreatic Cancer**

The anti-tumor efficacy and tolerability of MM-121 and nab-paclitaxel (paclitaxel protein-bound particles for injectable suspension) combination treatment, with or without gemcitabine, was evaluated using COLO-357 cells (ECACC Cat # 94072245) implanted as xenografts in nu/nu nude mice. COLO-357 cells were derived from a lymph node metastasis of a human non-endocrine pancreatic cancer, and have been reported to harbor KRAS G12S and BRAF V600E mutations.

Xenograft-bearing mice were prepared as described except 5 x 10\(^6\) COLO-357 cells were used. A dose escalation study was performed to determine optimal doses of MM-121 in preparation for combination therapy using the COLO-357 xenograft model.

Xenograft-bearing mice were randomized into seven groups of five mice, containing mice with a similar size distribution of tumors. Six groups were treated with escalating doses of i.p. MM-121 (18.75, 37.5, 75, 150, 300 or 600 \(\mu\text{g} \text{ Q3D per group}\)), and another control group was treated with PBS. Treatment continued for 4 weeks. Tumors were measured twice weekly, and tumor volume was calculated. As depicted in Figure 3, MM-121 suppressed tumor growth in a dose-dependent manner. The "suboptimal" doses for evaluation in combination therapy in COLO-357 cells xenografts were identified as 300 \(\mu\text{g} \text{ Q3D for MM-121, and the "optimal" dose was identified as 600\(\mu\text{g} \text{ Q3D}.}\)

A combination therapy study was performed to demonstrate the effects of various combinations of MM-121, nab-paclitaxel (Abraxis; Catalog # NDC68817-134-50), and gemcitabine (LC labs; Catalog # G1477).

Xenograft-bearing mice were randomized into 10 groups of 9-10 mice, containing mice with a similar size distribution of tumors. Four groups were treated with i.p. doses of a single agent alone, as follows: (1) 10 mg/kg Q3D i.p. of nab-paclitaxel, (2) 20 mg/kg Q3D i.p. of nab-paclitaxel (3) 300 \(\mu\text{g} \text{ Q3D i.p. of MM-121, (4) 150mg/kg Q7D i.p. of gemcitabine.}\)

Three groups were treated with duo combination therapy, as follows: (1) MM-121 and nab-paclitaxel (10 mg/kg), (2) MM-121 and nab-paclitaxel (20 mg/kg), and (3) MM-121 and gemcitabine (150mg/kg). Two groups were treated with triple combination therapy, as follows: (1) MM-121, nab-paclitaxel (10 mg/kg) and gemcitabine, and (2) MM-121, nab-paclitaxel (20 mg/kg) and gemcitabine. A control group was treated with PBS, Q3D, i.p..

Treatment continued for 7 weeks. Tumors were measured twice weekly, and tumor volume was calculated.

As shown in Figures 4A-B, MM-121 as a single agent, at the suboptimal dose of 300 \(\mu\text{g} \text{ Q3D, significantly suppressed tumor growth in a dose-dependent manner.}\) However, the COL-357 xenograft
model responded poorly to nab-paclitaxel alone (Figure 4A) and moderately to gemcitabine alone (Figure 4B) for the doses tested.

With respect to the combination therapies, MM-121 in combination with nab-paclitaxel showed a dose-dependent additive effect on tumor growth suppression when compared to each drug alone (Figure 4A). Additionally, MM-121 in combination with gemcitabine shows little if any enhancement over MM-121 single therapy (Figure 4B) in COLO-357 tumors.

Moreover, while CPT-11 and MM-398 alone each inhibit tumor growth in vivo, treatment with the combinations of MM-121 and CPT-11 or MM-121 and MM-398 resulted in an additive effect on suppression of tumor growth, as compared to treatment with each of the individual agents. Furthermore, treatment with either CPT-11 or MM-398 in combination with the optimal dose of MM-121 (600μg Q3D) resulted in pronounced increase in cell death, as shown in figure 4.

The triple combination therapy of MM-121, nab-paclitaxel and gemcitabine suppressed tumor growth to a similar extent as the dual MM-121 and nab-paclitaxel combination, indicating that gemcitabine did not enhance the inhibitory effect of this dual combination (Figure 4B) in COLO-357 tumors.

**Example 3**  Triple Combination Treatment with MM-121, gemcitabine, and erlotinib Inhibits Tumor Growth in Pancreatic Cancer

A) A combination therapy study was performed to demonstrate the effects of various combinations of MM-121, erlotinib (LC Laboratories - Catalog # E4007), and gemcitabine. Specifically, the anti-tumor efficacy of MM-121 and erlotinib in combination, with or without gemcitabine, on tumor-bearing mice was analyzed using COLO-357 cells. Xenograft bearing mice were prepared as described in the preceding Example.

Five groups were treated with single agents, as follows: (1) 50 mg/kg Q5D oral of erlotinib, (2) 100 mg/kg Q5D oral of erlotinib, (3) 300 μg Q3D i.p. of MM-121, (4) 150 mg/kg Q7D i.p. of gemcitabine, and (5) 300 mg/kg Q7D i.p. of gemcitabine. Additional groups were treated with double combination or triple combination therapy, as set forth in Table 1 below. A control group was treated with PBS, Q3D, i.p. Treatment continued for 7 weeks. Tumors were measured twice weekly and tumor volume was calculated.

**Table 1**

<table>
<thead>
<tr>
<th>Group</th>
<th>Test Article</th>
<th>Dose</th>
<th>Route</th>
<th>Dose Schedule</th>
<th>Dose Volume</th>
<th>Mice (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Vehicle Control</td>
<td>NA</td>
<td>IP</td>
<td>Q3D X 12</td>
<td>0.1 ml</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>MM-121</td>
<td>300 μg</td>
<td>IP</td>
<td>Q3D X 12</td>
<td>0.1 ml</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Drug Combination</td>
<td>Dosage</td>
<td>Administration</td>
<td>Schedule</td>
<td>Volume</td>
<td>Repeat Dosing</td>
</tr>
<tr>
<td>---</td>
<td>-----------------</td>
<td>----------------</td>
<td>----------------</td>
<td>-----------------</td>
<td>--------</td>
<td>--------------</td>
</tr>
<tr>
<td>3</td>
<td>erlotinib</td>
<td>50 mg/kg</td>
<td>PO</td>
<td>QD (5x a week)</td>
<td>0.2 ml</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>erlotinib</td>
<td>100 mg/kg</td>
<td>PO</td>
<td>QD (5x a week)</td>
<td>0.2 ml</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>gemcitabine</td>
<td>150 mg/kg</td>
<td>IP</td>
<td>Q7D X 5</td>
<td>0.4ml</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>gemcitabine</td>
<td>300 mg/kg</td>
<td>IP</td>
<td>Q7D X 5</td>
<td>0.4ml</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>MM121 + erlotinib + gemcitabine</td>
<td>300µg+50mpk+150mpk</td>
<td>IP+PO+IP</td>
<td>Q3D X 12+ QD (5x a week)+ Q7D X 5</td>
<td>0.1 ml+0.2 ml+0.4ml</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>MM121 + erlotinib + gemcitabine</td>
<td>300µg+50mpk+300mpk</td>
<td>IP+PO+IP</td>
<td>Q3D X 12+ QD (5x a week)+ Q7D X 5</td>
<td>0.1 ml+0.2 ml+0.4ml</td>
<td>10</td>
</tr>
<tr>
<td>9</td>
<td>MM121 + erlotinib + gemcitabine</td>
<td>300µg+100mpk+150mpk</td>
<td>IP+PO+IP</td>
<td>Q3D X 12+ QD (5x a week)+ Q7D X 5</td>
<td>0.1 ml+0.2 ml+0.4ml</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>MM121 + erlotinib + gemcitabine</td>
<td>300µg+100mpk+150mpk</td>
<td>IP+PO+IP</td>
<td>Q3D X 12+ QD (5x a week)+ Q7D X 5</td>
<td>0.1 ml+0.2 ml+0.4ml</td>
<td>10</td>
</tr>
<tr>
<td>11</td>
<td>erlotinib + gemcitabine</td>
<td>50 mpk+150 mpk</td>
<td>PO+IP</td>
<td>QD (5x a week)+ Q7D X 5</td>
<td>0.2 ml+0.4ml</td>
<td>10</td>
</tr>
<tr>
<td>12</td>
<td>erlotinib + gemcitabine</td>
<td>100 mpk+300 mpk</td>
<td>PO+IP</td>
<td>QD (5x a week)+ Q7D X 5</td>
<td>0.2 ml+0.4ml</td>
<td>10</td>
</tr>
<tr>
<td>13</td>
<td>erlotinib + gemcitabine</td>
<td>50 mpk+300 mpk</td>
<td>PO+IP</td>
<td>QD (5x a week)+ Q7D X 5</td>
<td>0.2 ml+0.4ml</td>
<td>10</td>
</tr>
<tr>
<td>14</td>
<td>erlotinib + gemcitabine</td>
<td>100 mpk+150 mpk</td>
<td>PO+IP</td>
<td>QD (5x a week)+ Q7D X 5</td>
<td>0.2 ml+0.4ml</td>
<td>10</td>
</tr>
</tbody>
</table>

IP: interperitoneal administration - PO: oral administration

As shown in Figures 5A-E, the triple combination of MM-121, erlotinib and gemcitabine was superior in inhibiting tumor growth compared to all doses tested of the standard of care therapy (i.e.,
These results indicate that the addition of MM-121 to the standard of care regimen is beneficial for tumor growth control.

B) To further demonstrate the effects of various combinations of MM-121, erlotinib and gemcitabine on pancreatic cancer, a pancreatic primary tumor explant model (i.e., low passage Champions Tumorgrafts™ CTG-0289 (PANC002), which is reported to harbor KRAS mutations) was used. Immunocompromised mice (Harlan®; nu/nu) between 4-6 weeks of age were implanted unilaterally on the right flank with tumor fragments harvested from 2-4 host animals each implanted from a specific passage lot. Pre-study tumor volumes were recorded for each experiment beginning approximately one week prior to its estimated start date. When tumors reach approximately 125-225 mm³, animals were matched by tumor volume into treatment and control groups and dosing initiated (Day 0), as set forth in Table 2. Animals in all studies were tagged and followed individually throughout the experiment.

Beginning Day 0, tumor dimensions were measured twice weekly by digital caliper, and data including individual and mean estimated tumor volumes (Mean TV ± SEM) were recorded for each group. Tumor volume was calculated using the formula (1): TV= width² x length x 0.52. At study completion, percent tumor growth inhibition (%TGI) values was calculated and reported for each treatment group (T) versus control (C) using initial (i) and final (f) tumor measurements by the formula (2): %TGI= 1- Tf-Ti / Ci-Cf.

The results are set forth in Table 2 and Figure 6.

Table 2: In Vivo Evaluation of MM-121 in Pancreas Tumorgraft™ Model

<table>
<thead>
<tr>
<th>Group</th>
<th>-n-</th>
<th>Agent</th>
<th>Dose (mg/kg/dose)</th>
<th>ROA/ Schedule*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9</td>
<td>Vehicle Control</td>
<td>--</td>
<td>i.p./ q3dx10</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>MM-121</td>
<td>30</td>
<td>i.p./ q3dx10</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>erlotinib</td>
<td>35</td>
<td>p.o./ qdx28</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td>gemcitabine</td>
<td>60</td>
<td>i.p./ q3dx4</td>
</tr>
<tr>
<td>5</td>
<td>9</td>
<td>erlotinib</td>
<td>35</td>
<td>p.o./ qdx28</td>
</tr>
<tr>
<td></td>
<td></td>
<td>gemcitabine</td>
<td>60</td>
<td>i.p./ q3dx4</td>
</tr>
<tr>
<td>6</td>
<td>9</td>
<td>MM-121</td>
<td>30</td>
<td>i.p./ q3dx10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>erlotinib</td>
<td>35</td>
<td>p.o./ qdx28</td>
</tr>
<tr>
<td>7</td>
<td>9</td>
<td>MM-121</td>
<td>30</td>
<td>i.p./ q3dx10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>gemcitabine</td>
<td>60</td>
<td>i.p./ q3dx4</td>
</tr>
<tr>
<td>8</td>
<td>9</td>
<td>MM-121</td>
<td>30</td>
<td>i.p./ q3dx10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>erlotinib</td>
<td>35</td>
<td>p.o./ qdx28</td>
</tr>
<tr>
<td></td>
<td></td>
<td>gemcitabine</td>
<td>60</td>
<td>i.p./ q3dx4</td>
</tr>
</tbody>
</table>
*gemcitabine was dosed first and MM-121 was dosed second with administration occurring two hours apart from each other.

As shown in Figure 6, MM-121, gemcitabine or erlotinib treatment as single agents yielded suboptimal effects on tumor growth inhibition for the doses tested. Specifically, this pancreatic primary tumor explant model was moderately sensitive to gemcitabine and exhibited lesser responses to erlotinib or MM-121.

The combination of gemcitabine and erlotinib was no more efficacious than gemcitabine alone. Additionally, while MM-121 in combination with gemcitabine showed an additive effect as compared to the single agents, MM-121 in combination with erlotinib was not more efficacious than MM-121 alone in this model.

In contrast, the triple combination of MM-121, erlotinib, and gemcitabine had an additive effect on tumor growth inhibition, as compared to the agents alone or paired. In sum, the addition of MM-121 addition to the standard of care combination (erlotinib plus gemcitabine) in this primary pancreatic explant model provided enhanced tumor growth inhibition.

**Example 4. Effect of MM-121 in combination with chemotherapies in an orthotopic model of pancreatic cancer**

Luciferase-labeled human pancreatic cancer cells (BxPC-3-luc2 Bioware® Ultra, Caliper Life Sciences) were expanded in culture and inoculated orthotopically into nude mice (Charles River, nu/nu). Mice were anesthetized and a 0.5cm incision was made on the left flank region. The spleen and the tail of the pancreas were exteriorized. Cells were inoculated at 1x10^6 cells/20µl into the sub-capsular space into the tail of the pancreas. The spleen and the pancreas were then placed back into the peritoneal cavity, and the cavity was sutured and skin closed with surgical staples.

*In vivo* whole body biophotonic imaging was performed weekly throughout the study. Seven days after inoculation of tumor cells the first bioluminescent imaging was performed and mice were randomized into 7 treatment groups (10 mice/group) and treated with PBS (Q3D, i.p.), MM121 600µg, 1200ug (Q3D, i.p.), MM398 10mg/kg (Q7D, i.v.), nab-paclitaxel 15mg/kg (Q3D, i.p.), or combination of MM121 600µg with either MM398 or nab-paclitaxel at the doses mentioned above.

Mice were treated via the regimen described above for 35 days; bioluminescent imaging was performed once every 7 days. At the end of the study, the mice were sacrificed 24 hours after the final dose of each treatment was administered, and final images were taken. The tumors were removed, imaged and placed in formalin for future evaluation. Selected organs such as lung, diaphragm, liver and gastrointestinal-associated lymph nodes were also removed at the end of study, placed in petri dishes and imaged for bioluminescence, as a measurement of tumor cell migration.
As shown in Figure 7, treatment with the combination of MM-121 and either MM-398 or nab-paclitaxel significantly decreased the tumor growth as compared to either drug treatment alone. In addition, MM-121 treatment significantly diminished tumor cell migration from pancreas to lung (Figure 8A) and liver (Figure 8B). Similar results were seen in the diaphragm and gastrointestinal-associated lymph nodes. Thus, these combination treatments are useful for inhibiting the spread of cancer cells from the pancreas to other organs.

**SUMMARY OF SEQUENCES**

<table>
<thead>
<tr>
<th>10</th>
<th>MM-121 Heavy Chain Variable Region Nucleotide Sequence (SEQ ID NO:1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>gaggtgcagc tgctggagag cgcggcaagg ctgttccagc cagcgccagcg cctgaggtgc 60</td>
</tr>
<tr>
<td></td>
<td>tcttgccgc ccacgcccc gactctagtt cacctcagc cactactgta tggctctgtg gccgacagc 120</td>
</tr>
<tr>
<td>15</td>
<td>ccacgcagc gcctggact ggcttcacag atcagcagca gcggcggctg gacccctgtac 180</td>
</tr>
<tr>
<td></td>
<td>gcggagcgc gcctggagcg gctttgcttg gactactcag cagcgctgtg actactgcac caggggcctg 240</td>
</tr>
<tr>
<td>20</td>
<td>ctcggattg caagcttgag gcggaaggac accgccggtg cacccctgtac 300</td>
</tr>
<tr>
<td></td>
<td>aagatggcag cactcttcga ctactggggc cagggcaccc tggctgcagc gagctgcagc 357</td>
</tr>
</tbody>
</table>

**MM-121 VH amino acid sequence (SEQ ID NO:2)**

EVQLLESGGGLVQPGSRLSLCAASGFTSFHYVMWVRQAPGKGLEWVSSISGGLWTLVQPSGP

**MM-121 Light Chain Nucleotide Sequence (SEQ ID NO:3)**

|    | cagttgccac ccagctgcc caagcgccagct ggtgtccagctgtatcttcgctactactgc 30 |
|    | tgcagctac gcgaggccg cacccctgtac 60 |
|    | cacccgcc agcgggcccc ggtgaccgtc eta 333 |
MM-121 VL amino acid sequence (SEP ID NO:4)
QSAITQPASVSQPQGQSITI5CTGTSSDVGSYNVSWYQQHPGKAPKLIIYEVSQRPSGVSNRFSG
SKSNTASL TISGLQTEDEADYYCCSYAGSSIFVIFGGGTKVTL

5 MM-121 VH CDR1 (SEP ID NO:5)
HYVMA

MM-121 VH CDR2 (SEP ID NP :6)
SISSSGGWTL YADSVKG

10 MM-121 VH CDR3 (SEP ID NP :7)
GLKMATIFYD

MM-121 VL CDR1 (SEP ID NP:8)
TGSTSDVGSY NVVS

MM-121 VL CDR2 (SEP ID NP:9)
EVSPrPS

20 MM-121 VL CDR3 (SEP ID NO: 10)
CSYAGSSIFV1

ErbB3 (SEP ID NP :i1)
SEVGNSpAVCPGTLNGLSVTGDAENpYpTYLYKLYERCEVVMGNLEIVLTGHNADLSFLpWIRE

25 VTGYVLVAMNEFSTLPLPNLRVVRGTpVYDGKFAI FVMLNYNTNSSHALpLRpLRTLpLTEILSGG
VYIEKNKLCHMDTIDWRDJVRDRDAEI VKDNGRSCPPCEHEVCKGRCWPGPSEDCpTLTKTIC
APpCNHCHEFNGPNNpCCHDECAGCGSPpDTDFACRHFNDSGACVPRCPpPLVYNKLTpLFPpLEP
NPHTKYpYGVCVAQCSPHNFVVDpTSCVRACPPDKMEVDKNGLKMCEPCGGLCPKACETGTS
GSRfpTVDSNNIDGFVNCTKILGNLDFLITGLNGDPWHKIPADPEKLNVFRTVREITGYLNlpSW

30 PPHHNFVSFSNLTTIGGRSLYNRGFSLLIMKLNVTSLGFRLKEISAGRIYISANRpLCYHHSNLN
WTKVLRGPEERLDIKHNPRRDCVAEGKVDPLCSSGGCWPGPpCLSCRNYSRGGVCVTH
CNFLNGEPREF AHAEACFSCHPECpPMETATCNGSGDTCApCAHFRDGPHCVS SCPHGV LG A
KGPIYKYPDpNECRPCHENCTpGCKGPELPDCGPpTLVVGKTHLMTA VLAGLVVIFMLMG
GTFLYW RGRRIpKN R LLVM RYLERGESIEPLDPSEKANKVLARIFKETELRLKLVLSGVDGFVTVH
MM-121 Heavy Chain Amino Acid Sequence (SEQ ID NO: 12)

1 EVQLLESGGGLVQPGGSLRLSCAASGFTFSHYVMAWVRQAPGKGLEWVSS
5 1 ISSSGGWTLYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCTRGL
15 101 KMATIFDYWGQTGLTVTSSASTGKPSVFPLAPCSRSTQATTAALGCLVKD
20 151 YFPEPVTVSWNGALTSGVHTFPAVLQSSGLYSLSSVVTVTSNNGFGTQTY
25 201 TCNVDHKPSNKTVDKTVVERCKCCECPCPCAIVPAGPSVFLFPKPKDTLM
30 251 ISRTPEVTCVVDVSHELDEVFQNWYVDGVEEHNAKTKPEEQFNTFRV
35 301 VSLTVQTVHDWNGKEYKCKVSNKGLPAPIEKTISKTKQPREQPQYTLP
40 351 PSREEMTKQNSLTLCLVKGFYPSDIAVEWESNGQPPENYKTTPPMLDSDG
45 401 SFFLYSLKLTVDKSRWQQSGVNFSCSVMEALHNHYTQKSLSSLSPGK

MM-121 Light Chain Amino Acid Sequence (SEQ ID NO: 13)

1 QASALTQPASVSGPQGSSITICTGTSSDVGSYNVVSWYQHPGKAPKLII
5 1 YEVSQRPQSGVSNRFSGKSQTASLTISGQTQEDEADYYCQSYAGSSIFV
10 51 IFGGGGTKVTQLGQPAAVSPVTLPFPSSSEQLQANKATLVCVSDFYPGAVT
15 101 VAWKADGPSVKGVTETKPSQKSNKAYASVSYLTPEQWKSRSYSCHR
20 151 THEGSTVEKTVAPECS
25 201

Ab # 3 VH amino acid sequence (SEQ ID NO: 14)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSAYNMRWVRQAPGKGLEWVSVIYPSSGGATRYADS
VKGRFTISRDNSKNICALYMNSLRAEDTAVYYCARGYYYYGMDVWGGQGTLTVS

- 25 -
Ab # 3 VL amino acid sequence (SEP ID NO: 15)
QSVLTQPPSAGTPQVRVTSCGSNSNIGRNYIYWYQFPGTAPKLIIYRNQRPSGVPSDRSGS
KSGTSASLAISGLRSEDEAEYHCGRTWDDLSGPVFGGGTKLTVL

5 Ab # 3 VH CDR1 (SEP ID NO: 16)
AYNMR

Ab # 3 VH CDR2 (SEP ID NO: 17)
VIYPSGGATRYADSVKG

10 Ab # 3 VH CDR3 (SEP ID NP:18)
GYYYGMDV

Ab # 3 VL CDR1 (SEP ID NO: 19)
SGSDNSNIGRNYIY

15 SGSDNSNIGRNYIY

Ab # 3 VL CDR2 (SEP ID NP:20)
RNNpRPS

20 Ab # 3 VL CDR3 (SEP ID NP:21)
GTWDDLSGPV

Ab # 14 VH amino acid sequence (SEP ID NP:22)
EVpLLESGGGLVpPGGSLRLSCAASGFTFSAYGMGWVpAPGKGLEWVSYISPSSGHTKYADS

25 VKGRFTISRDNSKNTLYLpMNSLRAEDTAVYYCAKVLETGLLVDAFDIWpGTMVTTVSS

Ab # 14 VL amino acid sequence (SEP ID NP:23)
pYELTpPpSVSVYPGpTASITCGDpLGSKFVSWYppRPpSPVLPVMYKDKRPSEIPERFSGSN
SGNTATLTISGpAIEDAYYCPAWDSSTYVFpGTTKVTVL

30 Ab # 14 VH CDR1 (SEP ID NP:24)
AYGMGM
Ab # 14 VH CDR2 (SEP ID NO:25)
YISPSGGHTKYADSVKG

Ab # 14 VH CDR3 (SEP ID NO:26)
VLETGLLVDAFDI

Ab # 14 VL CDR1 (SEP ID NP:27)
SGDpLGSKFVS

Ab # 14 VL CDR2 (SEP ID NP:28)
YKDKRRPS

Ab # 14 VL CDR3 (SEP ID NP:29)
pAWDSSTYV

Ab # 17 VH amino acid sequence (SEP ID NP:30)
EVpLLESGGGLVpPGGSLRLSCAASGFTFSWYGMGWVRpAPGKGLEWVSYISPSGGITVYADS
VKGRFTISRDNKNTLYlpMNSLRAEDTAVYYCARLNYYGLDVWpGTTTVSS

Ab # 17 VL amino acid sequence (SEP ID NP:31)
pDlpMTpSPSSLASVGDRITTITpASpDIGDSLNWYppKPpGKAPRLLIYDASNLETGVPRFSGS
GSGTDFFTFRSLpPEDIATYFCppSANPFTFGPTKVDIK

Ab # 17 VH CDR1 (SEP ID NP:32)
WYGMG

Ab # 17 VH CDR2 (SEP ID NP:33)
YISPSGGITVYADSVKG

Ab # 17 VH CDR3 (SEP ID NP:34)
LNYYGLDV

Ab # 17 VL CDR1 (SEP ID NP:35)
pASpDIGDSLN
Ab # 17 VL CDR2 (SEP ID NO:36)
DASNLET

Ab # 17 VL CDR3 (SEP ID NO:37)
ppSANAPFT

Ab # 19 VH amino acid sequence (SEP ID NP :38)
EVpLLESGGGLVpPGGLRLSCAAAGFTFSRYGMWWVRpAPKGLEWVSYIGSSGPTYYVDS

Ab # 19 VL amino acid sequence (SEP ID NP :39)
pYELTpPASVSGSPGpSITISCTGTSSDlGrWNIVSVPpHPGKAPKLMIIYDVSNRPSGVSNRFSG
SKSGNTASLTISGLpAEDEADYYCSSYTSSTWVFGGTKLTVL

Ab # 19 VH CDR1 (SEP ID NP :40)
RYGMW

Ab # 19 VH CDR2 (SEP ID NP :41)
YIGSSGPTYYVDSVKG

Ab # 19 VH CDR3 (SEP ID NP :42)
GRGTPYYFDS

Ab # 19 VL CDR1 (SEP ID NP :43)
TGTSSDGWRWIVS

Ab # 19 VL CDR2 (SEP ID NP :44)
DVSNRPS

Ab # 19 VL CDR3 (SEP ID NP :45)
SSYTSSSTWV
What is claimed is:

1. A method of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents, wherein the one of the one or more additional therapeutic agents comprise an EGFR inhibitor.

2. The method of claim 1, wherein the one or more additional therapeutic agents is an EGFR inhibitor that is selected from, gefitinib, erlotinib, afatinib and lapatinib.

3. The method of claim 1, wherein the one or more additional therapeutic agents is an EGFR inhibitor that is selected from MM-151, Sym004, cetuximab, panitumumab, zalutumumab, nimotuzumab, and matuzumab.

4. The method of claim 1, wherein the one or more additional therapeutic agents further comprise a nucleoside metabolic inhibitor.

5. The method of claim 4, wherein the nucleoside metabolic inhibitor is gemcitabine.

6. The method of claim 5, wherein the EGFR inhibitor is erlotinib.

7. A method of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents wherein the one or more additional therapeutic agents comprise a nucleoside metabolic inhibitor.

8. The method of claim 7, wherein the one or more additional therapeutic agents is gemcitabine.

9. A method of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents, wherein the one or more additional therapeutic agents comprise a microtubule stabilizing agent.

10. The method of claim 9, wherein the microtubule stabilizing agent is selected from the group consisting of paclitaxel injection, nab-paclitaxel, cabazitaxel and docetaxel.
11. The method of claim 8, wherein the one or more additional therapeutic agents is nab-paclitaxel.

12. The method of claim 11, wherein co-administration of the anti-ErbB3 antibody and the nab-paclitaxel has an additive or superadditive effect on suppressing pancreatic tumor growth, wherein the effect on suppressing pancreatic tumor growth is measured in a mouse xenograft model using BxPC-3 or COLO-357 cells implanted as xenografts in nude mice.

13. A method of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents wherein the one or more additional therapeutic agents comprise a topoisomerase 1 inhibitor and optionally wherein the topoisomerase 1 inhibitor is formulated for intravenous administration.

14. The method of claim 13, wherein the wherein the topoisomerase 1 inhibitor is a camptothecin selected from the group consisting of 9-aminocamptothecin, 7-ethylcamptothecin, 10-hydroxycamptothecin, 9-nitrocamptothecin, 10,11-methylenedioxyacamptothecin, 9-amino-10,ll-methylenedioxyacamptothecin, 9-chloro-10,ll-methylenedioxyacamptothecin, topotecan, lurtotecan, silatecan, and irinotecan.

15. The method of claim 14, wherein the camptothecin is irinotecan or topotecan and the irinotecan or topotecan is liposomally encapsulated irinotecan or liposomally encapsulated topotecan.

16. The method of claim 15, wherein the one or more additional therapeutic agents is liposomally encapsulated irinotecan or liposomally encapsulated topotecan and the liposomally encapsulated irinotecan or liposomally encapsulated topotecan is in the form of a sucrose octasulfate salt.

17. A method of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents, wherein the one or more additional therapeutic agents is chosen from the group consisting of a bispecific anti-ErbB2/anti-ErbB3 antibody, an anti-IGF-1R/anti-ErbB3 antibody, an anti EGFR/anti-ErbB3 antibody, or a mixture of anti-EGFR and anti-ErbB3 antibodies.

18. The method of claim any of claims 1 to 17, wherein the anti-ErbB3 antibody comprises CDRH1, CDRH2, and CDRH3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 5 (CDRH1) SEQ ID NO: 6 (CDRH2) and SEQ ID NO: 7 (CDRH3), and further comprises CDRL1,
CDRL2, and CDRL3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 8 (CDRL1) SEQ ID NO: 9 (CDRL2) and SEQ ID NO: 10 (CDRL3).

19. The method of claim 18, wherein the anti-ErbB3 antibody comprises $V_H$ and/or $V_L$ regions comprising the amino acid sequences set forth in SEQ ID NOs: 2 and 4, respectively.

20. The method of claim any of claims 1 to 17, wherein the anti-ErbB3 antibody is selected from 8B8, 1B4C3, 2D1D12, GE-huMab-HER3, MEDI3379, AMG888 and AV-203.

21. The method of claim any one of claims 1 to 20, wherein co-administration of the anti-ErbB3 antibody and the additional chemotherapeutic agent or agents has an additive or superadditive effect on suppressing pancreatic tumor growth, as compared to administration of the anti-ErbB3 antibody alone or the one or more additional chemotherapeutic agents alone, wherein the effect on suppressing pancreatic tumor growth is measured in a mouse xenograft model using BxPC-3 or COLO-357 cells.

22. The method of any one of claims 1 to 20, wherein at least one of the one or more additional therapeutic agents is administered at a dosage that comprises at least one reduced dose that provides less of the at least one additional therapeutic agent than is provided by a dosage recommended by the manufacturer of the at least one additional therapeutic agent for administration for the treatment of cancer in a patient who is not receiving concurrent anti-ErbB3 antibody therapy.

23. The method of any one of claims 4 to 6 or 17 to 20, wherein at least one of the one or more additional therapeutic agents is administered at a dosage that comprises at least one reduced dose that provides less of the one or more additional therapeutic agents than is provided by a dosage recommended by the manufacturer of the one or more additional therapeutic agents for administration for the treatment of cancer in a patient who is not receiving concurrent anti-ErbB3 antibody therapy.

24. The method of claim 22 or 23, wherein the reduced dose is about half the dose recommended by the manufacturer.

25. The method of any one of claims 1 to 24 or the composition of any one of claims 58-79, wherein the antibody is formulated for intravenous administration.
26. The method of any one of claims 1 to 24 or the composition of any one of claims 58-79, wherein
the patient has recurrent or persistent pancreatic cancer following primary chemotherapy.

27. The method of any one of claims 1 to 24 or the composition of any one of claims 58-79, wherein
the patient has failed prior therapy with a platinum-based therapeutic agent.

28. The method of any one of claims 1 to 24 or the composition of any one of claims 58-79, wherein
the patient has failed prior treatment with, or become resistant to treatment with one or more of a) a
nucleoside analog therapeutic agent, b) a platinum-based therapeutic agent, c) a therapeutic agent, that is a
topoisomerase 1 inhibitor and d) a therapeutic agent that is a tyrosine kinase inhibitor.

29. The method of any one of claims 1 to 20, wherein each of the additional therapeutic agent or
agents is administered following the administration of the anti-ErbB3 antibody.

30. The method of any one of 13 to 17 or 28, wherein the topoisomerase 1 inhibitor is administered
before the administration of the anti-ErbB3 antibody.

31. The method of any one of claims 13 to 17 or 28, wherein the topoisomerase 1 inhibitor and the
anti-ErbB3 antibody are administered simultaneously.

32. The method of any one of claims 9 to 12, wherein the microtubule stabilizing agent is formulated
for intravenous administration.

33. The method of any one of claims 9 to 12, wherein the microtubule stabilizing agent is
administered following the administration of the anti-ErbB3 antibody.

34. The method of any one of claims 9 to 12, wherein the microtubule stabilizing agent is
administered before the administration of the anti-ErbB3 antibody.

35. The method of any one of claims 9 to 12, wherein the microtubule stabilizing agent and the anti-
ErbB3 antibody are administered simultaneously.

36. The method of any one of claims 1 to 6, wherein the EGFR inhibitor is formulated for oral
administration.
37. The method of claim 7 or 8, wherein the nucleoside metabolic inhibitor is formulated for intravenous administration.

38. The method of claim 7 or 8, wherein the EGFR inhibitor and the nucleoside metabolic inhibitor are administered following the administration of the anti-ErbB3 antibody.

39. The method of claim 7 or 8, wherein the EGFR inhibitor and the nucleoside metabolic inhibitor are administered before the administration of the anti-ErbB3 antibody.

40. The method of claim 7 or 8, wherein the EGFR inhibitor, the nucleoside metabolic inhibitor and the anti-ErbB3 antibody are administered simultaneously.

41. The method of any one of claims 1 to 40, wherein the one or more additional therapeutic agents comprise two or more additional therapeutic agents.

42. The method of any one of claims 1 to 6 and 9 to 41, wherein the one or more additional therapeutic agents comprise two or more additional therapeutic agents, one of which is gemcitabine.

43. The method of claim 41, wherein the two or more additional therapeutic agents is a combination of folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX).

44. The method of claim 41, wherein the two or more additional therapeutic agents is a combination of folinic acid, 5-fluorouracil, and oxaliplatin (FOLFOX).

45. The method of claim 41, wherein the one or more additional therapeutic agents is a combination of folinic acid, 5-fluorouracil, and irinotecan (FOLFIRI).

46. The method of any one of claims 1 to 45, wherein the anti-ErbB3 antibody is formulated for intravenous administration and is selected from the group comprising AMG888, AV-203, 8B8, 1B4C3 and 2D1D12.
47. The method of any one of claims 1 to 45, wherein the anti-ErbB3 antibody is formulated for intravenous administration and comprises $V_H$ and/or $V_L$ regions comprising the amino acid sequences set forth in SEQ ID NOs: 2 and 4, respectively.

48. The method of any one of claims 1 to 47, wherein the pancreatic cancer is an exocrine pancreatic cancer selected from the group consisting of acinar cell carcinoma, adenocarcinoma, adenosquamous carcinoma, giant cell tumor, intraductal papillary-mucinous neoplasm (IPMN), mucinous cystadenocarcinoma, pancreaticoblastoma, serous cystadenocarcinoma, and solid and pseudopapillary tumors.

49. The method of claim 48, wherein the adenocarcinoma is pancreatic ductal carcinoma.

50. The method of any one of claims 1 to 47, wherein the pancreatic cancer is an endocrine pancreatic cancer selected from the group consisting of: Gastrinoma (Zollinger-Ellison Syndrome), Insulinoma, Nonfunctional Islet Cell Tumor, Somatostatinoma, and Vasoactive Intestinal Peptide-Releasing Tumor (VIPoma or Verner-Morrison Syndrome).

51. The method of any one of claims 1 to 47, wherein the pancreatic cancer comprises a KRAS gene comprising a KRAS mutation.

52. The method of claim 51, wherein the KRAS mutation is KRAS G12S.

53. The method of claim 50, wherein the one or more additional therapeutic agents comprise an mTOR inhibitor selected from the group consisting of temsirolimus, everolimus, sirolimus, and ridaforolimus.

54. The method of claim 53, wherein the mTOR inhibitor is everolimus.

55. The method of any one of claims 1 to 47, wherein the pancreatic cancer comprises a BRAF gene comprising a BRAF mutation and optionally wherein one of the one or more additional therapeutic agents is a BRAF kinase inhibitor, optionally vemurafenib.

56. The method of claim 55, wherein the BRAF mutation is BRAF V600E.
57. The method of any one of claims 1 to 56, wherein the treatment produces at least one therapeutic effect selected from the group consisting of: reduction of the rate of tumor growth, reduction in size of tumor, reduction of tumor mitotic index, reduction in number of metastatic lesions over time, complete response, partial response, stable disease, increase in overall response rate, or a pathologic complete response.

58. A composition for the treatment of pancreatic cancer, or for the manufacture of a medicament for the treatment of pancreatic cancer, in a patient, said treatment comprising co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents, wherein the one or more additional therapeutic agents comprise an EGFR inhibitor.

59. The composition of claim 58, wherein the one or more additional therapeutic agents is an EGFR inhibitor that is selected from, gefitinib, erlotinib, afatinib and lapatinib.

60. The composition of claim 58, wherein the one or more additional therapeutic agents is an EGFR inhibitor that is selected from, MM-151, Sym004, cetuximab, panitumumab, zalutumumab, nimotuzumab, and matuzumab.

61. The composition of claim 58, wherein the one or more additional therapeutic agents further comprise a nucleoside metabolic inhibitor.

62. The composition of claim 61, wherein the nucleoside metabolic inhibitor is gemcitabine.

63. The composition of claim 62, wherein the EGFR inhibitor is erlotinib.

64. A composition for the treatment of pancreatic cancer, or for the manufacture of a medicament for the treatment of pancreatic cancer, in a patient, said treatment comprising co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents wherein the one or more additional therapeutic agents comprise a nucleoside metabolic inhibitor.

65. The composition of claim 64, wherein the one or more additional therapeutic agents is gemcitabine.
66. A composition for the treatment of pancreatic cancer, or for the manufacture of a medicament for the treatment of pancreatic cancer, in a patient, said treatment comprising co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents wherein the one or more additional therapeutic agents comprise a microtubule stabilizing agent.

67. The composition of claim 66, wherein the microtubule stabilizing agent is selected from the group consisting of pative taxel injection, nab-paclitaxel and docetaxel.

68. The composition of claim 65, wherein the one or more additional therapeutic agents is nab-paciitaxel.

69. The composition of claim 68, wherein co-administration of the anti-ErbB3 antibody and the nab-paclitaxel has an additive or superadditive effect on suppressing pancreatic tumor growth, as compared to administration of the anti-ErbB3 antibody alone or the nab-paclitaxel alone, wherein the effect on suppressing pancreatic tumor growth is measured in a mouse xenograft model using BxPC-3 or COLO-357 cells.

70. A composition for the treatment of pancreatic cancer, or for the manufacture of a medicament for the treatment of pancreatic cancer, in a patient, said treatment comprising co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents wherein the one or more additional therapeutic agents comprise a topoisomerase 1 inhibitor.

71. The composition of claim 70, wherein the wherein the topoisomerase 1 inhibitor is a camptothecin selected from the group consisting of 9-aminocamptothecin, 7-ethylcamptothecin, 10-hydroxycamptothecin, 9-nitrocamptothecin, 10,11-methylenedioxyamptothecin, 9-amino-10,ll-methylenedioxyamptothecin, 9-chloro-10,ll-methylenedioxyamptothecin, topotecan, lurtotecan, silatecan, and irinotecan.

72. The composition of claim 71, wherein the camptothecin is irinotecan or topotecan and the irinotecan or topotecan is liposomally encapsulated irinotecan or liposomally encapsulated topotecan.

73. The composition of claim 72, wherein the one or more additional therapeutic agents is liposomally encapsulated irinotecan or liposomally encapsulated topotecan and the liposomally encapsulated irinotecan or liposomally encapsulated topotecan is in the form of a sucrose octasulfate salt.
The composition of any of claims 58 to 73, wherein the ErbB3 inhibitor is an anti-ErbB3 antibody.

The composition of claim 74, wherein anti-ErbB3 antibody comprises CDRH1, CDRH2, and CDRH3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 5 (CDRH1) SEQ ID NO: 6 (CDRH2) and SEQ ID NO: 7 (CDRH3), and further comprises CDRL1, CDRL2, and CDRL3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 8 (CDRL1) SEQ ID NO: 9 (CDRL2) and SEQ ID NO: 10 (CDRL3).

The composition of claim 75, wherein the anti-ErbB3 antibody comprises $V_H$ and/or $V_L$ regions comprising the amino acid sequences set forth in SEQ ID NOs: 2 and 4, respectively.

The composition of claim 74, wherein the anti-ErbB3 antibody is selected from 8B8, 1B4C3, 2D12, AMG888, and AV-203.

The composition of any one of claims 58 to 68 and 70 to 77, wherein co-administration of the anti-ErbB3 antibody and the additional chemotherapeutic agent or agents has an additive or superadditive effect on suppressing pancreatic tumor growth, as compared to administration of the anti-ErbB3 antibody alone or the one or more additional chemotherapeutic agents alone, wherein the effect on suppressing pancreatic tumor growth is measured in a mouse xenograft model using BxPC-3 or COLO-357 cells.

The composition of any one of claims 58 to 77, wherein at least one of the one or more additional therapeutic agents is administered at a dosage that is a reduced dose that provides less of the at least one additional therapeutic agent than is provided by a dosage recommended by the manufacturer of the at least one additional therapeutic agent for administration for the treatment of pancreatic cancer in a patient who is not receiving concurrent anti-ErbB3 antibody therapy.

The composition of any one of claims 61 to 63 or 74 to 77, wherein at least one of the one or more additional therapeutic agents is administered at a dosage that is a reduced dose that provides less of the one or more additional therapeutic agents than is provided by a dosage recommended by the manufacturer of the one or more additional therapeutic agents for administration for the treatment of pancreatic cancer in a patient who is not receiving concurrent anti-ErbB3 antibody therapy.
81. The composition of claim 79 or 80, wherein the reduced dose is a dose that is about half the dosage recommended by the manufacturer.

82. The composition of any one of claims 58 to 81, wherein the patient has recurrent or persistent pancreatic cancer following primary chemotherapy.

83. The composition of any one of claims 58 to 77, wherein each of the additional therapeutic agent or agents is administered following the administration of the anti-ErbB3 antibody.

84. The composition of any one of claims 70 to 74, wherein the topoisomerase I inhibitor is administered before the administration of the anti-ErbB3 antibody.

85. The composition of any one of claims 70 to 74, wherein the topoisomerase I inhibitor and the anti-ErbB3 antibody are administered simultaneously.

86. The composition of any one of claims 66 to 69, wherein the microtubule stabilizing agent is formulated for intravenous administration.

87. The composition of any one of claims 66 to 69, wherein the microtubule stabilizing agent is administered following the administration of the anti-ErbB3 antibody.

88. The composition of any one of claims 66 to 69, wherein the microtubule stabilizing agent is administered before the administration of the anti-ErbB3 antibody.

89. The composition of any one of claims 66 to 69, wherein the microtubule stabilizing agent and the anti-ErbB3 antibody are administered simultaneously.

90. The composition of any one of claims 58 to 63, wherein the EGFR inhibitor is formulated for oral administration.

91. The composition of claim 64 or 65, wherein the nucleoside metabolic inhibitor is formulated for intravenous administration.
92. The composition of claim 64 or 65, wherein the EGFR inhibitor and the nucleoside metabolic inhibitor are administered following the administration of the anti-ErbB3 antibody.

93. The composition of claim 64 or 65, wherein the EGFR inhibitor and the nucleoside metabolic inhibitor are administered before the administration of the anti-ErbB3 antibody.

94. The composition of claim 64 or 65, wherein the EGFR inhibitor and the nucleoside metabolic inhibitor and the anti-ErbB3 antibody are administered simultaneously.

95. The composition of any one of claims 58 to 97, wherein the one or more additional therapeutic agents comprise two or more additional therapeutic agents.

96. The composition of any one of claims 58 to 63 and 66 to 96, wherein the one or more additional therapeutic agents comprise two or more additional therapeutic agents, one of which is gemcitabine.

97. The composition of claim 95, wherein the two or more additional therapeutic agents is a combination of folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX).

98. The composition of claim 95, wherein the two or more additional therapeutic agents is a combination of folinic acid, 5-fluorouracil, and oxaliplatin (FOLFOX).

99. The composition of claim 95, wherein the one or more additional therapeutic agents is a combination of folinic acid, 5-fluorouracil, and irinotecan (FOLFIRI).

100. The composition of any one of claims 58 to 99, wherein the anti-ErbB3 antibody is selected from the group comprising AMG888, AV-203, 8B8, 1B4C3 and 2D1D12.

101. The composition of any one of claims 58 to 99, wherein the anti-ErbB3 antibody comprises \( V_H \) and/or \( V_L \) regions comprising the amino acid sequences set forth in SEQ ID NOs: 2 and 4, respectively.

102. The composition of any one of claims 58 to 101, wherein the pancreatic cancer is an exocrine pancreatic cancer selected from the group consisting of acinar cell carcinoma, adenocarcinoma, adenosquamous carcinoma, giant cell tumor, intraductal papillary-mutinous neoplasm (IPMN), mucinous **

- 39 -
cystadenocarcinoma, pancreatoblastoma, serous cystadenocarcinoma, and solid and pseudopapillary tumors.

103. The composition of claim 102, wherein the adenocarcinoma is pancreatic ductal carcinoma.

104. The composition of any one of claims 58 to 101, wherein the pancreatic cancer is an endocrine pancreatic cancer selected from the group consisting of: Gastrinoma (Zollinger-Ellison Syndrome), Insulinoma, Nonfunctional Islet Cell Tumor, Somatostatinoma, and Vasoactive Intestinal Peptide-Releasing Tumor (VIPoma or Verner-Morrison Syndrome).

105. The composition of any one of claims 58 to 101, wherein the pancreatic cancer comprises a KRAS gene comprising a KRAS mutation.

106. The composition of claim 105, wherein the KRAS mutation is KRAS G12S.

107. The composition of claim 104, wherein the one or more additional therapeutic agents comprise an mTOR inhibitor selected from the group consisting of everolimus, sirolimus, and ridaforolimus.

108. The composition of claim 107, wherein the mTOR inhibitor is everolimus.

109. The composition of any one of claims 58 to 101, wherein the pancreatic cancer comprises a BRAF gene comprising a BRAF mutation and optionally wherein one of the one or more additional therapeutic agents is a BRAF kinase inhibitor, optionally vemurafenib.

110. The composition of claim 109, wherein the BRAF mutation is BRAF V600E.

111. The composition of any one of claims 58 to 110, wherein the treatment produces at least one therapeutic effect selected from the group consisting of: reduction of the rate of tumor growth, reduction in size of tumor, reduction of tumor mitotic index, reduction in number of metastatic lesions over time, complete response, partial response, stable disease, increase in overall response rate, or a pathologic complete response.

112. A method of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents,
wherein i) the antibody is an antibody having the heavy chain sequence set forth in SEQ ID NO:2 and the light chain sequence set forth in SEQ ID NO:4, and ii) the one of the one or more additional therapeutic agents comprises erlotinib.

113. A method of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents, wherein i) the antibody is an antibody having the heavy chain sequence set forth in SEQ ID NO:2 and the light chain sequence set forth in SEQ ID NO:4, and ii) the one of the one or more additional therapeutic agents comprises erlotinib and gemcitabine.

114. A method of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents, wherein i) the antibody is an antibody having the heavy chain sequence set forth in SEQ ID NO:2 and the light chain sequence set forth in SEQ ID NO:4, and ii) the one of the one or more additional therapeutic agents comprises everolimus.

115. A method of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents, wherein i) the antibody is an antibody having the heavy chain sequence set forth in SEQ ID NO:2 and the light chain sequence set forth in SEQ ID NO:4, and ii) the one of the one or more additional therapeutic agents comprises irinotecan.

116. A method of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents, wherein i) the antibody is an antibody having the heavy chain sequence set forth in SEQ ID NO:2 and the light chain sequence set forth in SEQ ID NO:4, and ii) the one of the one or more additional therapeutic agents comprises everolimus and exemestane.

117. A method of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents, wherein i) the antibody is an antibody having the heavy chain sequence set forth in SEQ ID NO:2 and the light chain sequence set forth in SEQ ID NO:4, and ii) the one of the one or more additional therapeutic agents comprises nab-paclitaxel.
118. A method of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents, wherein i) the antibody is an antibody having the heavy chain sequence set forth in SEQ ID NO:2 and the light chain sequence set forth in SEQ ID NO:4, and ii) the one of the one or more additional therapeutic agents comprises cetuximab.

119. A method of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents, wherein i) the antibody is an antibody having the heavy chain sequence set forth in SEQ ID NO:2 and the light chain sequence set forth in SEQ ID NO:4, and ii) the one of the one or more additional therapeutic agents comprises MM-151.

120. A method of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents, wherein i) the antibody is an antibody having the heavy chain sequence set forth in SEQ ID NO:2 and the light chain sequence set forth in SEQ ID NO:4, and ii) the one of the one or more additional therapeutic agents comprises gemcitabine.

121. A method of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents, wherein i) the antibody is an antibody having the heavy chain sequence set forth in SEQ ID NO:2 and the light chain sequence set forth in SEQ ID NO:4, and ii) the one of the one or more additional therapeutic agents comprises eribulin.
**1/11**

**MM-121 dose escalation efficacy study**
**in BxPC3 xenografts**

![Graph showing tumor volume over days for different doses of MM-121](image)

**Fig. 1A**

**CPT-11 dose escalation efficacy study**
**in BxPC3 xenografts**

![Graph showing tumor volume over days for different doses of CPT-11](image)

**Fig. 1B**
2/11

MM-121 suboptimal dose in combination with CPT11 or MM-398 in BxPC3 model xenograft

**Fig. 2A**

MM-121 optimal dose in combination with CPT11 or MM-398 in BxPC3 model xenograft

**Fig. 2B**
MM-121 dose escalation efficacy study in COLO-357 xenografts

Fig. 3
MM-121 suboptimal dose in combination with paclitaxel in COLO-357 xenograft

**Fig. 4A**

MM-121 suboptimal dose in combination with paclitaxel with or without gemcitabine in COLO-357 xenograft

**Fig. 4B**
MM-121 suboptimal dose in combination with erlotinib and gemcitabine in COLO-357 xenograft (first graph with all groups included followed by graphs with each distinct dose combination)

Fig. 5A
**Fig. 5B**

Colo357: MM-121 + erlotinib (50) + gem (150)

- Group 1 - PBS Vehicle Control
- Group 2 - MM121 (300μg)
- Group 3 - erlotinib (50mpk)
- Group 5 - gemcitabine (150mpk)
- Group 7 - MM121 (300μg), erlotinib (50 mpk), gemcitabine (150mpk)
- Group 11 - erlotinib (50mpk), gemcitabine (150mpk)

**Fig. 5C**

Colo357: MM-121 + erlotinib (50) + gem (300)

- Group 1 - PBS Vehicle Control
- Group 2 - MM121 (300μg)
- Group 3 - erlotinib (50mpk)
- Group 6 - gemcitabine (300 mpk)
- Group 13 - erlotinib (50mpk), gemcitabine (300mpk)
- Group 8 - MM121 (300μg), erlotinib (50mpk), gemcitabine (300mpk)
**Fig. 5D**

Colo357: MM-121 + erlotinib (100) + gem (150)

- Group 1 - PBS Vehicle Control
- Group 2 - MM121 (300µg)
- Group 4 - erlotinib (100mpk)
- Group 5 - gemcitabine (150mpk)
- Group 14 - erlotinib (100mpk), gemcitabine (150mpk)
- Group 9 - MM121 (300µg), erlotinib (100mpk), gemcitabine (150mpk)

**Fig. 5E**

Colo357: MM-121 + erlotinib (100) + Gem (300)

- Group 1 - PBS Vehicle Control
- Group 2 - MM121 (300µg)
- Group 4 - erlotinib (100mpk)
- Group 6 - gemcitabine (300mpk)
- Group 10 - MM121 (300µg), erlotinib (100 mpk), gemcitabine (300mpk)
- Group 12 - erlotinib (100mpk), gemcitabine (300mpk)
Tumor volume for CTG-0289 (PANC002) treated mice

Fig. 6
In-Vivo Kinetics of BxPC3 Tumor Growth (normalized bioluminescence)

- Vehicle
- MM121 (0.6mg/mouse)
- MM121 (1.2mg/mouse)
- MM398 (10mg/kg)

Fig. 7
Ex vivo Lung Bioluminescence

- G1 (vehicle)
- G2 (MM121 0.6mg/mouse)
- G3 (MM121 1.2mg/mouse)
- G4 (MM398 10mg/kg)
- G5 (MM121 0.6mg/mouse + MM398 10mg/kg)
- G6 (nab-paclitaxel 15mg/kg)
- G7 (nab-paclitaxel 15mg/kg + MM121 0.6mg/mouse)

Treatment Groups

**Fig. 8A**
Ex vivo Liver Bioluminescence

- G1 (vehicle)
- G2 (MM121 0.6mg/mouse)
- G3 (MM121 1.2mg/mouse)
- G4 (MM398 10mg/kg)
- G5 (MM121 0.6mg/mouse + MM398 10mg/kg)
- G6 (nab-paclitaxel 15mg/kg)
- G7 (nab-paclitaxel 15mg/kg + MM121 0.6mg/mouse)

Treatment Groups

Fig. 8B
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 39/00; C12P 21/08 (2013.01)
USPC - 424/133.1, 424/139.1; 530/387.3, 530/387.9

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 39/00; C12P 21/08; A61K 39/395; C07K 16/00 (2013.01)
USPC - 424/133.1, 424/139.1; 530/387.3, 530/387.9; 424/130.1, 424/141 (classification shown)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
IPC(8) - A61K 39/00; C12P 21/08; A61K 39/395; C07K 16/00 (2013.01) - see keyword below
USPC - 424/133.1, 424/139.1; 530/387.3, 530/387.9; 424/130.1, 424/141 (classification shown)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST/(USPT,PGPB,EPAB,JPAB); PatBase; Medline, Google: anti-HER3, HER3, antibody, EGFR, inhibitor, antagonist, gefitinib, erlotinib, pancreatic, cancer, malignant, neoplastic, tumor, B88, 184C3, ZD1839, GE-huMab-HER3, MED13379, AMG888, AV-203

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category* Citation of document, with indication, where appropriate, of the relevant passages

X US 2010/0266584 A1 (SCHOEBERL et al) 2 1 October 2010 (21.10.2010), para [0005], [0008], [0036], [0040], [0041], [0047], [0148], [0153], [0155], [0206], [0209], [0220], [0228], [0374], [0388], SEQ ID NO: 1 and SEQ ID NO: 2


A MOHAMMED et al. The epidermal growth factor receptor inhibitor gefitinib prevents the progression of pancreatic lesions to carcinoma in a conditional LSL-KrasG12D/+ transgenic mouse model Cancer Prev Res (Phila). 2010, Vol. 3(1), p. 1417-26. Entire documentation, especially Abstract; pg 1421, col 2, lower para, and Fig 2; and pg 1424, col 2, top para


Date of the actual completion of the international search
26 June 2013 (26.06.2013)

Date of mailing of the international search report
1 JUL 2013

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-3201

Authorized officer: Lee W. Young
PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)
Box No. II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. □ Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. □ Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. □ Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. II  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group 1 is, claims 1-20, 32-40, 58-77, 86-94, 112-121, drawn to methods of treating pancreatic cancer in a patient comprising: co-administering to the patient an anti-ErbB3 antibody and one or more additional therapeutic agents; and compositions thereof. The first invention (claims 1-2, 18-20(1-2), 36(1-2), 58-59, 74-77(58-59), 90(58-59)), is restricted to co-administering to the patient an anti-ErbB3 antibody and gefitinib (the first option for an EGFR inhibitor in claim 2), which will be searched without additional fee. Applicant is invited to elect additional therapeutic agents to be searched by paying an additional fee per additional therapeutic agent and clearly identifying the elected additional therapeutic agent(s) for co-administration. For example, applicant could elect EGFR inhibitor erlotinib (claims 1-2, 18-20(1-2), 36(1-2), 58-59, 74-77(58-59), 90(58-59), 112) with an additional fee; or applicant could elect a microtubule stabilizing agent (claims 9-12, 18-20(9-12), 32-35, 66-69, 74-77(66-69), 86-89, 117, 121) with an additional fee;

***************Continued in the the extra sheet ****************************

1. □ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. □ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. □ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.: 1-2, 18-20(1-2), 36(1-2), 58-59, 74-77(58-59), 90(58-59), 112, limited to gefitinib and erlotinib.

4. □ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-2, 18-20(1-2), 36(1-2), 58-59, 74-77(58-59), 90(58-59), 112.

Remark on Protest

☐ The additional search fees were accompanied by the applicant’s protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant’s protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☒ No protest accompanied the payment of additional search fees.
INTERNATIONAL SEARCH REPORT

Continuation of: Boc No III (unity of invention is lacking)

(Continuation of Group I+) or applicant could elect EGFR inhibitor erlotinib and a nucleoside metabolic inhibitor [e.g. gemcitabine]
(claims 1-2, 4-8, 18-20(1-2, 4-6), 36(1-2, 4-6), 37-40, 58-59, 61-65, 74-77(58-59, 61-65), 90(58-59, 61-65), 91-94, 112, 113, 120) with 2X additional fees. The exact claims to be searched will depend on the election. Failure to clearly identify how any paid additional invention fees are to be applied to the +* group will result in only the first claimed invention to be searched.

The inventions listed as Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The inventions of Groups I+ share the technical features of a composition for the treatment of pancreatic cancer comprising an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents, and a method of treating pancreatic cancer in a patient comprising: co-administering to the patient an effective amount of each of an anti-ErbB3 antibody and one or more additional therapeutic agents. Some claims within Group I+ (partial) also share the technical features of wherein the one or more additional therapeutic agents comprise an EGFR inhibitor. Some claims within Group I+ (partial) also share the technical features of an anti-ErbB3 antibody having the heavy chain sequence set forth in SEQ ID NO:2 and the light chain sequence set forth in SEQ ID NO:4; or an anti-ErbB3 antibody comprises CDRH1, CDRH2, and CDRH3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 5 (CDRH1); SEQ NO: 6 (CDRH2) and SEQ ID NO: 7 (CDRH3), and further comprises CDR1L, CDR2L, and CDR3L sequences comprising the amino acid sequences set forth in SEQ ID NO:8 (CDRL1) SEQ ID NO: 9 (CDRL2) and SEQ ID NO: 10 (CDRL3); and wherein anti-ErbB3 antibody is selected from BB8, IB4C3, 2D12, GE-huMab-HER3, MEDI3379, AMG888 and AV-203.

However, these shared technical features do not represent a contribution over prior art as being anticipated by US 2010/0266584 A1 to Schoeffier et al. (hereinafter 'Schoeffier') as follows:

Schoeffier discloses a method of treating pancreatic cancer in a patient (para [0040], [0148]) comprising co-administering to the patient an effective amount of each of an anti-ErbB3 antibody (para [0005], [0040]- [0041], [0148], and one or more additional therapeutic agents, wherein the one of the one or more additional therapeutic agents comprise an EGFR inhibitor (claims 2 and 3; para [0041]- [0058] - 'binding to ErbB1 and ...the inhibition of such binding by cetuximab').

Schoeffier further discloses an anti-ErbB3 antibody heavy chain and light chain variable sequences (para [0047] - 'an anti-ErbB3 antibody (Ab #6); para [0008] - 'a heavy chain variable region (V.sub.H) ... SEQ ID NO:1; ... a light chain variable region (V.sub.L) ... SEQ ID Nm 2'; para [0389] - 'mapping of Ab #6 is performed ... the V.sub.H region (SEQ ID NO: 1) and the V.sub.L region (SEQ ID NO: 2)', wherein SEQ ID NO: 1 is 100% identical to the claimed SEQ ID NO: 2, and comprising a region between nucleotides 30-35, that is 100% identical to the claimed SEQ ID NO: 6 (CDRH2), and a region between nucleotides 99-108, that is 100% identical to the claimed SEQ ID NO: 7 (CDRH3); and wherein SEQ ID NO: 2 is 100% identical to the claimed SEQ ID NO: 4, and comprising a region between nucleotides 23-36, that is 100% identical to the claimed SEQ ID NO: 8 (CDRL1), a region between nucleotides 52-58, that is 100% identical to the claimed SEQ ID NO: 9 (CDRL2), and a region between nucleotides 91-101, that is 100% identical to the claimed SEQ ID NO: 10 (CDRL3), and different anti-ErbB3 including anti-ErbB3 antibody selected from the group consisting of 2D12, and AMG888 (Table I - Anti-ErbB3 antibodies Ab #14 described herein which bind different 1B4C3; 2D12, GE-huMab-HER3, MEDI3379, AMG888 and AV-203).

Without a shared special technical feature, the inventions lack unity with one another.

Therefore, inventions of Groups I+ lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.

Note re item 4: Claims 21-31, 41-57, 78-85, 95-111 are not drafted in accordance with the second and third sentences of Rule 6.4 (a).

These claims are improper multiple dependent claims.

Note:

I) Claims 11 and 68 are objected to as lacking a proper antecedent basis for the "the one or more additional therapeutic agents comprise a microtubule stabilizing agent" limitation. It is assumed that claim 11 depends upon claim 9 and claim 68 depends upon claim 66 (Specification: pg 4, in 9:1-0'a microtubule stabilizing agent, e.g., a taxane such as erubinib, ... nab-paclitaxel'). For the purposes of this ISR, claims 11 and 68 are construed as follows:

11. The method of claim 9, wherein the one or more additional therapeutic agents is nab-paclitaxel.

68. The composition of claim 66, wherein the one or more additional therapeutic agents is nab-paclitaxel.

II) Claims 20 and 77 are objected to as using an improper Markush group. For the purposes of this ISR, the term 'selected from' in each claim is construed as 'selected from the group consisting of.'