

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, the present invention refers to the use of a combination of Peptide Receptor Radionuclide therapy (PRRT) 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 said PRRT is a radiolabeled somatostatin analogue peptide. In one example, there is disclosed the 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 $[^{177}\text{Lu}]\text{DOTA}[\text{O}]\text{-Tyr}[3]\text{-Octreotate}$.

CLAIMS

1. Use of a combination of Peptide Receptor Radionuclide therapy (PRRT) and an inhibitor that 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 said PRRT is a radiolabeled somatostatin analogue peptide.
2. The use of claim 1 wherein said radiolabeled somatostatin analogue peptide 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 /CTLA-4 pathway is an antibody that targets PD-1.
5. The use of claim 1 wherein said inhibitor of the PD-1 /PD-L 1 /CTLA-4 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 treatment 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 methods of reducing the frequency of cancer stem cells or tumor initiating cells in a neuroendocrine tumor.
8. The use of claim 6 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 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, gastrointestinal stromal tumor (GIST), neuroblastoma, bile duct tumor, cervix tumor, Ewing sarcoma, osteosarcoma, non-small cell lung cancer (SCLC), prostate cancer, melanoma, meningioma, glioma, medulloblastoma hemangioblastoma, supratentorial primitive neuroectodermal tumor, and esthesioneuroblastoma.

9. The use of claim 6 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 6 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 1 wherein said cancer is non-responsive or has a low response to an inhibitor of the PD-1 /PD-L 1 /CTLA-4 pathway.
14. The use of claim 6 wherein said neuroendocrine tumor is a functional neuroendocrine tumor.
15. The use of claim 6 wherein said neuroendocrine tumor is a nonfunctional neuroendocrine tumor.