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PRRT a Literature Review

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I. Introduction:

Metastatic neuroendocrine tumors, just like other tumors, are difficult to treat because of the uncontrolled cellular growth that they exhibit. This paper seeks to review research on the treatment of neuroendocrine tumors as conducted by different scholars in order to develop the theoretical foundation for the current study. The paper is organized to include eight subsections that include treatment of neuroendocrine tumors, the importance of peptide receptor radionuclide therapy, methods of peptide receptor radionuclide therapy, radiolabelled 177Lu-DOTATOC therapy, and everolimus therapy for neuroendocrine tumors. Other subsections include somatostatin receptor affinity in somatostatin-based radionuclide therapy, the success of radiolabelled somatostatin analogs in targeted radionuclide therapy and combination of mTOR drug (everolimus) with targeted radionuclide therapy for neuroendocrine tumors.

Treatment of neuroendocrine tumors:

In a review paper published in by Mathew Kulke on the Journal of Gastrointestinal Cancer Research in 2008, the author sought to explore whether there exists a standard treatment for neuroendocrine tumors. In this paper, Kulke (2008) stated that neuroendocrine tumors present significant paradox because it is not only indolent but also difficult to treat. The author observes that the treatment of malignant neuroendocrine tumor has been undergoing a significantly rapid evolution, with such new methodologies as targeted therapies emerging to support the traditional methods of treatment. However, despite the presence of new options to the treatment of these malignancies there still no standard recommendation for the best treatment option for malignant neuroendocrine tumors. In this view, the author thinks that oncology practitioners are yet to agree on the standard treatment approach to these tumors. Neuroendocrine tumors do not have a standard treatment method because of their complex characteristics as the described by Kulke (2008). For example, these tumors are known to express high levels of vascular endothelial growth factor (VEGF) as well as its receptor and thus allowing researchers to develop better therapies over the cytotoxic therapies traditionally used on this disease. In this case, such a medication as bevacizumab has been developed to inhibit tyrosine kinases and block tumor progression. Another drug targeted against VEGF is mTOR inhibitors, which targets the downstream functions of tyrosine kinases. Other anti-tumor agents developed against neuroendocrine tumors include PI3 and IGFR1-R inhibitors, and their responses have been seen to be positive. The author also observes that traditional therapies, like somatostatin analogs, are also of significant value in neuroendocrine treatment as results to the improvement of the condition by controlling tumor growth as well as controlling the symptoms, with the emergence of radiolabelled somatostatin analogs presenting new hope in somatostatin-based anti-tumor therapy. Moreover, Kulke (2008) also observed that cytotoxic regimens are also important as they have also shown significant importance in the management of neuroendocrine tumor progression and presentation of clinical symptoms. By presenting these options, Kulke (2008) also presents the daunting task involving the classification of each of the options in order of importance to present the best treatment option for the disease. This paper was a review, and thus author's biases influenced the conclusion. Besides, most of the treatment options examined by the author were still under clinical investigations meaning that early conclusions may be overtaken by new developments after the completion of these clinical studies (Kulke, 2008). Another study related to the treatment of neuroendocrine tumors was presented by Harring, Nguyen, Goss, and O'Mahony (2011) in a review paper. Harring et al. (2011) were a comprehensive review paper that explored the treatment of metastases of the liver in patients with neuroendocrine tumors. The author states that 46%-90% of neuroendocrine tumor patients also have neuroendocrine liver metastases at the time of diagnosis. The author establishes a set of therapeutic approaches available for a patient with neuroendocrine liver metastasis, each of which has special attributes that give it an edge over the others. For surgical interventions, the author observes that it produces superior outcomes

as compared to the non-operative therapies. In this case, resection produces superior long-term outcomes as compared to complete surgical extirpation. Another treatment offered to individuals with neuroendocrine liver metastases is the liver-directed therapies where the introduction of chemotherapy creates hypoxic conditions to limit the progression of tumors in the liver. For example, radiofrequency ablation destroys the tumors using intense, destructive heat to provide symptomatic relief for the patient. Another liver-directed therapy presented by the author is hepatic artery embolization/chemoembolization, and its success rate is dependent on the level of liver involvement where patients with over 50 percent liver involvement do not record notable improvements. The authors also present selective internal radiation therapy and hepatic artery radioembolization where yttrium-90 radioactive microspheres are used to deliver selective internal radiation therapy leading to improvement of survival to above 20 months after the treatment (Harring et al., 2011). On the other hand, the non-surgical therapies presented by Harring et al. (2011) include biotherapy, targeted radiotherapy, and chemotherapy. For biotherapy, Harring et al. (2011) outline various somatostatin analogs that produce encouraging results on patients. These analogues include autogel, lanreotide, octreotide long-acting repeatable and octreotide, which produce tumor and symptomatic response at the rates of 64.4%, 46.6%, 6.8% and 57.4%, and 67.5%, 63.0%, 77.3% and 74.2%, respectively. Harring et al. (2011) also present interferon-alpha as another biotherapy approach that may be employed to address the problem of neuroendocrine liver metastases. On chemotherapy approaches, Harring et al. (2011) presented several drugs that have shown different efficacies in the treatment of neuroendocrine liver metastases. Some of the drugs presented by the author include platinum-based regimens, temozolomide, capecitabine, nitrosurea streptozocin, and oxaliplatin-based regimens, and they result in different survival rates and periods. Other treatments presented by Harring et al. (2011) in this write-up target such biological pathways as the microRNA-Regulated pathways, mTOR pathway as well as the vascular endothelial growth factors (VEGF) pathway. However, Harring et al. (2011) presented a review paper where evidence was based on secondary data. As a result, any limitations of the primary research could be carried on to Harring et al. (2011)'s work without giving enough options for controlling the reference experiments. Besides, by being a review paper, the quality Harring et al. (2011)'s work was subject to influence by their research experience and bias. A similar paper was published by Alonso-Gordoa et al. (2015) that was published in Rare Cancers and Therapy Journal in 2015. In this paper, Alonso-Gordoa et al. (2015) sought to present an overview of pancreatic neuroendocrine tumors' (pNETs) sequential treatment. According to Alonso-Gordoa et al. (2015), the treatment of pNETs depend on such factors as tumor characteristics, concomitant medication, comorbidities, somatostatin research findings, tumor-related symptoms, clinical course /stage of the tumor, and rate of tumor progression, amongst others. Like Harring et al. (2011) and Sulke (2008), Alonso-Gordoa et al. (2015) recognized the current treatments of neuroendocrine tumors to include mTOR inhibitors, cytotoxic drugs, and STZ-based chemotherapy, amongst others. Besides Alonso- Gordoa et al. (2015) observed that series of clinical trials are taking place to explore the best combinations of therapeutic approaches to offer better efficacies in the treatment of neuroendocrine tumors. About the current advancements in pancreatic tumor treatment, Alonso-Gordoa et al. (2015) observed that new treatment approaches are being developed to target VEGF pathway and DNA methylation. The authors also introduced other treatment methods, for example alkylating agents, endothelial growth factor receptor inhibitors, vascular endothelial growth factor receptor plus the fibroblast growth factor receptor dual inhibitors, antiangiogenics, and peptide receptor radionuclide therapy. On peptide receptor radionuclide therapy, Alonso-Gordoa et al. (2015) identified the most important radiolabeled somatostatin analogs as 177Lu-DOTATATE, 90Y-DOTATOC, and 111InDOTATOC as they have shown promising results in advanced-stage clinical trials. For antiangiogenic, Alonso-Gordoa et al. (2015) identified bevacizumab (anti-VEGF monoclonal antibody), and tyrosine kinase inhibitors as the most successful therapies because they have made it to the advanced phases of clinical trials. Moreover, for vascular endothelial growth factor receptor and fibroblast growth factor receptor dual inhibitors, Alonso-Gordoa et al. (2015) presented brivanib as the first-line medication and sorafenib as the second-line treatment after showing high efficacy levels in clinical trials. In addition, Alonso-Gordoa et al. (2015) presented such endothelial growth factor receptor inhibitors as sulfatinib, SNX-5422 mesylate (plus everolimus), small interfering RNA (TKM-080301), dovitinb, and gefinib, amongst others, as the likely successful medications as they have shown positive results in the early phases of their clinical trials. Moreover, Alonso-Gordoa et al. (2015) also presented some alkylating agents that may offer effective treatment of pancreatic neuroendocrine tumors. Some of the medications presented in this case include temozolomide, dacarbazine, and capecitabine, and the authors also highlight some of their unpleasant side effects. Like Harring et al. (2011) and Sulke (2008), the paper by Alonso-Gordoa et al. (2015) was also a review paper and thus its importance in research is limited by the use of secondary data as the basis for conclusions. Besides, the experience and personal biases of Alonso-Gordoa et al. were also of significant importance to the paper development (Alonso-Gordoa et al., 2015). Nevertheless, one of the primary research paper related to the treatment of neuroendocrine tumors was developed by Kim et al. who published the results on BMC Cancer. Kim et al. (2010) sought to establish the biological characteristics as well as the treatment outcomes of metastatic/recurrent neuroendocrine tumors. In this study, Kim et al. (2010) made a retrospective analysis of patients with metastatic/recurrent neuroendocrine tumors to study their biology, treatment patterns as well as

treatment outcomes. Kim et al. (2010) also found out that for the cases analyzed, liver comprises the primary metastatic site and that some of the treatment options availed to them included radiofrequency ablation, TACE, metastasectomy, chemotherapy, interferon, and somatostatin analogs. In the end, Kim et al. (2010) stated that treatment of neuroendocrine tumors would produce the best results after making enough considerations of the tumor characteristics in order to the device the treatment approach for individuals. However, this paper did not examine how different treatment options work to address the problem to stop tumor growth as well as to manage the symptomatic characteristics of the disease (Kim et al., 2010). An additional primary research about this problem was developed by Raymodn et al. (2011) who published the results in the New England Journal of Medicine. In this research Raymodn et al. (2011) sought to explore the use of sunitinib malate as a treatment regimen for pancreatic neuroendocrine tumors. Raymodn et al. (2011) stated that preclinical models and phase ½ trials have demonstrated the ability of multi-targeted tyrosine kinase inhibitor sunitinib to have antitumor activity against pancreatic neuroendocrine tumors. In order to assess the significance of this antitumor activity, Raymodn et al. (2011) conducted a randomized, double-blind placebo-controlled trial of sunitinib on subjects recruited from different countries. In the end, the study showed that sunitinib treatment with 37.5 mg daily dose results in increased overall survival and improvement of progression-free survival of the subjects. This study was a controlled one and thus the results were dependable for making a logic conclusion about sunitinib malate's efficacies in pancreatic neuroendocrine tumor treatment. Besides, it was multinational, allowing for more extended progression of results to cover people from different geographical locations of the globe. However, the research was made on pancreatic neuroendocrine tumors and thus it could not be used as a representative study for all neuroendocrine tumors. All these studies were summed up by Diez, Teule and Salazar (2012) in their paper that explored the diagnosis as well as the treatment of gastrointestinal neuroendocrine tumors. In this paper that was published in Annals of Gastroenterology, Diez, Teule and Salazar (2012) stated that gastroenteropancreatic neuroendocrine tumors could be sporadic or familial, and that successful diagnosis and treatment of these conditions are a product of an interdisciplinary approach involving numerous specialties. However, the summary of the treatment strategies used to treat these conditions effectively included radiological intervention, surgery, somatostatin analogs, everolimus, sunitinib, and cytotoxic chemotherapies. In this study, Diez, Teule and Salazar (2012) observed that peptide receptor radionuclide therapy should be used in the events where disease progresses beyond the ability to manage it using the strategies mentioned above. However, this paper was a review that utilized secondary research strategies and experience of the authors to come up with a conclusion. As a result, it is limited by the author's biases (Diez, Teule and Salazar, 2012).

The importance of peptide receptor radionuclide therapy:

Several studies have demonstrated the importance of peptide receptor radionuclide therapy in ensuring better health for individuals after its administration. One of such studies was presented by Delpassand et al. (2012) in a paper published in the Journal of Theranostics. In this paper, Delpassand et al. (2012) sought to explore the long-term survival as well as the toxicity profile in patients suffering from progressive neuroendocrine tumors after peptide receptor radionuclide therapy with 111In-pentreotide. In order to establish the benefits of the therapy to the recipients, the authors used F-18 FDG PET-CT scan for prognosis in order to explore these benefits. In this paper, Delpassand et al. (2012) stated that the standard chemotherapy approaches the treatment of neuroendocrine tumors are lowly effective and that they that they have numerous adverse effects on the recipient leading to low survival rates as well as several effects of their high toxicity profiles. Also, the authors observed that the introduction of peptide receptor radionuclide therapy in the 1990s provided new hopes for successfully battling neuroendocrine tumors. In this case, the authors referred to the radiolabelled somatostatin analogs as an efficacious treatment method for patients with inoperable and/or metastatic neuroendocrine tumors with elevated expression of somatostatin receptors (Delpassand et al., 2012). Delpassand et al. (2012) found out that the therapy does not cause significant acute toxicity meaning that the recipients could not develop toxic reactions to the therapy immediately after the therapy. In addition, the authors found out that this therapy causes grade-I renal toxicity on 6.1 percent of the recipients, and liver toxicity in 18.4 percent of the recipients. Besides, the study found out that grade II and grade III hematological toxicity occurs in 7.6 percent of the patients. Moreover, the study reported an average of 18.9 months survival after the last administration of the regimen. Besides, the regimen was found to produce 85 percent patients with stable disease, 7.5 percent with partial response and only 7.5 percent with progressive disease and this was indicative of the therapy as a highly efficacious strategy. In the end, the study established that 111Inpentreotide therapy is an important approach that increases the survival time of the individual to up to 45 months after the last cycle administration. However, it highlighted the therapy like the one that is toxic to such organs and tissues as the liver, the hematological tissue and the kidney, which is the source of its contraindications (Delpassand et al., 2012). This study was primary, and it utilized one of the popular somatostatin analogs for the investigations. Its results could be extrapolated to cover similar analogs of the somatostatin nature, for example, DOTATOC and DOTATATE. As a result, it presented important insights about the significance of applying radiolabelled

somatostatin analogs in the treatment of neuroendocrine tumors. However, the study was limited by the fact that it was a nonrandomized clinical trial. Besides, the study was also negatively affected by the use of a small population to explore the survival advantages of neuroendocrine tumors about the radiolabelled somatostatin treatment. A similar study was published by Vinjamuri et al. (2013) in the British Journal of Cancer. In this study, Vinjamuri et al. (2013) sought to explore the response, toxicity and survival aspects related to the treatment of patients with progressive metastatic neuroendocrine tumors using 90Y-DOTATATE and 90Y-DOTATOC. Vinjamuri et al. (2013) stated that treatment of patients with metastatic neuroendocrine tumors with peptide receptor radionuclide therapy had gained popularly not only among patients but also among oncologists, but the overall survival advantage of the approach remains unclear. Out of the 57 patients put through this therapy by Vinjamuri et al. (2013), the radiological response was achieved in 71.5 percent, with progressive disease cases achieving 18 months overall survival. In the same vein, cases of positive response and stable disease achieved overall survivals of 51 and 56 months, respectively. In the end, the study established that peptide receptor radionuclide therapy with 90Y-DOTATATE and 90Y-DOTATOC results in increased overall survival advantage for the recipients in comparison with biochemical therapeutic approaches. This study supported Delpassand et al. (2012) findings with regard to the overall survival of the patients, but it did not explore the importance of the toxicity profiles of the therapies and thus created a requirement for further investigations about the subject. A better understanding of the importance of peptide receptor radionuclide therapy was made by Filice et al. (2012) in a paper published in the Journal of Nuclear Medicine. In this paper, by Filice et al. (2012) sought to explore the role played by peptide receptor radionuclide therapy (90Y-DOTATOC and 177Lu-DOTATOC) in patients suffering from neuroendocrine lung tumors. The researchers administered 90Y-DOTATOC to five patients, 177LuDOTATOC to two patients and a combination of the two analogs to six patients in order to establish their roles in cancer treatment. In the end, 7 out of 13 patients treated with this regimen recorded partial response, 3 out of 13 patients recorded progression disease, and 3 out of 13 recorded stable disease. Besides, for combination therapy, 67 percent of the recipients recorded partial response while 3 percent of the recipients recorded stable disease. Moreover, the treatment with 90YDOTATOC resulted in 40 percent partial response and 60 percent progression disease. However, 50 percent of patients treated with 177Lu-DOTATOC recorded partial response while the other 50 percent had a stable disease. In the end, the study established that pulmonary neuroendocrine tumors could benefit from the use of peptide receptor radionuclide therapy using either 90YDOTATOC or 177Lu-analogues alone, with combination therapy yielding superiors results. This study demonstrated the specific importance of 177Lu-DOTATOC in the treatment of neuroendocrine tumors. However, the research was limited by the small number of the subjects that limited the generalizability of the results. As a result, it created a need for further studies on a larger sample for the confirmation of the results (Filice et al., 2012). The importance of peptide receptor radionuclide therapy in the treatment of neuroendocrine tumors was further explored by Praasad, Brenner and Modlin who published a review in the European Journal of Nuclear Medicine and Molecular Imaging. Praasad, Brenner, and Modlin (2013) sought to present the perspective of the clinician regarding the smartness of peptide receptor radionuclide therapy when treating neuroendocrine tumors (with a special interest in the salvage settings). In this review, Praasad, Brenner and Modlin (2013) observed that emergence and advancement of new technologies in the biological perception of the disease have resulted in increased confusion in the managerial protocols because, for example, therapeutic drugs target not only the tumor cells but also the healthy cells leading to toxicity. Praasad, Brenner and Modlin (2013) observed that one of the importance of the peptide receptor radionuclide therapy over the generalized treatment is that it allows for the reduction of therapy toxicity by targeting only the tumor cells without affecting the normal tissues laying close to the tumor. Another importance of peptide receptor radionuclide therapy, according to Praasad, Brenner and Modlin (2013), is that it allows for specific targeting of a tumor when dealing with a complex and heterogeneous disease. However, they also observed that peptide receptor radionuclide therapy has a major shortcoming, which is toxicity, as evidence in different studies assessing toxicity profiles of such somatostatin analogs as DOTATOC and DOTATE. They observed that major toxicities of peptide receptor radionuclide therapy are observed within the first few months of treatment and that if some resultant somatostatin receptor positive lesions are left untreated they may progress within 6-14.3 months of the last treatment cycle. However, this paper only made a review of the issues of the therapy without showing how empirical evidence was achieved (Prasad, Brenner and Modlin, 2013). Nevertheless, an empirical approach was employed by Wedinger et al. in 2011 when they published a similar paper in the World Journal of Nuclear Medicine. In this paper, Wedinger et al. (2011) sought to explore the importance of peptide nuclides in improving the quality in patients. The authors stated that although peptide receptor radionuclide therapy has been popularized as a significant treatment strategy for patients with somatostatin receptor-expressing tumors little evidence is available to show the importance of the approach in terms of the improvement of the patient's quality of life. In this research, Wedinger et al. in 2011 administered cycles of 90Y-DOTALAN and/or 90Y-DOTATOC to patients before following them up until death to establish their response in terms of improvement of the quality of life through such indicators as the general symptoms, the karnosfsky score and pain intensity. For 90Y-DOTATOC therapy, all patients recorded stable disease while for 90Y-DOTALAN, one patient

recorded a stable disease and three recorded progressive diseases. Moreover, even with treatment with 90YDOTALAN or 90Y-DOTATOC 9 out of 13 patients died after the PRRT. In addition, the therapy achieved pain relief in 3 out of 3 patients, karnfsky score, general well-being, weight and appetite improved significantly for all individuals with the stable disease. The overall finding of this study was that PRRT offers a successful treatment options patients with somatostatin receptor positive tumors because of the marked improvement of their quality of life after the treatment as well as the presence of transient side-effects. However, Wedinger et al. (2011) used a very small sample of 13 patients and thus limiting the generalizability of the conclusion until further investigations confirm these results. A similar paper was developed by Romer et al. (2014), where they compared the use of 177Lu-DOTATOC and 90Y-DOTATOC in somatostatin-based radionuclide therapy for neuroendocrine tumors. In this study, Romer et al. (2014) hoped to establish benefits and harms of the two approaches. To accomplish this goal, the authors used a comparative cohort study targeting patients with advanced neuroendocrine tumors for treatment with 177Lu-DOTATOC or 90YDOTATOC to such endpoints as disease progression or permanent adverse events. After 1,804 cycles of 90Y-DOTATOC in 910 patients and 259 cycles of 177Lu-DOTATOC treatment, the median survival was established to be 45.5 months and 35.9 months, respectively. These results were comparable. However, for the subgroups with extra-hepatic and solitary tumors, or low tumor uptake, the median survival of patients treated with 177Lu-DOTATOc was higher compared to 90Y-DOTATOC. In the end, the only advantage identified with regard to the use of 177LuDOTATOC instead of 90Y-DOTATOC was its lower hemotoxic nature (Romer et al., 2014).

Techniques in peptide receptor radionuclide therapy:

Over time, several techniques of administering peptide receptor radionuclide therapy have been described. In a paper published in Best Practice & Research Clinical Gastroenterology in 2005, Teunissen et al. described peptide receptor radionuclide therapy as a new treatment modality for patients with neuroendocrine tumors where they presented radionuclides and somatostatin analogs applied. In this review article, Teunissen et al. (2005) indicated that the most commonly used radionuclides for targeted radiotherapy included lutetium (177Lu), indium (111In) and yttrium (90Y) and cited that they have been taken through several clinical trials in the past. Besides, Teunissen et al. (2005) also indicated that somatostatin analogs labeled with these radionuclides differ in their affinities for various subtypes of somatostatin receptors. Teunissen et al. (2005) also observed that somatostatin analogs with high affinities for somatostatin receptor-2 are of high therapeutic values because of their inherent affinities for neuroendocrine tumors that allows them to deliver the radionuclides to the tumor much rapid and without affecting tissues that do not express this receptor subtype. The paper also emphasized the higher affinity for sstr2 that is exhibited by analog DOTATATE in comparison with DOTATOC and stated that DOTATATE has nine times higher affinity for this receptor subtype in comparison with DOTATOC. On the other hand, Teunissen et al. (2005) highlighted the major somatostatin analogs used for peptide receptor radionuclide therapy to include DOTATOC, DOTATATE, and DPTA. Moreover, the study also highlighted some of the somatostatin analogs that have been subject to clinical studies to include [111In-DPTA] octreotide, [90Y-DOTA] lanreotide, 90Y-DOTATOC, 90YDOTATATE, and 177Lu-DOTATATE. For all these clinical trials, Teunissen et al. (2005) found out that there were varied levels of toxicity with hematological toxicity presenting in the form of low white blood cell counts, lowered hemoglobin levels and lowered platelet counts. In addition, other forms of toxicities presented in these studies include hepatotoxicity and renal toxicity. In the end, Teunissen et al. (2005) observed that advancements in peptide receptor radionuclide therapy have led to promising trials with several radiolabelled somatostatin analogs, leading to an opportunity for targeting tumors efficiently. This paper was a review of various works, and it was based on secondary data to develop a conclusion. As a result, it is limited by the likely incorporation of the authors' biases during the review. A similar paper was developed by Jong and Krenning in 2002, and it was published in the Journal of Nuclear Medicine. In this paper, Jong and Krenning (2002) sought to explore new peptide receptor radionuclide therapy advances in a review. Jong and Krenning (2002) observed that multicenter preclinical and clinical studies had established the usefulness of radiolabelled somatostatin analogs in treating somatostatin receptor positive tumors, but one of the major concerns is the high uptake of these analogs by the kidney leading to renal toxicity. One of the advances observed over years of clinical trials is the usefulness of DOTA as a chelator, where it has gained the importance of universal chelator that can be used to form complexes with such radioisotopes as 65Cu, 68Ga, 111In, 86Y, and 67Ga. Another advance made in this area is the increased tumor responses to 90Y-DOTATOC, and 177Lu-DOATATE, which according to Jong and Krenning (2002) can vary up to 100 percent cure depending on the size of the tumor. In this paper, the early results of clinical trials of radiolabelled somatostatin analogs are presented to have recorded varying levels of successes depending on the analog somatostatin type and the radionuclide employed in technique. However, the paper was limited by being a review of various clinical trial reports as well as being old since its publication. Since it was published in the early years of the 20th century, it does not include advancements made after 2001. Another paper that highlights a method of administering peptide receptor radionuclide therapy was presented by Jong et al. in 2005 and it was published in the Journal of nuclear medicine. In this paper, Jong et al. (2005)

explored the peptide receptor radionuclide therapy by combining 90Y- and 177Lu- labeled somatostatin analogs. Jong et al. (2005) observed that the use of radiolabelled somatostatin analogs is promising due to their likely use in administering therapies for somatostatin receptor-expressing tumors. The added that application of 90Y- and 177Lu- labeled somatostatin analogs offers an advantage of delivering higher amounts of beta particles because both particles are beta-emitters of different capacities. In the end, the 90Y- and 177Lu- labeled somatostatin analogs' radiotherapeutic effects were shown in rats in varying intensities. However, the overall effect of combined therapy of 90Y- and 177Lu- labeled somatostatin analogs was more significant as compared to those of the two radiolabelled therapeutic somatostatin analog when used alone. In the end, Jong et al. (2005) established that combination of two radiolabelled somatostatin analogs in a therapeutic modality generates superior results to the application of a single radiolabelled somatostatin analog. The paper produced insightful information regarding the development of combined radiolabelled somatostatin receptor analogs by presenting the therapeutic advantage of that approach. However, it used animal models (rats) for the study and thus limiting the projections of results and conclusions to cover humans. As a result, it presented a need for further research on humans through clinical trials. A similar research to Jong et al.'s was made by Bison et al. in 2015 and the report was published in EJNMMI Research Journal. In this paper, Bison et al. (2015) sought to explore methods of optimizing combined peptide receptor radionuclide therapy and temozolomide in mice (after multimodality molecular imaging studies). Bison et al. (2015) observed that both temozolomide and somatostatin receptor radionuclide therapy by the use of 177Lu-DOTATATE have individually resulted in significant success in the treatment of somatostatin receptor-expressing neuroendocrine tumors, and that additive results could be achieved if both the two agents are used in a combination (Bison et al., 2015). As a result, they set a test model using murine to study the tumor characteristics as well as the therapeutic responses after the administration of peptide receptor radionuclide therapy in combination with temozolomide in the model murine. This method was found to cause enhanced tumor perfusion as well a reduction in the tumor size, in addition to an increased uptake of somatostatin analogs due to temozolomide administration. Moreover, the study found out that a complete response to 177Lu-DOTATATE was possible at day fourteen of temozolomide administration. In the end, Bison et al. (2015) concluded that the use of temozolomide in peptide receptor radionuclide therapy results in enhanced uptake of somatostatin analogs leading to higher therapeutic efficacies. However, the study was carried out on murine models and thus limiting the extrapolation of results to cover human subjects and as a result, further studies on human subjects are necessary to confirm this conclusion in a clinically relevant way.

Immediate and long-term side effects of peptide receptor radionuclide therapy:

Traditional, surface radiotherapy, is associated with several adverse outcomes presenting immediately or sometime after completing the cycle. Similarly, peptide receptor radionuclide therapy also results in some adverse outcomes that present immediately or sometimes after the last cycle. Some researchers have taken an interest in this area as adverse effects of the therapy decrease the overall importance of a regimen. One of the scholarly work conducted with the aim of exploring the therapy side effects of the peptide receptor radionuclide therapy was conducted by Pach et al. who published a report in the Radiotherapy and Oncology Journal in 2012. In this study, Pach et al. (2012) sought to explore the levels of effectiveness of multiple cycles of peptide receptor radionuclide therapy when administered to individuals with malignant neuroendocrine tumors, in addition to the resultant side effects of the therapy. Pach et al. (2012) 16 out of 89 patients were treated on a repeated cycle, of which one was subjected to peptide receptor radionuclide therapy as neoadjuvant therapy. The analysis of the side effects of the treatment showed that the use of PRRT as a neoadjuvant therapy resulted in a reduction of the tumor sizes. In addition, stabilization of the disease was achieved in a period of 6-18 months, but death occurred in ten individuals who received repeated PRRT cycles. However, Pach et al. (2012) observed that repeated PRRT cycles do not cause significant toxicities to the hematological functions as well as the kidney because toxic changes were transient. Nevertheless, the paper was based on results of a small sample that is unrepresentative. Besides, sample collection was not randomized and thus results and conclusions were of little generalizability. A similar study was conducted in Germany by Horsch et al. in 2016 and the report was published in the European Journal of Cancer. In this paper, Horsch et al. (2016) wished to determine the effectiveness as well as the sideeffects of PRRT for neuroendocrine neoplasms among patients in Germany. Horsch et al. (2016) followed 450 patients for 24.4 months (averagely), where 54 percent of them were treated with Lu177, 17 percent with Y-90, and 29 percent with both nuclides. Ultimately, Horsch et al. (2016) conducted overall and progression-free survival determination using univariate log-rank test COX models and Kaplan-Meier curves, where the median overall survival of the patients was found to be 59 months. However, patients treated with Lu-177 recorded longer survival as compared to those treated with Y-90, with survival rates of patients having grade II and grade III neuroendocrine neoplasms being lower than those with grade-I neuroendocrine neoplasms. From the study, 0.2-1.5 percent cases of adverse events of kidney and bone marrow function higher than grade III were recorded. In the end, the paper showed that peptide receptor radionuclide therapy results in lowgrade adverse events. However, the research was conducted on a localized population in

Germany and result may not be generalized to cover a wide global region as different regions may be subject to differential local influences (Horsch et al., 2016).

Receptor affinity and pharmacokinetics/pharmacodynamics of radiolabelled somatostatin analogs: Different somatostatin analogs have distinctive receptor affinities as pharmacodynamics characteristics. A study published in Anticancer Research Journal by Laznicek, laznickova, and maecke in 2012 revealed some of the characteristic features of radiolabelled somatostatin analogs with regard to receptor affinity and bio-distribution. In this study, Laznicek, laznickova, and maecke (2012) explored how different radiolabelled somatostatin analogs are taken up by somatostatin-rich tissues in relation to the affinity to somatostatin receptor subtype2. Laznicek, laznickova, and maecke (2012) administered six derivatives of 111In-labelled octreotide and octreotide to adrenals and pancreas in vivo before measuring the associated organ radioactivity 24 and 48 hours after administration in order to correlate the results with the affinity to somatostatin subtype2 determined in vitro – IC-50 values. Adrenal uptake of radiolabeled analogs was determined by establishing the exponential dependence best fit against IC-50 while linear dependence was used for correlation regarding pancreas. In the end, Laznicek, laznickova and maecke (2012) established that adrenal and pancreas radioactivity correlates with in vitro determined receptor affinities for specific subtypes of somatostatin. However, the study used rat models to come up with the conclusion and thus it cannot be applied for clinical purpose until further investigations involving clinical work. In another paper published by Harris (1994), the author offers as a comprehensive exploration of the pharmacokinetics and pharmacodynamics effects of somatostatin and somatostatin analogs. In this paper, Harris (1994) described the structures of the two somatostatin molecules, namely somatostatin 14 and somatostatin 28, as well as their biological distributions in the body. In this case, Harris (1994) observed that the gut lumen, the endocrine cells, the visceral autonomic nervous system and the pancreas form the primary localization sites of somatostatin. Regarding actions, Harris (1994) observed that somatostatin is an inhibitory molecule that blocks endocrine and exocrine secretion. The natural somatostatin has a short half-life making its effects short lived as well as insufficient in controlling unspecific growth that characterizes tumors. As a result, for tumor treatment somatostatin analogs are used to overcome the problem of shortened half-life. For example, octreotide is one of the analogs of somatostatin, and it has a half-life of 113 minutes as opposed to 2-3 minutes that natural somatostatin takes to reduce by half its original quantity. According to Harris (1994), after administration of octreotide in the body, a 50 percent reduction in growth hormone secretion is recorded. One of the pharmacokinetics characteristics of octreotide is that its oral administration is characterized by low rates of gastrointestinal absorption leading to lowered bioavailability. However, administration by intravenous or subcutaneous injection results in similar bioavailability and a peak serum concentration within 30 minutes of administration. The increase in the concentration of octreotide in the serum after administration increases linearly and its plasma clearance in persons with renal impairment is 50 percent lower than those without renal malformations. The endocrine effects of octreotide are similar to those produced by natural somatostatin molecules. Harris (1994) concluded by presenting similarities between octreotide as a representative somatostatin analog and the natural somatostatin. Ultimately, Harris (1994) provided a resourceful overview of the pharmacodynamics and pharmacokinetics characteristic of octreotide with regard to its application as a pharmaceutical. However, the paper was a review, and it depended on secondary data to make conclusions. Another study by Lesche et al. (2009) sought to establish the differences between octreotide and pasreotide with regard to somatostatin receptor internalization as well as trafficking in vitro. In this paper, Lesche et al. (2009) observed pasreotide has a high binding affinity to such receptors subtypes as sstr1, sstr2, sstr5 and sstr3, unlike octreotide that has a high affinity for sstr2 only. However, results showed that octreotide has a higher potency for causing internalization as well as signaling of sstr2 in human embryonic renal cells. Additionally, octreotide-mediated activation of the receptor was shown to cause events leading to the internalization of beta-arrestin-2 and sstr2 into the same endocytic vesicles while receptor activation by SOM230-mediated receptor led to the formation of lowly stable complexes that disintegrated at the plasma membrane. However, both octreotide and lanreotide caused rapid sstr3 down-regulation. In the end, Lesche et al. (2009) found out that octreotide and somatostatin modulate receptor trafficking distinct ways as compared to pasreotide.

Everolimus therapy for neuroendocrine tumors:

Everolimus is one of the most recent breakthroughs in neuroendocrine tumor therapy as it stops tumor progression by targeting the downstream reactions of the mTORC1 pathway. As a result, numerous studies have been made to ascertain the importance of this breakthrough. One of such studies was conducted by Yao et al. and the report was published in the New England Journal of Medicine in 2011. In this study, Yao et al. (2011) sought to explore the use of Everolimus for advanced pancreatic neuroendocrine tumors. In this study, Yao et al. (2011) stated that pancreatic neuroendocrine tumors are difficult to treat as most of the cases they are diagnosed lately. Besides about 65 percent of the cases diagnosed in the late stage present with the inoperable or metastatic disease, making surgical strategies infeasible. As a result, oncologist result to the recommendation of chemotherapeutic agents for the management of this disorder, where streptozocin is prescribed for use by

patients. However, according to Yao et al. (2011) Everolimus is a promising agent that has shown high antitumor efficacies in several phase-2 clinical trials. Yao et al. (2011) stated that everolimus treats pancreatic neuroendocrine tumors by suppressing cell proliferation, growth, and angiogenesis, by inhibiting mTOR. In their study, Yao et al. (2011) made a phase 3 study on everolimus to evaluate it in a perspective and a randomized way where 410 patients with low-grade, advanced or intermediate-grade pancreatic neuroendocrine tumors received everolimus at a daily dose of 10 mg (207 patients) or placebo (203 patients). In addition to this medication, each group also got highprofile supportive care for the condition. In the end, Yao et al. (2011) investigated the survival of the two groups to establish the effectiveness of the therapy, where those who received everolimus recorded 11.0 months median survival while those who received placebo recorded a median survival of 4.6 months. Besides, at the eighteenth month after the treatment, only 34 percent of those treated with everolimus were alive, compared to only 5 percent that had received placebo treatment. In addition, drug-related adverse effects were higher among those treated with everolimus while it was lower among those treated with placebo, at the rate of 34 percent and 9 percent, respectively. Additionally, the some of the commonest adverse events recorded by those treated with everolimus included anemia, hyperglycemia, diarrhea, fatigue, infections, rash, and stomatitis. Moreover, the study revealed a median exposure rate of 34 weeks for everolimus compared to 16 weeks for placebo. As a conclusion, Yao et al. (2011) observed that everolimus therapy results in prolongation of progression-free survival of the recipients as compared to placebo treatment. Additionally, the study also concluded that use of everolimus results in numerous, severe adverse effects as compared to the administration of placebo. This study was generalizable as it was randomized and with a high number of participants. However, it was conducted on pancreatic neuroendocrine tumors making it difficult to extrapolate the findings to cover other classes of neuroendocrine tumors and thus further studies are necessary to establish where the treatment of other neuroendocrine tumors with this agent results in similar outcomes (Yao et al., 2011). Another study that explored the use of everolimus in the treatment of neuroendocrine tumors was conducted by Porta, Paglino and Mosca and reported in Frontiers in Oncology in 2014. In this study, Porta, Paglino and Mosca (2014) sought to explore the cancer treatment by targeting PI3K/Akt/mTOR pathway. Porta, Paglino and Mosca stated that mTOR and PI3K are important pathways in determining the growth as well as the growth of cells both in physiology and pathology. In this review paper, Porta, Paglino and Mosca (2014) described the functions of mTOR in the normal cellular physiology as well as the likely targeting in the event of tumor development to offer treatment. While exploring the importance of everolimus in neuroendocrine tumors therapy Porta, Paglino and Mosca (2014) explained that rapamycin inhibitors act by inhibiting the mTOR pathway by forming an FKBP-12 to prevent the mTOR activity and as a result inhibiting three events, namely, angiogenesis, survival and cell cycle progression. With this idea in mind, Porta, Paglino and Mosca (2014) described everolimus phase-III trials that have resulted in noteworthy successes in the treatment of neuroendocrine tumors. Porta, Paglino and Mosca (2014) observed that the use of everolimus in combination with octreotide LAR in a phase-II trial had demonstrated a significant anti-tumor activity that resulted in a median in 15.7 months of progression-free state, 80 percent of stable disease, and 17 percent remission. In RADIANT-1 phase-II trial 115 participants were put on everolimus at a dosage of 10 mg per day while 45 patients have put on ten everolimus 10 mg per day and octreotide LAR at a dosage of 30 mg per 28 days. Porta, Paglino and Mosca (2014) found a 9.6 percent response rates in individuals put on everolimus alone, and 4.4 percent response rate among those put on everolimus in combination with octreotide LAR. In addition, the progression-free survival time for those who took everolimus alone was 9.7 months, but the progression-free survival of those put on both everolimus and octreotide LAR was 16.7 months. These results were confirmed in phase-2 and phase-3 (RADIANT-II and RADIANTIII, respectively) studies - randomized, placebo-controlled, multicentre, and internalized studies. Following the RADIANT-3 study, in 2011, everolimus was approved for the use as a therapeutic agent for neuroendocrine tumors, and the medication has ever since been in the market. This paper provided important theoretical backgrounds regarding mTOR as well as the mechanism of action of mTOR inhibitors with regard to neuroendocrine tumors. Besides it also confirmed the theory by presenting the clinical trial results of everolimus (Porta, Paglino and Mosca, 2014). However, the paper was a review and its quality highly dependent on the experience of the authors in this field as well as the quality of the primary data, which was out of their control. Besides, the paper was also subject to the biases of the authors, and these factors could affect the conclusions made by the authors. Another paper regarding the use of everolimus in the treatment of neuroendocrine tumors was presented by Neychev et al. (2015) in the Biomedical Journal (BMJ). In this paper, Neychev et al. (2015) set a phase-II clinical trial to explore the effectiveness of mutation-targeted treatment using sunitinib or everolimus in cases of intermediate-grade or advanced-level pancreatic or gastrointestinal neuroendocrine tumors with or without cytoreductive surgery. Neychev et al. (2015) observed that several studies and works are in progress in order to find the optimal strategies for managing such inoperable or metastatic neuroendocrine tumors as pancreatic neuroendocrine tumors or gastrointestinal neuroendocrine tumors. Neychev et al. (2015) were a prospective study that designed an open-label phase-II trial to determine whether nutationtargeting treatment with everolimus or sunitinib could result in longer progression-free survival of patients with intermediate-grade or low-grade neuroendocrine tumors. The research

design involved putting patients on sunitinib or everolimus and making a prospective study on them until disease progression warranted switching to the other drug and consequently following the patient until unacceptable toxicity, consent to withdrawal or disease progression. The paper explored the importance of sunitinib and everolimus as important therapeutic agents for treating neuroendocrine tumors, in addition to the effect of the mutation on the progression of the disease during the treatment course. However, the paper was incomplete as it did not report the findings (Neychev et al., 2015).

Other studies:

By everolimus being among the first mTOR drug to be approved for use in the treatment of neuroendocrine tumors, numerous studies have been conducted to explore different aspects of the drug. In a paper published in the Therapeutic Drug Monitoring Journal, Taber et al. (2015) explored the pharmacokinetics as well as the pharmacodynamics characteristics of everolimus. In this study, Taber et al. (2015) sought to make a comparative analysis of the pharmacokinetic and pharmacodynamics characteristics of everolimus with regard to different racial groups comprising of adult kidney transplant recipients. In this paper, Taber et al. (2015) stated that limited data exists with regard to both the pharmacodynamics and pharmacokinetic properties of everolimus with regard to two races, namely, Caucasians and African-Americans, and thus it is difficult to establish their differences. According to Taber et al. (2015), both races exhibit similar baseline demographics, immunologic risk, and immunosuppression. However, after experimental treatment with everolimus, the African-American group of recipients exhibited higher concentrations as compared to the Caucasian cohort. However, the overall outcome demonstrated everolimus as an effective way of preventing as well as causing an improvement in the graft function regardless of the race of the recipient. This study provided important insights of the pharmacokinetics and pharmacodynamics characteristics of everolimus in African-American as well as the Caucasian users, but it provided no information with regard to neuroendocrine tumor therapy. As a result, it necessitated for further studies on the pharmacodynamics and pharmacokinetic properties of everolimus with regard to the treatment of neuroendocrine tumors. Besides, no randomization was made and thus making it difficult to generalize the conclusion. Another study on everolimus and octreotide was made by Tippeswamy et al. in 2015 and published in the Indian Journal of Cancer. Tippeswamy et al. (2015) presented an Indian experience of the use of everolimus in combination with octreotide long-repeatable for treating advanced neuroendocrine tumors performed in tertiary cancer care setting. In this study, Tippeswamy et al. (2015) explained that the treatment of neuroendocrine tumors is challenged by their insensitivity to the conventional system chemotherapy. As a result, the successful management of this condition involves using three strategies, namely antiangiogenic therapy, rapamycin inhibition and somatostatin analogs. In this study, patients with prior exposure to chemotherapy were put on everolimus at a dose of 10 mg per day in addition to intramuscular injection of octreotide long-repeatable at a dose of 30 mg per 30 days for a period leading to unacceptable toxicity or disease progression. In the end, 69 percent of the recipients recorded clinical benefits – with 63 percent of them recording stable disease and 6 percent recording partial response – after administration of everolimus in combination with octreotide long-acting repeatable. The patients also showed high tolerance to this therapy as well and thus allowing Tippeswamy et al. (2015) to conclude that combination of everolimus and octreotide long-acting repeatable has is highly efficacious as well as safe for use in the treatment of neuroendocrine tumors. However, the paper did not explore the use of everolimus in combination with a radiolabelled octreotide molecule and thus being different from the current study (Tippeswamy et al., 2015). A similar study was conducted by Bajetta et al. who published the findings in the American Cancer Society Journal in 2014. In this study, Bajetta et al. (2014) sought to explore the efficacy of a combined regimen of everolimus and octreotide LAR when used in the first-line setting for neuroendocrine tumor patients. Bajetta et al. (2014) stated that suggestions from preclinical as well as clinical studies indicate that the concurrent use of everolimus and somatostatin analogues produces synergy in the treatment of neuroendocrine tumors and, as a result, they sought to assess the activity as well as the safety of the regimen with regard to the treatment of neuroendocrine tumors of lung and gastroenteropancreatic origin. They used the 2-stage minimax design developed by Simon to set a phase-2 multicenter trial where the participants were treated with a daily dose of 10 mg everolimus, combined with a 28-day dose of 30 mg octreotide long-acting repeatable. As a result, Bajetta et al. (2014) found out that most adverse events were of grade 1 or 2, with one patient recording grade-4 adverse events (mucositis), but grade 3 adverse events included 1 case of skin rash, 4 cases of stomatitis and 11 cases of diarrhea. Additionally, the study resulted in 18 percent overall response rate and 92 percent clinical benefit. As a result, the study suggested the combined use of everolimus and octreotide long-acting repeatable as an effective regimen for first-line treatment of patients with neuroendocrine tumors. However, Bajetta et al. (2014) used a small sample of fifty patients that was unrepresentative. Besides, the study was also not randomized leading to the lack of generalizability of related conclusions. Combined therapy of neuroendocrine tumors using a somatostatin analog and everolimus was also explored by Claringbold and Turner (2015) with the aim of establishing the safe dose of this combined therapy. In this study, Claringbold and Turner (2015) sought to establish the dose-limiting toxicity of combined use of 177Lu-octreotate and everolimus when used for the

treatment of progressive gastro-entero-pancreatic neuroendocrine tumors. In this study, all the patients with unresectable, progressive GEP-NETs received 7 GBq 177Lu-octreotate at intervals of 8 weeks, while successive cohorts of 4, 9 and three patients received escalating doses of everolimus of 5, 7.5 and 10 mg for 24 weeks, respectively. This combined therapy resulted in 44 percent response rate, and the maximum allowable dose of everolimus was established to be 10 mg, at a point where reduced creatinine clearance, neutropenia, and thrombocytopenia showed up. In the end, the maximum tolerable dose of everolimus was found to be 7.5 mg daily (Claringbold and Turner, 2015). The only shortcoming of this study was the use of a small sample of 16 patients, which limited the generalizability of conclusions. A different study that explored the importance of everolimus with regard to the treatment of neuroendocrine tumors was published by Liu, Marincola and Oberg who reported their findings in the Therapeutic Advances in Gastroenterology journal in 2013. In this paper, Liu, Marincola and Oberg (2013) reviewed the latest studies with the aim of interpreting the use of everolimus as a treatment approach for patients with advanced pancreatic neuroendocrine tumors. Additionally, Liu, Marincola and Oberg (2013) stated that the traditionally available treatment option for pancreatic neuroendocrine tumors involves the use cytotoxic agents, most commonly streptozotocin in addition to doxorubicin or 5-fluorouracil. However, the authors also recognize the emergence of sunitinib (a tyrosine kinase inhibitor) and everolimus (an mTOR inhibitor) as the latest additions to the treatment options. Liu, Marincola and Oberg (2013) reviewed the results of three clinical studies, namely RADIANT-1, RADIANT-2 and RADIANT-3, and their importance with regard to the use of everolimus in treating pancreatic neuroendocrine tumors. Regarding RADIANT-1, the study established that the use of everolimus resulted in a median overall survival of 24.9 months, confirming the previous studies that had established high rates of disease stabilization with the use of everolimus. In addition, with regard to RADIANT-2 Liu, Marincola and Oberg (2013) found out that disease progression-free survival was higher with the use of everolimus as compared to the use of placebo, even though its use was associated with a wide range of outcomes. Moreover, regarding RADIANT-3, v Liu, Marincola and Oberg (2013) found several clinical benefits of using everolimus over placebo (including 11 months progressionfree survival versus 4.6 months, 5 percent response rate versus 2 percent, and 73 percent stable disease versus 51 percent).

Another study that is related to the current study was conducted by Petrik et al. (2011) with the aim of radiolabeling peptides using a fully automated disposable cassette system in order to produced PET, SPECT, and therapeutic agents. In this study, Petrik et al. (2011) wished to radiolabel DOTA derivatives with 177Lu, 90Y, 68Ga and 11In, and meet both the radiation safety requirements as well as their pharmaceutical requirements. According to Petrik et al. (2011), the system's major components include a syringe pump, a holder, a heater and radiation shielding, which is removable. This system uses an acetate buffer for 68Ga labeling and ascorbate buffer for 177Lu, 90Y, and 111In labeling. On the other hand, use of disposable cassettes and thin-layer chromatography prevented cross-contamination and radiochemical purity, respectively. According to Petrik et al. (2011), the system produced radiolabeled products of over 80 percent radiochemical purity and radiochemical yield respectively. However, the method utilized in this system cannot be generalized to cover other somatostatin analogs as different such analogs have different chemical properties.

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