

have been approved for the treatment of progressive non-functioning pNETs, with limited survival benefit.

[0012] As discussed above in [0010], the first of these targeted therapies is the use of Afinitor® (everolimus), a mammalian target of the rapamycin (mTOR) inhibitor, however, treatment with Afinitor® may cause severe skin and gastrointestinal disorders, kidney and liver toxicity and bone marrow damage.

[0013] The only other treatment is the use of Sutent® (sunitinib), a multi-targeted receptor tyrosine kinase inhibitor, or RTK, approved by the FDA and the EMA in 2011 for the treatment of unresectable or metastatic, well-differentiated pNETs with disease progression in adults on the basis of PFS of 11.4 months observed in Phase 3 trials. Again, this is a less than ideal intervention as treatment with Sutent® may cause severe side effects such as renal failure, heart failure, gastrointestinal disorders, hemorrhages and hematological disorders (e.g., neutropenia, thrombocytopenia, and anemia), which are among its most common adverse drug reactions.

[0014] Thus, traditional chemotherapy has little place in treatment of well-differentiated NETs, since most of these tumors are slow growing and difficult to treat. A rigorous assessment of the efficacy of chemotherapy in literature is hampered by the prevalence of retrospective studies on heterogeneous series of patients, where toxicity is relevant, and the responses are short-lived and sporadic, particularly in "midgut carcinoids". Many schemes, including single or multiple agents, have been attempted.

[0015] Streptozotocin based schemes in pancreatic tumors yielded significant objective responses, but none of the schemes used in "midgut carcinoids" showed any activity in treating NETs. Some better initial responses have been reported for small populations for the combination of temozolomide plus capecitabine⁴ but again, these early data make it clear that the currently available therapies for NETs are inadequate and there is a long-felt need for additional robust therapies that can produce a significant therapeutic outcome.

[0016] The present invention, described in greater detail below, provides a combination therapy approach that effectively treats NETs.

SUMMARY

[0017] In one aspect, there is provided use of a combination of a Peptide Receptor Radionuclide and an inhibitor that inhibits the PD-1/PD-L 1/CTLA-4 pathway in the manufacture of a medicament for treating a patient that has a cancer that over-expresses somatostatin receptors, wherein the combined effect of the Peptide Receptor Radionuclide and the inhibitor of PD-1/PD-L 1 pathway produces a therapeutic effect on said cancer. The present disclosure also provides methods of treating a patient affected by a tumor that over-expresses somatostatin receptors comprising administering to said

patient a combination of a Peptide Receptor Radionuclide therapy (PRRT) and an I-O therapy

[0018] In specific examples, the PRRT is $[^{177}\text{Lu}]$ Lutetium-DOTA[O]-Tyr[3]-Octreotate.

[0019] In specific examples the I-O therapy comprises administering an inhibitor that inhibits the PD-1/PD-L 1 and CTLA-4 pathway. In other examples, the inhibitors of the PD-1/PD-L 1 and CTLA-4 pathway are antibodies that target the PD-1/PD-L 1 axis or the CTLA-4/B7 receptor complex. In still further examples, the inhibitor of the PD-1/PD-L 1 pathway is a combination of inhibitors that target both PD-1 and PD-L 1.

[0020] In particular examples, the PD-1/PD-L1 or CTLA-4/B7 pathways are selected from the group consisting of Nivolumab, MK-3475, MPDL3280A, MED14736, ipilimumab, and tremelimumab.

[0021] In some examples, the cancer is a neuroendocrine tumor. In some examples, said treating comprises one or more of inhibiting the growth of a neuroendocrine tumor, inhibiting proliferation of neuroendocrine tumor cells, inhibiting neuroendocrine tumor metastases, reducing tumorigenicity of neuroendocrine tumor cells and methods of reducing the frequency of cancer stem cells or tumor initiating cells in a neuroendocrine tumor.

[0022] Any neuroendocrine tumor that expresses or overexpresses somatostatin receptors may be treated by the methods as disclosed herein. Exemplary such tumors include but are not limited to the group consisting of a gastroenteropancreatic neuroendocrine tumor, carcinoid tumor, pheochromocytoma, paraganglioma, medullary thyroid cancer, pulmonary neuroendocrine tumor, thymic neuroendocrine tumor, a carcinoid tumor or a pancreatic neuroendocrine tumor, pituitary adenoma, adrenal gland tumors, Merkel cell carcinoma, breast cancer, Non-Hodgkin lymphoma, Hodgkin lymphoma, Head & Neck tumor, urothelial carcinoma (bladder), Renal Cell Carcinoma, Hepatocellular Carcinoma, GIST, neuroblastoma, bile duct tumor, cervix tumor, Ewing sarcoma, osteosarcoma, SCLC, prostate cancer, melanoma, meningioma, glioma, medulloblastoma hemangioblastoma, supratentorial primitive, neuroectodermal tumor, and esthesioneuroblastoma.

[0023] In particular examples, the neuroendocrine tumor is selected from the group consisting of functional carcinoid tumor, insulinoma, gastrinoma, vaso active intestinal peptide (VIP)oma, glucagonoma, serotoninoma, histaminoma, ACTHoma, pheochromocytoma, and somatostatinoma.

[0024] The neuroendocrine tumors treated by the present disclosure may be defined by grade, and may be low grade, medium grade, or high grade neuroendocrine tumors. In specific examples, the tumor is a functional neuroendocrine tumor. Alternatively, the neuroendocrine tumor is a non-functional neuroendocrine tumor.

[0025] In some examples, the cancer is a small cell lung cancer. In other examples, the cancer is a progressive midgut neuroendocrine tumor. In some examples, the disclosure provides therapy for such neuroendocrine

tumors that are not responsive to Sandostatin (Novartis) or Somatuline® (Ipsen). In other examples, the neuroendocrine tumor is non-responsive or has a low response to an inhibitor of the PD-1/PD-L 1 pathway.

BRIEF DESCRIPTION OF SEVERAL VIEWS OF THE DRAWINGS

[0026] [Not Applicable]

DETAILED DESCRIPTION OF THE INVENTION

[0027] The present invention provides methods of inhibiting the growth of a neuroendocrine tumor, methods of inhibiting proliferation of neuroendocrine tumor cells, methods of treating or stabilizing a neuroendocrine cancer, methods of inhibiting neuroendocrine tumor metastases, methods of reducing tumorigenicity of neuroendocrine tumor cells and methods of reducing the frequency of cancer stem cells or tumor initiating cells in a neuroendocrine tumor. More specifically, the methods provided herein comprise administering a combination of Peptide Receptor Radionuclide with an immune-oncology therapy. In some embodiments, the Peptide Receptor Radionuclide Therapy (PRRT) is a therapy using a radiolabeled SSA peptide with high affinity for Somatostatin receptors (sstr) that carries a radioactive isotope such as Lu-177 within its overall structure. In the present invention, the PRRT is combined with PD-1 and/or PD-L 1/CDLA-4 inhibitors.

[0028] Lutathera:

[0029] SSAs are synthetic versions of Somatostatin endogenous hormone that have a longer half-life than the wild-type endogenous Somatostatin hormone. In specific embodiments, the preferred molecule used PRRT is Lutathera ([177]Lutetium-DOTA[O]-Tyr[3]-Octreotate), which is a ready-to-inject solution of a Lu-177-labeled-SSA.

[0030] Lutathera is comprised of three components. The first component is the SSA Octreotate. This component is the peptide that targets the NET cells. The second component is DOTA, a compound able to combine metals (such as Lu-177) into complexes through a ring structure; and the third component is Lu-177, a radioisotope.

[0031] Lutathera treats certain NETs by selectively binding to SSTR2 receptors, the most commonly expressed receptors on these types of tumors. Lutathera then destroys NET cells in a targeted fashion by delivering a local emission of high-energy electrons. Because Lutathera also emits gamma radiation, it can also be useful as a disease management tool, as this kind of emission can be captured with a SPECT camera and thus be used for determining the drug's distribution and pharmacokinetics and also for dosimetric estimations.

CLAIMS

1. Use of a combination of a Peptide Receptor Radionuclide and an inhibitor that inhibits the PD-1/PD-L 1/CTLA-4 pathway in the manufacture of a medicament for treating a patient that has a cancer that over-expresses somatostatin receptors, wherein the combined effect of the Peptide Receptor Radionuclide and the inhibitor of PD-1 IPD-L 1 pathway produces a therapeutic effect on said cancer.
2. The use of claim 1, wherein said Peptide Receptor Radionuclide is [177]Lutetium-DOTA[O]Tyr[3]-Octreotate.
3. The use of claim 1, wherein said inhibitor of the PD-1/PD-L1/CTLA-4 pathway is an antibody that targets PD-L 1.
4. The use of claim 1 wherein said inhibitor of the PD-1/PD-L 1 pathway is an antibody that targets PD-1.
5. The use of claim 1 wherein said inhibitor of the the PD-1 IPD-L 1 pathway is selected from the group consisting of Nivolumab, MK-3475, MPDL3280A, MED14736, ipilimumab, and tremelimumab.
6. The use of claim 1, wherein said cancer is a neuroendocrine tumor.
7. The use of claim 5, wherein said treating comprises one or more of inhibiting the growth of a neuroendocrine tumor, inhibiting proliferation of neuroendocrine tumor cells, inhibiting neuroendocrine tumor metastases, inducing neuroendocrine tumor cell differentiation, reducing tumorigenicity of neuroendocrine tumor cells and reducing the frequency of cancer stem cells or tumor initiating cells in a neuroendocrine tumor.
8. The use of claim 5, wherein said neuroendocrine tumor is selected from the group consisting of a gastroenteropancreatic neuroendocrine tumor, carcinoid tumor, pheochromocytoma, paraganglioma, medullary thyroid cancer, pulmonary neuroendocrine tumor, thymic neuroendocrine tumor, a carcinoid tumor or a pancreatic neuroendocrine tumor, pituitary adenoma, adrenal gland tumors, Merkel cell carcinoma,

breast cancer, Non-Hodgkin lymphoma, Hodgkin lymphoma, Head & Neck tumor, urothelial carcinoma (bladder), Renal Cell Carcinoma, Hepatocellular Carcinoma, GIST, neuroblastoma, bile duct tumor, cervix tumor, Ewing sarcoma, osteosarcoma, SCLC, prostate cancer, melanoma, meningioma, glioma, medulloblastoma, hemangioblastoma, supratentorial primitive, neuroectodermal tumor, and esthesioneuroblastoma..

9. The use of claim 5, wherein said neuroendocrine tumor is selected from the group consisting of functional carcinoid tumor, insulinoma, gastrinoma, vaso active intestinal peptide (VIP)oma, glucagonoma, serotoninoma, histaminoma, ACTHoma, pheochromocytoma, and somatostatinoma.

10. The use of claim 5, wherein said neuroendocrine tumor is a low grade, medium grade, or high grade neuroendocrine tumor.

11. The use of claim 1, wherein said cancer is a small cell lung cancer.

12. The use of claim 1, wherein said cancer is a progressive midgut neuroendocrine tumor.

13. The use of claim 11, wherein said cancer is not responsive to Sandostatin (Novartis) or Somatuline® (Ipsen).

14. The use of claim 1, wherein said cancer is non-responsive or has a low response to an inhibitor of the PD-1/PD-L1 pathway.

15. The use of claim 5, wherein said neuroendocrine tumor is a functional neuroendocrine tumor.

16. The use of claim 5, wherein said neuroendocrine tumor is a nonfunctional neuroendocrine tumor.