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Everolimus in treatment of neuroendocrine tumors: efficacy, side-effects, resistance and factors affecting its place in the treatment sequence.

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Abstract

Introduction: Since the initial approval of everolimus in 2011, there have been a number of important changes in therapeutic/diagnostic modalities as well as classification/staging systems of neuroendocrine tumors (NETs), which can significantly impact the use of everolimus in patients with advanced NETs.

Areas covered: The efficacy of everolimus monotherapy and combination therapy demonstrated in clinical studies involving patients with advanced NETs are reviewed. Several factors affecting everolimus' use are described including: the development and routine use of NET classification/staging systems; widespread use of molecular imaging modalities; side-effects; drug resistance; and the availability of other treatment options. Furthermore, the current position of everolimus in the treatment approach is discussed, taking into account the recommendations from the recent guidelines.

Expert opinion: Although everolimus demonstrated its high efficacy and tolerability in the RADIANT trials and other clinical studies, there still remain a number of controversies related to everolimus treatment in the management of NETs. The synergistic anti-growth effect of other agents in combination with everolimus or its effect on overall survival have not been established. The appropriate order of the use of everolimus in the treatment of advanced NETs still remains unclear, which needs to be defined in further studies and will be addressed in the new guidelines.

Keywords

Neuroendocrine tumor (NET); everolimus; mammalian target of rapamycin (mTOR) inhibitor; RADIANT trials

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1. Background

Neuroendocrine tumors (NETs) are rare malignancies derived from the neuroendocrine system throughout the body [1]. The annual incidence of NETs is increasing and was 6.98 per 100,000 persons in 2012 reported from Surveillance, Epidemiology, and End Results (SEER) program[2], with most NETs commonly arising from lung and gastroenteropancreatic (GEP) sites[2,3]. NETs comprise a heterogeneous group of neoplasms with a wide spectrum of clinical and malignant behaviors depending on various clinicopathological factors. NETs are usually indolent by nature and slow growing, however, poor prognosis of those in advanced stage have not improved dramatically until recently[2–4], and thus effective therapeutic options are highly warranted.

The phosphatidylinositol-3-kinase (PI3K)/Akt and mammalian target of rapamycin (mTOR) signaling pathway is well known to play a crucial role in controlling cancer cell-cycle and growth[5], and its activation is involved in the pathogenesis of NETs[6]. Upregulation of mTOR signaling components[7–11], downregulation of its upstream negative regulators; phosphatase and tensin homolog deleted on chromosome 10 [PTEN] and tuberous sclerosis complex 2 [TSC2] [12–14], and genomic mutation of mTOR pathway[15,16] in NETs were reported from numerous groups. The anti-proliferative effect of mTOR pathway inhibition was reported in preclinical models of NETs [12,17], and thus it was a promising therapeutic target[6,18]. The efficacy and safety of everolimus, an oral inhibitor of the mTOR pathway[19], in patients with advanced NETs of different origins was examined in a series of phase II/III clinical studies; RADIANT trials (Table 1) [20–23]. Of these, RADIANT-3 trial was a randomized, double-blind, placebo-controlled, phase III trial that demonstrated significant clinical benefit in the largest number of patients with advanced pancreatic NETs (panNET) [22]. Based on this result, the Food and Drug Administration (FDA) approved everolimus as an anti-tumoral drug for the treatment of panNETs with progressive disease on May 5, 2011, and it is now commercially available in >110 countries.

The purpose of this article is to evaluate at present (7 years post initial approval), the clinical utility of everolimus in NET patients. This is not possible without first considering the advances in the diagnosis and treatment of NETs that are currently influencing anti-tumor treatment approaches to advanced NETs, which have occurred since everolimus' initial approval in 2011 (Table 2). An understanding of these is essential to exploring the current options that are available and the place of everolimus within these for the current treatment of NETs.

Shortly after the approval in May, 2011 of everolimus for treatment of patients with advanced panNETs, sunitinib, an oral multi-targeted tyrosine kinases inhibitor, was shown to have efficacy in patients with advanced panNETs, prolonging progression free survival (PFS) in a phase III trial[24], and it was approved as a standard therapeutic agent in those patients worldwide (Table 2), thus offering an additional treatment choice. Three years later, lanreotide autogel was shown to improve PFS in a phase III trial (CLARINET) in patients with advanced grade 1 or 2 NETs, and it was approved by FDA as an anti-growth therapy in GEP-NET[25](Table 2). Therefore, by 2014, there were three new anti-tumor medications (everolimus, sunitinib, and somatostatin analogues [SSAs]) available to treat patients with

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advanced panNETs, in addition to older therapies such as chemotherapy. In 2016, the RADIANT-4 trial showed the benefit of everolimus in lung and all gastrointestinal (GI) NETs to extend PFS in patients with advanced disease[23], leading to its additional approval for extrapancreatic NETs. In 2018, peptide receptor radionuclide therapy (PRRT) using ^{177} Lutetium (Lu) -DOTATATE was globally approved for the treatment of GEP-NETs[26,27] (Table 2). This approval was based on the results of the phase III (NETTER-1) trial in which ^{177} Lu-DOTATATE markedly extended PFS in patients with advanced somatostatin-receptor (SSTR) -positive midgut NETs with acceptable safety[26], and on data from 504 patients treated with advanced panNETs and other NETs in Rotterdam[27]. In addition, over the last 7 years, therapeutic options have been developed for the treatment of patients with liver predominant metastatic disease from malignant NETs. These treatments include the increasing use of selective internal radiation therapy (SIRT) with ^{90}Yttrium (Y) labeled microspheres to reduce the hepatic tumor burden[28,29](Table 2).

There have also been additional drugs approval to treat the clinical symptoms of functional NETs (F-NETs), such as the carcinoid syndrome or F-panNETs syndromes. In the management of carcinoid syndrome, one new drug became available recently (Table 2). Telotristat ethyl, a peripheral-acting tryptophan hydroxylase inhibitor, which blocks serotonin synthesis, has been shown to cause a significant reduction in bowel movement frequency in a phase III trial (TELESTAR) in patients with carcinoid syndrome[30]. In combination with SSA, it was approved by FDA for the treatment of SSA-refractory carcinoid syndrome in February, 2017 (Table 2). In addition, SSAs such as octreotide and lanreotide have been approved for the treatment of F-NETs, and in a recent phase III trial (ELECT), lanreotide autogel reduced bowel movement frequency in patients with carcinoid syndrome, regardless of primary location (Table 2)[31].

In addition to new treatments for patients with NETs, there was a number of changes in the management of these patients over the past 7 years since the initial approval of everolimus which affect current practices (Table 2). Histopathological classification and TNM staging systems proposed by World Health Organization (WHO), European Neuroendocrine Tumor Society (ENETS) and American Joint Committee on Cancer (AJCC) are now routinely used in clinical practice to predict prognosis and to select optimal treatments. The WHO classification system separates NETs into several groups based on the proliferative index and tumor differentiation assessed by Ki-67 labeling index and mitotic counts, including NET G1, NET G2 and G3 for GEP-NETs[32], and typical carcinoids (TC), atypical carcinoids (AC) and neuroendocrine carcinoma (NEC) for lung NETs[33], respectively (Table 3). The prognostic value of these systems was validated by several studies[34–36], however, heterogeneity remained in the high-grade G3 that showed different prognosis, genetic profiles, and treatment response to platinum-based chemotherapy in different groups of G3 patients[37–45]. To address this issue, the recent 2017 WHO classification for panNETs has divided the G3 group for panNETs into well-differentiated G3 NETs (WDNEC) as a distinct subgroup from poorly-differentiated NEC (PDNEC, Table 2,3)[46]. The use of these classification/grading systems is now mandatory in all recent guidelines, and their widespread use is having an effect on the management of these patients[34–36]. It affects anti-tumor drug use, because cisplatin-based regimens are recommended for G3 NEC and

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the role of everolimus in NET G3 patients, as well as other therapeutic options, in these patients is still being defined.

Diagnostic modalities, especially molecular imaging, have now been validated[1], and are now routinely used with ^{68}Gallium (Ga) -DOTATATE positron emission tomography (PET/CT) imaging receiving FDA approval on June 2016, supported by several studies[47–49] that demonstrated its high sensitivity/specificity for the detection of location and extent of SSTR positive NETs (Table 2). In addition, ^{18}F-fluorodeoxyglucose (FDG) PET is being increasingly used in combination with ^{68}Ga-DOTATATE to define patients with aggressive tumors, usually of high grade (Table 2)[50,51]. These modalities can influence treatment options, because they are better defining the extent of the disease as well as pattern of growth, which can be important in selecting different anti-tumor treatments.

Despite these many recent advances (Table 2), mentioned above, the treatment of advanced NETs still has many unanswered questions. These will be discussed in a separate, later section. Prior to discussion of the current controversies as well as the clinical use of everolimus at present in patients with advanced NETs, the findings from studies of the efficacy/safety of everolimus in these patients will be briefly reviewed.

2. An overview of the current market

As described in depth in the previous background section, since the approval by the FDA of everolimus for its anti-growth effect in patients with advanced panNETs in May 5, 2011, and the subsequent approval for GI and lung NETs in May 26, 2016, there have been numerous changes in the diagnosis and treatment of these diseases which affects the potential use of everolimus at present. These are summarized in Table 2 and includes both the introduction of other anti-tumor agents (sunitinib, lanreotide, PRRT, and liver-directed therapy) and changes in the management of NETs that affect its treatment. These include the demonstration of efficacy of everolimus in controlling the hormone-excess state, as well as changes in tumor imaging and tumor classification which provide prognostic information which can affect the anti-tumor treatment.

3. Introduction to the Compound

As reviewed in the background, numerous *in vitro* and *in vivo* studies in animals with NETs, as well as preliminary human studies (Table 4) provide evidence that the PI3K/Akt/mTOR pathway plays an important role in proliferation of NETs. Everolimus (40-O-[hydroxyethyl]-rapamycin), also known as RAD001, is a rapamycin analog that directly inhibits the mTORC1 pathway by binding to intracellular receptor FK506-binding protein (FKBP-12), which subsequently inhibits activation of its downstream mediators such as p70S6K/4E-BP1 (Box 1)[5,52]. Its efficacy in patients with NETs was established in numerous studies (Table 1,3). Before the approval of everolimus for the treatment of panNETs in 2011, it was already approved by FDA for its anti-growth effect in patients with renal cell carcinoma in 2009[53] and TSC-associated subependymal glial cell astrocytoma in 2010[54], as well as for immunosuppression to prevent organ rejection in kidney transplants recipients in 2010[55], and had proven safe/effective in these patients. Subsequent to its

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approval for patients with advanced NETs, everolimus also received FDA approval for the anti-proliferative treatment of hormone receptor-positive breast cancer (in combination with exemestane)[56] and TSC-associated renal angiomyolipoma[54] in 2012.

4. Pharmacokinetics and Pharmacodynamics

Oral everolimus is rapidly absorbed after oral administration, and reaches a peak serum concentration after 1.3–1.8 hours[57]. Steady-state serum concentrations are reached within a week, and both maximum serum concentration and the area under the curve, increased in a dose-proportional manner[58]. Everolimus is metabolized mainly by cytochrome P450 (CYP) 3A1, 3A5 and 2C8 in the gut and liver, and is a substrate for P-glycoprotein (P-gp). Approximately 98% and 2% of everolimus is excreted in the bile in the form of metabolites and urine, respectively (for detail, see[57]).

5. Efficacy of everolimus

5.1 RADIANT trials (Table 1)

The results of the RADIANT trial series[20–23] and sub-analyses[59–71] are summarized in Table 1. The efficacy of everolimus in NETs was initially investigated in the RADIANT-1 trial, an open-label, phase II pilot dose-finding study involving patients with metastatic, low- to intermediate-grade NETs of pancreas, small bowel, and lung origin[20]. Sixty patients were treated with either everolimus 5 mg or 10 mg in combination with octreotide. Among those received everolimus 10 mg, median PFS was 72 weeks, and 30% achieved a partial response[PR]. Based on these results, further phase III studies with large number of patients with NETs were carried out.

The RADIANT-2 trial was an international randomized, double-blind, placebo-controlled phase III trial that compared everolimus plus octreotide and octreotide alone in 426 patients with NETs with carcinoid syndrome[21]. PFS in everolimus arm was 5.1 months longer than the control arm with a 23% risk reduction of disease progression, but prolongation of PFS did not reach the predefined level of statistical significance ($P = 0.026$ reached, needed $P = 0.024$) (Table 1). This result may have been affected by the imbalance of patient characteristics between the everolimus and the control arms (i.e., WHO performance status, lung origin). Several sub-group analyses were performed from the results of the RADIANT-2 trial (Table 1)[59–64]. Although the numbers were small, everolimus plus octreotide demonstrated superior anti-tumor activity in patients with lung[60] and colorectal NETs[61]. Another sub-group analysis showed the efficacy of everolimus regardless of prior SSA exposure[62]. These results suggest that everolimus may be beneficent in patients with extrapancreatic NETs.

The RADIANT-3 trial was an international randomized, double-blind, placebo-controlled phase III trial involving patients with advanced panNETs. Patients were randomized (1:1) to receive everolimus or placebo plus best supportive care, including concomitant SSA use in 40% of patients[22](Table 1). Everolimus significantly prolonged PFS (11.0 vs 4.6 months), representing 65% risk reduction of PFS. Sub-group analyses revealed that prolonged PFS with everolimus treatment was irrespective of WHO performance status, age, sex, ethnicity,

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tumor grade, and prior chemotherapy/SSA therapy[22,66,67]. Everolimus treatment was associated with low objective response rate (ORR 5% [i.e. sinficant decrease in tumor size by RECIST criteria]), however, patients treated with everolimus achieved a high rate of disease stabilization (i.e. stable disease (SD) achieved in 73%, Table 1). The final analysis of overall survival (OS) showed a 6.3 month prolongation in the everolimus arm (44.0 vs 37.7 months), however, this difference was not statistically significant, likely due to the high proportion (85%) of patients in the placebo arm who crossed over to everolimus treatment after disease progression.

The RADIANT-4 trial was an international randomized, double-blind, placebo-controlled phase III trial that studied everolimus efficacy in 302 patients with advanced GI and lung NETs without carcinoid syndrome (Table 1)[23]. Everolimus significantly improved the median PFS by 7.1 months compared to placebo (11.0 vs 3.9 months), with risk reduction of disease progression or death by 52%. High disease stabilization was observed in the everolimus arm (81%), which was comparable to that reported in the RADIANT-3 trial[22]. Sub-group analyses showed clinically meaningful anti-tumor activity of everolimus regardless of its primary site[68,69] and prior therapies[70].

5.2 Other phase I/II trials and retrospective studies related to efficacy of everolimus (Table 4)—Table 4 summarize the results of other phase I/II studies in NETs related to the efficacy of everolimus, commonly combined with SSA[72–75,75–79], which were performed following the evidence from preclinical studies that showed enhanced anti-tumor effect of everolimus in combination with SSA[80–82].

An open-label phase II study assessed the efficacy of everolimus in 160 patients with advanced panNETs who progressed after prior systemic chemotherapy[72]. In a total of 45 patients who were taking octreotide for at least 3 months at study entry (documentation of disease progression was required), when treated with everolimus plus octreotide, the median PFS and ORR were 16.7 months and 4.4%, respectively. In 115 patients who were not being treated with octreotide, everolimus responses for PFS and ORR were 9.7 months and 9.6%, respectively[72]. Another multicenter phase II trial with a single arm everolimus plus octreotide treatment in a first-line setting was reported from Italian group[73,74]. Among 50 patients with GEP and lung NETs, ORR was 18%, and median time to progression(TTP) and OS were 33.6 months and 61.0 months, respectively[73,74]. Although the patient numbers included in these studies were small, these studies raise the possibility that the use of octreotide combined with everolimus may have additional anti-tumor benefit in NETs, similar to the results shown in the RADIANT-2 trial[21].

A number of studies have examined the efficacy of everolimus with other non-octreotide anti-tumor agents (Table 4). Theses includes the combination of everolimus with pasireotide[75–77,79], bevacizumab[75], SIRT[79], temozolomide[83], sorafenib[84], or PRRT[85](Table 4). In a phase I study of pasireotide plus everolimus in 22 patients with GEP and lung NETs[77], the PFS at 6 months was 76%. Disease stability was achieved in 90%, and 81% showed some tumor shrinkage (which did not meet the RECIST PR criteria [less than 30% decrease in tumor size])[77]. In the COOPERATE-2 trial, an open-label phase II study[75], 160 patients were randomized to everolimus plus pasireotide or

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everolimus alone. The primary endpoint was PFS, but the addition of pasireotide to everolimus failed to show significant superiority in the prolongation of PFS compared to everolimus alone (16.8 vs 16.6 months)[75]. The LUNA trial was a three-arm, randomized, open-label phase II study comparing everolimus plus pasireotide with either agent alone in 112 patients with advanced lung or thymus NETs[76]. All three arms achieved the pre-planned statistical objective of a 9-month PFS rate >20%, with a median PFS of 11.8, 12.5 and 8.5 months in combination arm, everolimus arm, and pasireotide arm, respectively[76]. Taken together with the higher ORR observed in the combination therapy in the COOPERATE-2 (20% vs 6%)[75], combination therapy of pasireotide plus everolimus may have enhanced activity in panNETs and extrapancreatic NETs. Further studies are warranted to elucidate the synergistic effect of these agents.

Other phase I/II trials have investigated the efficacy of other therapeutic agents alone or in combination with everolimus (Table 4) [75,78,83–87]. Of these, the CALGB 80701 trial was a randomized phase II trial that compared the vascular-endothelial growth factor (VEGF) inhibitor, bevacizumab, plus everolimus and everolimus alone in panNETs[75]. Despite encouraging results from preliminary phase II studies[88–90], the results of this study were disappointing in not showing enhanced value of bevacizumab[75]. Accordingly, bevacizumab plus everolimus showed a 2.7 months prolongation in PFS compared to everolimus alone ($P = 0.12$). Significantly higher ORR were also observed[75] (Table 4), which is consistent with another study evaluating efficacy of temsirolimus combined with bevacizumab in panNETs (ORR 41%) [88]. Although prolongation in PFS was deemed statistically significant (pre-determined P value threshold; 0.15), this was not a clinically satisfying improvement. The high type I error rate of this study design requires further well-designed trial to confirm the true efficacy of this combination therapy. Other studies showed the positive results of everolimus combination therapy in the small number of patients with other therapeutic agents including temozolomide[83], PRRT[85], and SIRT[79], and further studies were planned in some cases.

Since the global approval of everolimus, numerous retrospective studies from various countries have reported the efficacy of everolimus in NETs in the real clinical practice, particularly in those of GEP origin (Table 5)[91–100]. Overall, the median PFS (12–27.5 months) and ORR (0–28%) among these study populations were similar or superior to those reported in RADIANT-3 trials[22]. In addition, several patients remained on treatment more than 5 years after everolimus initiation[94,101]. Clinically meaningful prolonged PFS reported from these studies might contribute to the improvement of OS[102]. Considering that the anti-tumor activity of everolimus is mainly presented as high disease stabilization, long-term continuation of everolimus might be important in maximizing its efficacy. Although several limitations such as study design and small number of patients could have overestimated everolimus's efficacy, these results were important in supporting the conclusion that everolimus can provide significant and prolonged clinical benefit not only in the clinical trials but also in the real-world clinical setting.

5.3 Efficacy of everolimus in functioning NETs—A number of studies demonstrated in some patients with refractory F-NETs, everolimus may be helpful for

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treatment of hormone-excess state, independent of its anti-growth effect[103], which will be discussed in more detail below.

To understand the possible importance of everolimus for control of symptoms in F-NET patients, the current treatment options need to be briefly reviewed. In the management of F-NETs, control of the hormone hypersecretory syndrome is a key factor for maintaining quality of life (QOL) and also survival in many cases[103,104]. Carcinoid-syndrome is the most frequent ectopic hormonal syndromes in NETs[104], and SSA is the standard initial treatment [104–106]. In the recent phase III TELESTAR trial, telotristat ethyl, a peripheral tryptophan hydroxylase inhibitor, in combination with SSA demonstrated significant reduction in bowel movement frequency in NETs with SSA refractory carcinoid syndrome[30]. For some of the other F-NET symptoms, there are reports of the effectiveness of everolimus when other antisecretory therapies fail. In Zollinger–Ellison syndrome (ZES) in patients with gastrinomas, which invariably have hyperchlorhydria/gastrin hypersecretion [107–109], the standard therapy for control of the hypersecretion is the use of proton pump inhibitors (PPIs), occasionally high-dose histamine H_2 receptors, and rarely SSA[110–113]. These are generally successful in all patients, thus everolimus is not needed to control the acid hypersecretion in these patients[110,113,114]. Most patients with insulinomas are cured surgically, thus the medical therapy of the hormone-excess state is usually only needed during the preoperative period or the small percentage with malignant tumors(5–15%) [103,114,115]. The primary treatment is frequent small feedings and the use of diazoxide and SSA[103,111], however, SÁ can cause severe hypoglycemia by attenuating counter-regulatory hormone release[116]. In patients with malignant insulinomas, control of the hypoglycemia can be difficult and may not be satisfactory[103,114,115]. VIPomas are uncommon, but the hormone excess state can be difficult to treat. The first option is SSA, however, continuation may lose its effectiveness and additional treatment is needed[103,111].

Some reports and small series provide evidence that everolimus can be helpful in some patients with refractory F-NET symptoms[103]. Recently, the effect of everolimus on gastrin levels was reported in patients with panNETs from RADIANT-1 and RADIANT-3 trials [117]. Accordingly, everolimus rapidly reduced median gastrin levels to approximately 60% in the RADIANT-1 trial and by greater than 50% in the RADIANT-3 trial (everolimus vs placebo, $p < 0.001$), respectively. In addition, these down-regulatory effects of everolimus were irrespective of prior or concomitant SSA use. Whether this will also apply to ZES patients is unclear. Several studies in small number of patients and case reports also indicated the usefulness of everolimus in controlling carcinoid syndrome[118,119]. Inhibition of mTOR pathway was reported to attenuate insulin secretion in an insulinoma cell line[120]. Furthermore, everolimus controlled hypoglycemic symptoms in patients with insulinomas[103,121,121–127].

5.4 Efficacy of everolimus in G3 NETs/NEC—Chemotherapy with platinum-based regimens is widely accepted as a standard treatment among patients with PDNEC[1,128]. In contrast, patients with WDNEC/G3 NETs usually do not responds well to this chemotherapy regimen[37–41], and the best treatment as for this group of patients is not resolved. In a retrospective study including 15 patients with well to moderately differentiated panNET G3

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treated with everolimus, median PFS and OS were 6 and 28 months, respectively, and 40% achieved disease stabilization for >1 year [129]. Other groups also reported the favorable response to everolimus in small number of patients with panNET G3[42,94,130–132]. Taken together, everolimus could be a potential anti-tumor therapy in panNET G3 as well as possibly extrapancreatic WDNEC.

With respect to the PDNEC, several immunohistochemical analyses reveal high expression and activation of mTOR [7,133], and an anti-proliferative effect of everolimus was shown in a preclinical study[134]. A case study reported a patient with PDNEC who was successfully treated with everolimus for 15 months[135]. Although everolimus alone had limited efficacy[136], combination therapy with paclitaxel showed preliminary anti-tumor activity in patients with previously treated small-cell lung NEC[137]. In a phase II trial, everolimus combined with paclitaxel and carboplatin was active in 49 patients with large-cell lung NEC[138]. Accordingly, the median PFS, OS and ORR were 4.4 months, 9.9 months and 45%, respectively. Considering the poor prognosis due to its aggressive nature of PDNEC[139], further studies are warranted to evaluate possible synergistic effects of everolimus with platinum-based regimen in PDNEC.

6. Markers predicting efficacy of everolimus

The recent increase in therapeutic options for patients with advanced NETs show variable responses in different patients, and thus have raised the importance of biomarkers in predicting response to treatment that could enable optimal treatment selection and change in therapy[140]. In the RADIANT-1 trial, early response in serum chromogranin A (CgA) or neuron-specific enolase (NSE) levels was a significant predictor for prolonged PFS with everolimus treatment[72]. In addition, elevated baseline CgA and NSE levels were associated with shorter PFS and OS with everolimus treatment[141]. Similarly, sub-analysis of RADIANT-3 trial also showed that high baseline CgA, NSE, placental growth factor (PIGF) or soluble vascular endothelial growth factor receptor 1 (sVEGFR1) levels were associated with poor OS[65], however, baseline CgA levels were not predictive for everolimus treatment effect on OS in the RADIANT-2 trial[59]. Another study genotyped the fibroblast growth factor receptor 4 (FGFR4) using DNA isolated from tissue or blood in panNETs, and found that patients homozygous for FGFR-G388 demonstrated greater tumor shrinkage with everolimus treatment than those harboring only one FGFR4-R388 allele[142]. Although longer PFS and OS were also observed in those homozygous for FGFR4-G388, these were not statistically significant due to small number of patients, which is consistent with the result from another group showing that FGFR4 polymorphism did not have predictive value on everolimus treatment[143].

The efficacy of other markers, specifically the components of mTOR pathway, has been evaluated by several groups. In 17 patients with NETs treated with everolimus and octreotide, high tumor p-Akt levels in pre-treatment ($R = 0.476$, $P = 0.053$) and on-treatment ($R = 0.604$, $P = 0.015$) tumor biopsy specimens correlated with longer PFS[144]. In an immunohistochemical analysis of bronchial NETs in 21 patients, protein levels of the total and phosphorylated form of mTOR and its component (p70S6K [ribosomal protein S6 kinase, 70 kDa], Akt and ERK 1/2) were upregulated in everolimus sensitive patients

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compared to everolimus resistant patients[145]. The efficacy of monitoring intra-tumor p-p70S6K [80,146–148] was suggested by other groups, however, the relationship to PFS and tumor response with everolimus were conflicting. Other clinicopathologic factors including histological grade [22,93–95], Ki-67 index[91,94] and hepatic metastasis burden[93] were also reported to affect PFS of everolimus treatment. In addition, the results of imaging modalities, such as ^{89}Zirconium (Zr)-bevacizumab PET[149] and perfusion CT[96], in predicting response to everolimus was suggested by several groups. Furthermore, patients experienced stomatitis within 8 weeks of everolimus initiation had longer PFS than those without stomatitis in the RADIANT-3 trial (13.9 vs 8.3 months, hazard ratio [HR] 0.70) and in RADIANT-2 trial (HR 0.87) [150]. Similar to this, occurrence of hypercholesterolemia was also suggested as a possible marker of response[146].

7. Safety of everolimus (Table 6)

Treatment with everolimus is well known to cause a spectrum of adverse events (AEs) in various patients. According to meta-analyses including patients with NETs, treatment with everolimus as well as other mTOR inhibitors, is most commonly associated with an increased risk of stomatitis [150–153], rash[151,154], fatigue[155], infection[156], pulmonary toxicities [152,157,158], hyperglycemia[155,159], anemia[160,161], and thrombocytopenia[160]. The pharmacokinetic analysis of RADIANT-2 trial also revealed that an increased everolimus minimum concentration was associated with higher risk for pulmonary and metabolic events[64]. In addition, the development of severe AEs, such as infection and pneumonitis[162], could result in treatment discontinuation[163] and fatal outcome[162,164]. The frequencies of common AEs associated with everolimus treatment observed in the previous studies were listed in Table 6. The majority of AEs in the different studies were mild to moderate, and treatment-related mortality did not occur in most of the studies (Table 6). Pulmonary toxicity (n=5) and infection/sepsis (n=3) were the most common fatal AEs that caused everolimus-related death[22,23,75,76,93]. Though patient-reported tolerance with everolimus treatment was reported to be poorer than SSA[165], health-related QOL was well maintained in large clinical trials[71,79,166]. These results strongly support the general tolerability of everolimus by most patients in both the clinical trial setting and real-world setting.

However, everolimus-associated AEs can be significant and have led 5–35% of patients to treatment discontinuation (Table 7). In addition, dose reduction and/or interruption are frequently (13–100%) required to control the severity of the AEs (Table 7). Like other targeted agents, the importance of appropriate dose modification for the management of everolimus-associated AEs has been emphasized, especially for the long-term continuation of everolimus[94]. This is in line with the pharmacokinetic analysis including patients with NETs that showed significant correlation between elevated everolimus trough concentration (C_{min}) and increased risk of toxicity[152,167]. Regarding efficacy, higher C_{min} were associated with improved tumor size reduction[152], whereas lower C_{min} increased risk of progression[167]. It was reported that patients with high cumulative dose (>3000 mg) and dose intensity (> 9 mg/day) of everolimus experienced significantly longer OS[92]. Although dose intensities were reported to be well maintained in most previous studies[21,72,73,75,76,85], therapeutic drug monitoring (TDM) may be useful in prevention

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of developing severe AEs without lowering the efficacy of everolimus[167], in addition to the patients' education and physicians careful monitoring[168].

8. Mechanism of resistance to everolimus

Despite the high anti-tumor activity of everolimus, disease progression can occur early after everolimus initiation in some patients, and even in those who once experienced tumor response with everolimus treatment. In the previous studies, up to 57% of the patients terminated everolimus treatment due to disease progression (Table 7). Primary resistance, as well as acquired (secondary) resistance to everolimus is thought to play a role, thus understanding and overcoming the mechanisms underlying everolimus resistance may prove important in preventing patients from treatment discontinuation due to disease progression.

mTOR is the core components of 2 complexes, mTORC1 and mTORC2, which have distinct signaling pathways and functions[19,169]. The activation of mTORC1 subsequently phosphorylates its downstream p70S6K and 4E-BP1[5,52]. Everolimus specifically directly inhibits the mTORC1 and its downstream p70S6K/4E-BP1[170,171], resulting in attenuation of protein synthesis as well as cell growth[12,52,147,148]. The PI3K/Akt/mTORC1 pathway is normally regulated by in part from its upstream insulin-like growth factor 1 (IGF-1) receptors with IGF-1-dependent activation of the PI3K/Akt pathway leading to inhibition of signaling due to mTOR-mediated phosphorylation and degradation of insulin receptor substrate-1 (IRS-1) [80,81,172,173].

Suppression of these feedback loops by inhibiting mTORC1 causes over-activation of upstream signaling, including PI3K/Akt[174,175]. Several studies showed that everolimus may only partially inhibit mTORC1 and incompletely block its certain downstream target, especially 4E-BP1[176,177]. The inability of everolimus to block mTORC2 induces upstream Akt phosphorylation[19,170,178,179]. In addition, a genetic mutation in FKBP12 is reported to affect the sensitivity of mTOR inhibitor[180]. Other mechanisms of resistance to mTOR inhibitors have also demonstrated including; activation of mitogen activated protein kinase(MAPK); up-regulation of pro-angiogenic factors; and activation of Ras pathway[92,174,181,182]. All these mechanisms potentially counteract the anti-proliferative effects of mTORC1 inhibitors and lead to drug resistance[80,172,173].

Consistent with this hypothesis, histopathological analyses and preclinical studies reveal the increased activation of Akt in everolimus-sensitive cell lines and patients[80,144,183]. On the other hand, several studies have showed contrary results that high p-Akt levels were significantly associated with poor survival with everolimus treatment[9,12]. In addition, overexpression p70S6K was reported to be associated with shorter PFS[10,146]. Discrepancies between these studies may partly result from the small number of patients, and due to the heterogeneity in patient's background, especially their genetic profile[8,16,145,184].

Emerging evidence shows that dual inhibition of these pathways, particularly PI3K/Akt and the mTOR pathway, could be a novel therapeutic approach to overcome everolimus resistance [6,178,183–187]. The efficacy and safety of the dual PI3K/mTOR inhibitor,

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BEZ235, was examined in patients with advanced NETs[86,188,189]. In a phase II trial, 62 patients with mTOR inhibitor-naïve advanced panNETs were randomized to receive BEZ235 (n=31) or everolimus (n=31)[86]. Unfortunately, BEZ235 did not demonstrated superior efficacy compared with everolimus (Table 4). Despite the acceptable tolerability observed in a phase I trial in patients with advanced solid tumors[188], high toxicity of BEZ235 observed in this study led patients to require frequent dose modifications and treatment discontinuations. As a result, the shorter treatment duration of BEZ235 compared to everolimus (22.9 vs 39.4 weeks) might have negative impact on its anti-tumor activity. Poor tolerability of BEZ235 was also reported from a single-arm phase II trial in advanced patients with everolimus-refractory panNETs[189], which has led to its development being stopped. Further studies using other agents with better tolerability are warranted to clarify the effect of pan-PI3K inhibitors against resistance to everolimus.

9. Controversies in everolimus treatment in advanced NETs

9.1 General

To discuss the current controversies involving everolimus as well as the later discussion on expert opinion, some additional information related to current efficacy of competing therapies and current guideline recommendations are needed and will be briefly covered below.

9.2 Current efficacy of various therapeutic modalities

In general, prolonged treatment of NETs requires a multidisciplinary approach which may include biotherapies, targeted therapies, chemotherapies, liver directed therapies, and radiotherapies.

SSAs are generally the initial therapeutic agents used to control the tumor growth, in addition to the hormone excess symptoms as mentioned earlier, not only because they are effective, but they are well tolerated, as shown in a recent survey of patient-reported outcomes[165]. The anti-growth effects of octreotide have been shown in 2 phase III trials. In the PROMID trials, octreotide demonstrated prolonged TTP (14.3 vs 6.0 months, HR 0.34, $p < 0.001$) in patients with well-differentiated small intestine NETs[190]. Lanreotide autogel also showed further prolonged PFS in the CLARINET study (not reached vs 18.0 months in placebo arm, HR 0.47, $p < 0.001$) in NETs originated in pancreas, midgut and hindgut[25]; however, it is important to mention that 96% of the patients did not have disease progression in the 3–6 months before randomization. These studies demonstrated the efficacy of SSAs to control tumor growth in both advanced panNETs and GI-NETs.

In the pivotal phase III trial including 171 patients with advanced panNETs[24,191], sunitinib demonstrated significant improvement in PFS (11.4 versus 5.5 months, HR 0.42, $p < 0.001$) and a trend in prolongation of OS (38.6 vs 29.1 months, HR 0.73, $p = 0.094$) versus placebo. This study supports the use of sunitinib in advanced panNETs only.

Recently, a markedly prolonged PFS (estimated PFS rate at 20 months; 65.2% vs 10.8%) and high ORR (ORR 18% vs 3%, $p < 0.001$) of PRRT/octreotide compared to octreotide alone were shown in the phase III NETTER-1 trial in patients with advanced midgut

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NETs[26]. Because of the additional data showing efficacy/safety from the large, single-group trial (non-prospective) in 310 patients with advanced GEP-NETs (ORR 29%)[27] from the Rotterdam studies, the FDA approved ^{177}Lutetium-DOTATATE for both panNETs and GI-NETs.

The efficacy of streptozotocin- and temozolomide-based regimens in patients with advanced panNETs, especially in causing tumor reduction (range 28–70%), were confirmed by several retrospective studies and small numbers of patients in prospective studies[115,192–195]. Other studies demonstrated the possible activity of temozolomide-based chemotherapies in patients with extrapancreatic NETs, specifically originated from bronchus[196] and thymus[197]. Therefore, the high cytotoxic effect of chemotherapy may be beneficial in these patients with high tumor burden. However, it should be noted that almost all studies report lower response rates of GI-NETs to temozolomide-based chemotherapies compared to panNETs (ORR 0–7%) [90,198].

Liver directed therapies, including transarterial embolization/chemoembolization and SIRT using ^{90}Y-microspheres, are also generally used for the treatment of liver-dominant metastases and high tumor burden[28,29]. Although high level evidence (i.e., randomized, placebo-control, phase III trial) has been lacking, these options can provide clinically significant benefit in a subset of patients, particularly for those with progressive disease[199].

Surgical removal of advanced NETs is recommended whenever possible[1,200–204]. The effect of this in subsequent treatment with other anti-tumor options has in general not been well studied.

All of the above therapeutic options are well to moderately tolerated[24–29,190,192–194]. Similar to everolimus, treatment with sunitinib had no impact on health-related QOL in a recent phase III trial involving patients with advanced panNETs[205]. Furthermore, SIRT[79] and PRRT[206] were reported to improve QOL in patients with advanced NETs. On the other hand, patient-reported tolerance was reported to be poor with sunitinib, intravenous chemotherapy, and liver directed therapy, whereas PPRT had better tolerance compared to SSAs[165].

9.3 Current position of everolimus; recommendations from guidelines

Since the initial approval of everolimus in 2011, guidelines provided from several scientific societies have been updated reflecting recent advances in the treatment of NETs. In this section, important changes in the latest guidelines were reviewed and highlighted, especially by focusing on the position of everolimus.

According to the latest ENETS consensus guideline published in 2016[207], everolimus is generally recommended as second-line therapy after failure of SSA or cytotoxic chemotherapy in panNETs. However, it can be considered as first-line therapy if SSA is not an option, and if systemic chemotherapy is not clinically required, not feasible, or not tolerated. Similarly, in GI-NETs, everolimus may be used as a second-line therapy after failure of SSA or as a third-line therapy after failure of PRRT[207]. Due to the lack of

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approved therapeutic drugs in advanced lung NETs, everolimus is recommended as a first-line therapy in progressive disease, unless SSA may be considered as a first-line therapy (e.g. G1, TC, slow growth, strong SSTR expression)[207]. In these guidelines, the combination therapy of everolimus plus SSA for anti-proliferative purpose is not recommended in nonfunctional NETs regardless of their primary sites[207].

The National Comprehensive Cancer Network (NCCN) guidelines was upgraded in 2017 (version 3. 2017) [208]. In the treatment algorithm regarding panNETs, everolimus alone was recommended as second-line therapy after SSA failure, in patients with symptomatic, or clinically significant tumor burden/progressive disease. In GI-NET, everolimus is also recommended as second-line therapy after progression with SSA regardless of its clinical behavior[208]. Similar to the ENETS guidelines, everolimus with or without SSAs was recommended as first-line treatment of lung and thymus NETs in patients with AC or TC with high tumor burden[208]. All these recommendations were categorized as 2A (i.e. the intervention is appropriate based upon lower-level evidence).

In 2017, the North American Neuroendocrine Tumor Society (NANETS) provided consensus-based guidelines for the treatment of advanced midgut NETs[106]. Although SSAs are the generally recommended initial therapy, everolimus, as well as liver embolization, can be considered as first-line therapy in patients who are not indicated for radiolabeled SSAs (i.e. weak or absent SSTR expression). Everolimus is also recommended as an appropriate therapy in patients presenting massive extrahepatic metastases with weak/absent SSTR expression. The guidelines note that possibly stronger evidence of everolimus efficacy in non-midgut NETs (the majority of patients in the RADIANT-4 trial) than in midgut NETs (the majority of patients in the RADIANT-2 trial) should be taken into account when deciding second-line treatment after SSAs[106].

Similarly, consensus guidelines from Nordic neuroendocrine group in 2014[209] and Canadian experts in 2015[202] also considered everolimus as second-line treatment in panNETs and GI-NETs with progressive disease on SSAs. In the European Society of Medical Oncology (ESMO) guideline in 2012[203], SSAs are the standard recommended first-line treatment, whereas the treatment algorithm shows everolimus as first-line therapy in panNETs G1/2 (Ki-67 2–20%) and GI-NETs (Ki-67 10–20%).

When interpreting these recommendations, it should be noted that some of these guidelines were published several years ago[202,203,209,210], thus do not reflect the important findings from recent clinical trials, specifically RADIANT-4 and NETTER-1 trials, as well as other important changes in management of NETs patients listed in Table 2, which can strongly affect the current position of everolimus.

With respect to F-NETs, a number of guidelines shows the efficacy of everolimus in controlling symptoms of hormone-excess state in a number of F-NETs including insulinomas, and carcinoid syndrome[103–105,208–210]. In these patients, it is usually used when SSAs and other approved therapies have failed. The NANETS guidelines in 2017 also concluded that everolimus should be considered an option for patients with progressive midgut NETs, even if there is a history of carcinoid syndrome[106].

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Common recommendation for the standard treatment of G3 NEC (PDNEC) is systemic platinum-based chemotherapy [128,202,203,207,208,211]. Because the disease concept of WDNEC/NET G3 was recently established, high-level evidence is lacking for the preferred treatment in these patients. However, several guidelines proposed that temozolomide-based chemotherapy[207] and PRRT[212] may be potential treatment options. Even though everolimus has been successful in some patients with G3 tumors, no guidelines have made a recommendation for everolimus use in these patients.

10. Regulatory affairs

For the patients with NETs, everolimus (AFINITOR®) has been approved by the FDA for the treatment of panNETs on May 5, 2011, and for GI and lung NETs on May 26, 2016, respectively. The initial dose of AFINITOR® is 10 mg, to be taken once daily at the same time every day, either consistently with food or consistently without food. Dose reduction is recommended for patients with hepatic impairment depending on its severity and those who required co-administration of moderate inhibitors of CYP3A4 and/or P-gp. If patients require concomitant use of strong CYP3A4 and P-gp inducers, increase dose using increments of 5 mg or less increments to a maximum of 20 mg/day. Dose reduction is also used in controlling side effects.

11. Conclusion

Everolimus is a key therapeutic agent in the treatment of advanced NETs, which covers the spectrum of this heterogeneous groups of neoplasms, regardless of its primary site, histological grade, functional status, and radiological aggressiveness. Further studies are required to define its efficacy and safety in combination with other agents, mechanisms of resistance, and to better define its place in the current treatment options with the recent release of other anti-tumor agents such as PRRT.

12. Expert opinion

The RADIANT trials have corroborated the basic science results, isolated cell studies and studies in animals showing the anti-growth mechanisms of everolimus on NETs, and established its efficacy in patients with advanced NETs[20–23]. However, there still remain a number of controversies related to everolimus treatment in the management of NETs.

Despite the clinically meaningful prolongation of PFS with everolimus treatment demonstrated in the RADIANT trials, its effect on overall survival has not yet been established[22,23]. Treatment of advanced NETs requires a multidisciplinary approach, thus appropriate timing for everolimus initiation is important to evaluate long-term outcome. The exact order of the use of everolimus in the treatment cascade of patients with advanced NETs is at present unclear and being affected by a number of factors, such as the recent widespread use of WHO classification with its prognostic value and importance in treatment selection; everolimus's effectiveness in combination with other anti-tumor treatments; the recognition of long-term potential resistance to everolimus and other targeted therapies; side effects of long-term everolimus treatment; and the increasing development of competing

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therapies. The use of biomarkers that predict the sensitivity and response to each treatment could be useful in selecting optimal therapeutic options, however, their utility in real clinical practice is so far, not clear.

In recent guidelines, everolimus is generally recommended as second-line therapy behind SSAs[201–203,207–209], because of the low toxicity with high tolerability of SSAs treatment[165]. At present, everolimus is one of the most frequently used second line treatments in patients presenting clinically significant tumor burden and disease progression on SSAs. Other competing therapeutic agents including sunitinib for panNETs, PRRT, chemotherapy, and liver directed therapy for panNETs and other NETs, may also be indicated in these settings[201–203,207–209]. Of these, the recent approval of PRRT is most likely to change everolimus's order in the anti-tumor therapeutic approach. PRRT results in a longer PFS than everolimus, is well-tolerated by patients, a significant percentage of patients show a cytotoxic effect with reduced tumor burden[26,27], and thus it will likely have a significant impact on the use of cytostatic agents including everolimus and sunitinib, especially in patients with aggressive tumors. Severe AE/toxicity of PRRT is reported to be low (1–2%) (leukemia, myeloproliferative effects) [26,27,213]. With PRRT's general availability and use in all groups of NETs, AE/toxicity will be better defined, and this could play a role in its general use and the position of everolimus in the treatment sequence. It should be noted that most guidelines have not reflected the recent availability of PRRT, shown in the NETTER-1 trial and other recent studies[202,203,209,210].

The underlying mechanisms of primary and/or acquired resistance to everolimus occurring in as many as 17–90% of patients stopping treatment due to loss of efficacy is not entirely clear (Table 7) [80,172,173]. It has a strong impact on the long-term continuation of monotherapy with everolimus, as well as combination and subsequent treatment with other therapeutic agents. Emerging evidences from the preclinical studies have shown a number of likely mechanisms of resistance to everolimus, and several potent agents with or without combination with everolimus have been examined in clinical trials for the purpose of overcoming the resistance to everolimus as well as adding a synergistic anticarcinogenic effect. Some of these show encouraging results, however high toxicity may limit their anti-tumor effect[86,189]. The efficacy of combination therapy with everolimus still needs to be explored more widely in further studies.

It is reported that percentage of patients, which is generally low, stopped everolimus treatment in various regimens owing to AEs (Table 7). Everolimus is generally well tolerated, and most of these AEs/side effects are manageable with dose reduction and interruption. In contrast, decreased dose intensity of everolimus may impair its anti-tumor activity. Balancing the anti-tumor activity and treatment-associated toxicity, as well as maintaining QOL is important in term of long-term continuation. Although it is not required in the real clinical practice, therapeutic drug monitoring may provide important information in this regard[167], as recommended for the use of immunosuppressants after organ transplantation[214]. Development of severe AEs, especially pulmonary toxicities and infections (Table 7)[22,23,75,76,93], can result in fatal outcomes, thus screening of occult infections and pulmonary function is mandatory before everolimus initiation. Adequate control of comorbidities, such as diabetes and hyperlipidemia, could also prevent patients

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from unnecessary treatment discontinuation. From this viewpoint, one possible strategy for treatment decision-making could be based on patient tolerance, comorbidities, and toxicity profiles. Specifically, everolimus is not indicated in patients with impaired pulmonary function, uncontrolled infections and metabolic disorders[152,155–159].

Although a number of unanswered questions remained in this area, in the near future with more widespread use of PRRT and other treatment options, it is likely new guidelines will become available addressing some of these issues.

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Table 1.

RADIANT 1–4; studies related to the efficacy of everolimus in NETs and sub-analyses

Study, phase (year)	n	Treatment (n)	Population (n) [comment]	Progression-free Survival (PFS)	Overall Survival (OS)	Objective response rate (ORR)	Stable disease
RADIANT-1, phase II; Yao *et al* (2008)[20]	60	Eve 5 or 10 mg + Oct (n=30, each)	Low- to intermediate-grade NET; pancreas (n=29), small bowel (n=16), lung (n=4)	60 weeks (72 weeks for 10-mg cohort)	Not reached (3-yr: 78%)	22% (30% PRs in 10-mg cohort)	70% (67% in 10-mg cohort)
RADIANT-2, phase III; Pavel *et al* (2011)[21]	429	Eve + Oct (n=216) *vs* placebo + Oct (n=213)	NET with carcinoid syndrome; small bowel (n=224), lung (n=44), colon (n=28), pancreas (n=26)	16.4 *vs* 11.3 mo (HR 0.77, $p = 0.026$)	Not reached (HR 1.22)	2% *vs* 2%	84% *vs* 81%
Sub-analysis; Pavel *et al* (2017)[59]	429	Final OS	[High baseline CgA level was associated with poor prognosis, but not predictive for Eve effect on OS]	-	29.2 *vs* 35.2 mo (HR 1.17)	-	-
Sub-group analysis; Fazio *et al* (2013)[60]	44	Eve + Oct (n=33) *vs* placebo + Oct (n=11)	Lung NET (n=44)	13.6 *vs* 5.6 mo (HR 0.72, $p = 0.228$)	-	(Tumor shrinkage [a]; 67% *vs* 27%)	-
Sub-group analysis; Castellano *et al* (2013)[61]	39	Eve + Oct (n=19) *vs* placebo + Oct (n=20)	Colorectal NET (n=39)	29.9 *vs* 6.6 mo (HR 0.34, $p = 0.011$)	-	(Tumor shrinkage [a]; 67% *vs* 37%)	-
Sub-analysis; Anthony *et al* (2015)[62]	429	Comparison of previous SSA use (n=339) with SSA-naïve (n=90)	[Previous SSA use did not affect PFS]	SSA(+); 14.3 *vs* 11.1 mo SSA(−); 25.2 *vs* 13.6 mo	-	-	-
Sub-analysis; Strosberg *et al* (2015)[63]	196	Efficacy of Oct; comparison of previous SSA use (n=155) with SSA-naïve (n=41)	NET in placebo arm (n=196); midgut (n=143), foregut (n=32), hindgut (n=21)	SSA(+); 11.1 mo SSA(−); 13.6 mo (22.2 mo for SSA-naïve midgut NET)	SSA(+); 33.5 mo SSA(−); 50.6 mo	-	-
Sub-analysis; Pavel *et al* (2017)[64]		Effect of Eve co-administration on Oct pharmacokinetics	[Co-administration of Eve and Oct increased C_{min} of Oct, but did not impact efficacy]	-	-	-	-
RADIANT-3, phase III; Yao *et al* (2011)[22]	410	Eve (n=207) *vs* placebo (n=203)	panNET	11.0 *vs* 4.6 mo (HR 0.35, $p < 0.001$)	Not reached	5% *vs* 2%	73% *vs* 51%
Sub-analysis; Yao *et al* (2016)[65]	410	Final OS	[High baseline CgA, NSE, PIGF and sVEGFR1 levels were associated with poor OS]	-	44.0 *vs* 37.7 mo (HR 0.94, $p = 0.30$)	-	-
Sub-group analysis; Ito *et al* (2012)[66]	40	Eve (n=23) *vs* placebo (n=17)	Japanese panNET (n=40)	19.5 *vs* 42.8 mo (HR 0.19, $p < 0.001$)	-	4% *vs* 6%	83% *vs* 29%
Sub-analysis; Lombard-Bohas *et al* (2015)[67]	410	Comparison of previous CTx (n=206) with CTx-naïve (n=204)	[Previous CTx did not affect PFS]	CTx(+); 11.0 *vs* 3.2 mo CTx(−); 11.4 *vs* 5.4 mo	-	CTx(+); 5% *vs* 2% CTx(−); 5% *vs* 2%	CTx(+); 73% *vs* 45% CTx(−); 73% *vs* 56%

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RADIANT-4, phase III; Yao *et al* (2016) [23]	302	Eve (n=205) *vs* placebo (n=97)	NF-NET; GI (n=175) and lung (n=90)	11.0 *vs* 3.9 mo (HR 0.48, $p < 0.001$)	Not reached (HR 0.64)	2% *vs* 1%	80% *vs* 64%
Sub-group analysis; Singh *et al* (2017)[68]	211	Eve (GI; n=118, unknown; n=23) *vs* placebo (GI; n=57, unknown; n=13)	NF-NET; GI (n=175) and unknown primary (n=36)	GI; 13.1 *vs* 5.4 mo (HR 0.56), unknown primary; 13.6 *vs* 7.5 mo (HR 0.60)	-	-	-
Sub-group analysis; Fazio *et al* (2017)[69]	90	Eve (n=63) *vs* placebo (n=27)	NF-NET; lung (n=90)	9.2 *vs* 3.6 mo (HR 0.50)	-	2% *vs* 4% (Tumor shrinkage [a]; 58% vs 13%)	79% *vs* 56%
Sub-analysis; Buzzoni *et al* (2017)[70]	302	Effect of prior SSA therapy (n=163), CTx (n=77) and RTx (n=63) on Eve activity	[Prior therapy did not affect PFS]	SSA(+); 11.1 *vs* 4.5 mo SSA(−); 9.5 *vs* 3.7 mo CTx(+); 9.2 *vs* 2.1 mo CTx(−); 11.2 *vs* 5.4 mo RTx(+); 9.2 *vs* 5.4 mo RTx(−); 11.0 *vs* 3.0 mo	-	SSA(+); 1% *vs* 1% SSA(−); 3% *vs* 0% CTx(+); 2% *vs* 0% CTx(−); 2% *vs* 1% RTx(+); 0% *vs* 5% RTx(−); 3% *vs* 0%	SSA(+); 78% *vs* 65% SSA(−); 83% *vs* 63% CTx(+); 78% *vs* 44% CTx(−); 82% *vs* 70% RTx(+); 75% *vs* 47% RTx(−); 82% *vs* 68%
Sub-analysis; Pavel *et al* (2016)[71]		Report of health related quality of life (HRQOL)	[HRQOL was maintained in both Eve and placebo group]				

CgA, chromogranin A; C_{min}, minimum concentration; CTx, chemotherapy; Eve, everolimus; GI, gastrointestinal; HR, hazard ratio; NET, neuroendocrine tumor; NF, non-functioning; Oct, octreotide; NSE, neuron specific enolase; PIGF; placental growth factor, panNET, pancreatic neuroendocrine tumor; PR, partial response; RTx, radiotherapy; SSA, somatostatin analogue; St, stratum; sVEGFR; soluble vascular endothelial growth factor receptor.

[a]Included decrease in tumor size less than 30%.

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Table 2.

Recent important advances in the management/treatment of NETs since initial approval of everolimus by FDA (5/5/2011)[22]

Changes in anti-tumor treatment
1. Approval of sunitinib by FDA for anti-growth therapy in panNETs (5/20/2011) [24]
2. Approval of lanreotide by FDA for anti-growth therapy in GEP-NET (12/16/2014) [25]
3. Additional indication of everolimus in GI and lung NETs (FDA approved on 5/26/2016) [23]
4. Increased use of PRRT and its approval by FDA in GEP-NETs (1/26/2018) [26,27]
5. Increased use of new liver directed therapy (SIRT using ^{90}Yttrium microspheres)[28,29]
Changes in treatment of clinical symptoms in functioning NETs
6. Approval of telotristat ethyl by FDA for symptom control of carcinoid syndrome refractory to SSA (2/28/2017) [30]
7. Additional indication of lanreotide for treatment of carcinoid syndrome (FDA approved on 9/18/2017) [31]
Changes in imaging and management
8. Development and routine use of classification/staging system (WHO, ENETS, AJCC) with prognostic value [34–36]
9. Development and routine use of classification/staging system (WHO, ENETS, AJCC) for treatment selection [34–36]
10. Change in classification systems (WHO 2015, 2017) affecting prognosis/treatment (i.e. NET G3 vs NEC [G3]) [46]
11. Improvement and widespread use of molecular imaging modalities for diagnosis and tumor location[47–49] - SRS [^{111}Indium-pentetreotide with SPECT/CT] (FDA approved on 1994) - ^{68}Gallium-DOTATATE with PET/CT (FDA approved on 6/1/2016)
12. Increased use of molecular imaging to predict aggressiveness, survival, and grade (^{18}Fluorine-FDG PET/CT) [50,51]

AJCC, American Journal of Critical Care; ENETS, European Neuroendocrine Tumor Society; FDA; Food and Drug Administration, FDG; fluorodeoxyglucose, GEP, gastroenteropancreatic; NET, neuroendocrine tumor; panNET, pancreatic neuroendocrine tumor; PET, positron emission tomography; PRRT, peptide receptor radionuclide therapy; SIRT, selective internal radiation therapy; SPECT, single-photon emission computed tomography; SRS; somatostatin receptor scintigraphy; SSA, somatostatin analogue; WHO,World Health Organizationpan

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Table 3.

WHO classification of NETs of pancreas, GI tract, and lung.

2017, Pancreas [46]				2010, GI tract [32]			2015, Lung [33]		
Classification	**Differentiation**	**Ki-67 index (%)**	**Mitotic count (/10 HPF)**	**Classification**	**Ki-67 index (%)**	**Mitotic count (/10 HPF)**	**Classification**	**Mitotic count (/10 HPF)**	**Necrosis**
NET G1	Well	< 3	< 2	NET G1	≤ 2	< 2	Typical carcinoid	< 2	Absence
NET G2	Well	3–20	2–20	NET G2	3–20	2–20	Atypical carcinoid	2–10	Absence or punctiform
NET G3	Well	> 20	> 20	NEC	> 20	> 20	NEC, large cell type	> 10	Large
NEC (G3)	Poor (large cell or small cell type)	> 20	> 20				NEC, small cell type	> 10	Large

GI; gastrointestinal, HPF; high power field, NEC; neuroendocrine carcinoma, NET; neuroendocrine tumor, WHO; World Heath Organization.

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Table 4.

Phase I/II studies related to the efficacy of everolimus treatment with SSAs or studies with everolimus in combination with other agents in NETs

Study, phase (year)	n	Treatment (n)	Population (n) [comment]	PFS	OS	ORR	SD
Phase II; Yao *et al* (2010)[72]	160	Statrum 1; Eve, Statrum 2; Eve + Oct	panNET; Oct-naïve (St 1, n=115), patients on Oct for ≥3 mo (St 2, n=45)	St 1; 9.7 mo, St 2; 16.7 mo	St 1; 24.9 mo, St 2; not reached (2-yr; 54.7%)	St 1; 9.6%, St 2; 4.4%	St 1; 68%, St 2; 80%
Phase II: Bajetta *et al* (2014) [73](2017)[74]	50	Eve + Oct	NET; GI (n=11), pancreas (n=14), lung (n=11)	TTP; 33.6 mo	61.9 mo	18%	74%
COOPERATE-2, phase II; Kulke *et al* (2017)[75]	160	Eve + Pas (n=79) *vs* Eve (n=81)	panNET	16.8 *vs* 16.6 mo (HR 0.99, $p = 0.488$)	Not reached (HR 0.93, $p = 0.410$)	20% *vs* 6%	57% *vs* 77%
LUNA, Phase II; Ferolla *et al* (2017)[76]	124	Pas (n=41) *vs* Eve (n=42) *vs* Eve + Pas (n=41)	NET; lung (n=116), thymus (n=8)	8.5 *vs* 12.5 *vs* 11.8 mo (39% *vs* 33% *vs* 59% at 9 mo)	-	2.4% in each group (Tumor shrinkage [a]; 31% *vs* 49% *vs* 73%)	34% *vs* 31% *vs* 49%
Phase I; Chan *et al* (2012)[77]	22	Eve + Pas	NET; GI (n=14), pancreas (n=4), bronchus (n=2)	76% at 6 mo 65% at 12 mo	-	(Tumor shrinkage[a]; 81%)	90%
CALGB 80701, phase II; Kulke *et al* (2017)[75]	150	Eve + Oct + Bv (n=75) *vs* Eve + Oct (n=75)	panNET	16.7 *vs* 14.0 mo (HR 0.80, $p = 0.12$)	36.7 *vs* 35.0 mo (HR 0.75, $p = 0.16$)	31% vs 12% ($p = 0.005$)	-
Phase I; Dasari *et al* (2015)[78]	19	Eve + Oct + cixutumumab	NET; small bowel (n=6), pancreas (n=4), lung (n=4)	43.6 weeks	25.5 mo	(Tumor shrinkage [a]; 89%)	89%
Phase I; Kim *et al* (2018)[79]	13	Eve + Pas + SIRT	NET; GI (n=6), pancreas (n=3), lung (n=2)	18.6 mo	46.3 mo	46%	23%
Phase I/II; Chan *et al* (2013)[83]	43	Eve 5 or 10 mg + temozolomide	panNET	15.4 mo	-	40%	53%
Phase I; Chan *et al* (2013)[84]	21	Eve + sorafenib	NET; GI (n=13), bronchus (n=3), pancreas (n=3)	79% at 6 mo	-	6% (Tumor shrinkage [a]; 62%)	76%
NETTLE, Phase I; Claringbold *et al* (2015)[85]	16	Eve + PRRT	NET; GI (n=11), pancreas (n=5)	- (No disease progression in 6 mo treatment)	Not reached (1-yr; 88%, 2-yr; 63%)	44%	50%
Phase II; Salazar *et al* (2017)[86]	62	BEZ235 (n=31) *vs* Eve (n=31)	panNET	8.2 vs 10.8 mo (HR 1.53)	(6-mo; 96.6% *vs* 90.3%)	9.7% *vs* 9.7%	52% *vs* 81%
Phase II; Oh *et al* (2012)[87]	27	Eve	NF-GEP-NET	17.1 mo	Not reached	12%	88%

Bv, bevacizumab; Eve, everolimus; GI, gastrointestinal; HR, hazard ratio; NET, neuroendocrine tumor; NF; non-functioning, Oct, octreotide; ORR, objective response rate; OS, overall survival; Pas, pasireotide; panNET, pancreatic neuroendocrine tumor; PFS, progression free survival; PRRT, Peptide Receptor Radionuclide Therapy; SD, stable disease; St, statrum; TTP; time to progression.

[a]Included decrease in tumor size less than 30%.

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Table 5.

Other prospective/retrospective studies related to the efficacy of everolimus in NETs

Study, (year)	Design	n	Treatment	Primary	PFS	OS	ORR	SD
Panzuto (2014) [91]	Retro	169	Eve	P, GI, L	12 mo	32 mo	8%	68%
Berardi (2017) [92]	Retro	116	Eve	P	19 mo	44 mo	10%	73%
Liu (2016) [93]	Retro	53	Eve	P, GI	18.9 mo	63.9 mo	28%	55%
Lee (2017) [94]	Retro	47	Eve	P	27.5 mo	60.8 mo	19%	66%
Lee (2017) [95]	Retro	40	Eve	P	20 mo	-	0%	65%
Yao (2015) [96]	Pro	39	Bv or Eve [a] → Bv + Eve	P, GI, L	14.6 mo	27.9 mo	25%	69%
Kamp (2013) [97]	Retro	24	Eve	P, GI	13.1 mo	-	17%	63%
Angelousi (2017) [98]	Retro	21 11	Eve; 1st line Eve; 2nd line	P P	16.3 mo 15.5 mo	(2-yr; 83%) (2-yr; 69%)	- -	- -
Yoo (2017) [99]	Retro	11 6	Eve Eve	P GI	16.6 mo 14.7 mo	Not reached 27.7 mo	9% 17%	73% 83%
Capdevila (2015) [100]	Retro	57	Eve + lanreotide	P, GI	25.8 mo [b]	26.4 mo	18%	61%

Bv,bevacizumab; Eve, everolimus,; GI,gastrointestinal; L, lung; NET, neuroendocrine tumor; ORR, objective response rate; OS, overall survival; P, pancreas; PFS,progression free survival; Pro prospective; Retro, retrospective; SD, stable disease.

[a]Treated with either agents alone for 3 weeks prior to combination therapy.

[b]Reported as TTP (time to progression).

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Table 6.

Common adverse events (AEs) associated with everolimus in previous studies

Study (year)	n	Regimen	AEs, all grade (grade 3/4), %									
			Stomatitis	Rash	Diarrhea	Fatigue	Infection	Pneumonitis	Hyperglycemia	Plt decrease	Anemia	
Eve monotherapy												
Yao *et al* (2011)[22]	207	Eve	64(7) *	49(<1) *	34(3) *	31(2) *	23(2) *	17(2) *	13(5)	13(4) *	17(6) *	
Yao *et al* (2016)[65]	225	Eve	60(4)	37(1)	26(2)	20(3)	28(5)	10(<1)	-		10(4)	14(0)
Yao *et al* (2016)[23]	205	Eve	63(9) *	27(1) *	31(7) *	31(3)	29(7) *	16(1) *	10(3)	-(<1)	16(4) *	
Panzuto *et al* [91]	169	Eve	22(2)	-	-	-	-	19(8)	17(1)	22(8)	20(5)	
Pavel *et al* (2016) [166]	123	Eve (panNET)	19(3)	7(2)	32(9)	15(8)	39(19)	5(2)	5(3)	5(2)	11(3)	
	117	Eve (non panNET)	19(3)	7(2)	32(9)	15(8)	39(19)	5(2)	5(3)	5(2)	11(3)	
Berardi *et al* (2017)[92]	116	Eve	-(4)	-(1)	-(3)	-(2)	-	-(2)	-(3) [a]	-(4)	-(1)	
Liu *et al* (2016) [93]	53	Eve	36(2)	19(0)	-	15(2)	-	9(2)	23(9)	9(0)	13(8)	
Lee *et al* (2017) [94]	47	Eve	85(0)	57(0)	21(6)	-	53(21)	15(4)	34(4)	28(9)	34(6)	
Lee *et al* (2017) [95]	40	Eve	48(5)	33(3)	10(3)	-	-	3(0)	-	8(0)	13(3)	
Oh *et al* (2012)[87]	32	Eve	18(6)	29(0)	27(3)	-	-	-	12(6)	15(15)	12(6)	
Salazar *et al* (2017)[86]	31	Eve	65(6)	42(0)	55(3)	32(36)	-	16(3)	35(6)	23(0)	35(10)	
Angelousi *et al* (2017)[98]	20 11	Eve (1st line) Eve (2nd line)	10(0) 9(0)	25(0) 18(0)	15(0) [b] 45(9) [b]	10(0) 18(0)	- -	25(5) 18(9)	25(5) 18(0)	25(5)[c] 27(5)[c]	25(5)[c] 27(5)[c]	
Kamp *et al* (2013) [97]	24	Eve	42(4)	25(4)	4(4)	33(8)	8(0)	38(0)	25(13)	17(8)	21(0)	
Yoo *et al* (2017) [99]	17	Eve	59(6)	41(0)	29(0)	29(0)	-	18(12)	-	12(6)	29(0)	
Eve-combined therapy												
Pavel *et al* (2011)[21]	216	Eve + Oct	62(7) *	37(1) *	27(6) *	31(7)	20(5) *	12(2) *	12(5) *	14(5) *	15(1) *	
Yao *et al* (2010)[72]	115 45	Eve Eve + Oct	45(4) 49(2)	40(1) 44(0)	39(4) 31(0)	31(4) 36(2)	- -	6(0) 13(0)	13(4) 13(4)	8(3) 13(9)	13(4) 16(4)	
Yao *et al* (2008)[20]	60	Eve + Oct	69(8)	64(5)	-	-(11)	-	7(2)	70(9)	35(5)	-(3)	
Bajetta *et al* (2014)[73]	50	Eve + Oct	62(10)	48(2)	60(22)	-	-	6(0)	18(0)	12(0)	8(2)	
Dasari *et al* (2015)[78]	19	Eve + Oct + cixutumumab	63(11)	42(0)	58(0)	74(21)	16(5)	-	63(11)	53(0)	11(5)	
Kulke *et al* (2017)[75]	79 81	Eve + Pas Eve	59(9) 63(9)	24(0) 30(0)	63(5) 53(4)	27(4) 35(4)	15(0) 14(0	8(1) 12(1)	76(37) 27(11)	- -	27(5) 26(5	

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Study (year)	n	Regimen	AEs, all grade (grade 3/4), %								
			Stomatitis	Rash	Diarrhea	Fatigue	Infection	Pneumonitis	Hyperglycemia	Plt decrease	Anemia
Dasari *et al* (2015)[76]	42 41	Eve Eve + Pas	72(10) 37(5)	33(7) 12(0)	50(7) 76(20)	19(2) 34(10)	9(2) 12(0)	5(5) 15(5)	46(17) 83(24)	23(2) 17(0)	31(2) 25(5)
Chan *et al* (2012)[77]	22	Eve + Pas	48(5)	48(5)	62(5)	76(0)	-	-	90(38)	76(14)	76(0)
Chan *et al* (2013)[83]	43	Eve + temozolomide	63(2)	53(5)	51(2)	77(2)	-	7(0)	72(19)	67(16)	65(0)
Yao *et al* (2015)[96]	39	BV or Eve → Bv + Eve	61(2)	15(2)	49(15)	61(7)	56(7)	-	44(10)	20(5)	32(5)
Chan *et al* (2013)[84]	21	Eve + sorafenib	38(0)	81(14)	67(14)	76(0)	10(0)	5(5)	76(10)	86(14)	86(0)

Bv, bevacizumab; Eve, everolimus; Plt, platelet; panNET, pancreatic NET; Oct, octreotide; Pas, pasireotide.

[*]Frequencies of all grade AEs more than 10% higher than control arm.

[a]Reported as metabolic toxicities.

[b]Reported as gastrointestinal intolerance.

[c]Reported as haematologic toxicities.

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Table 7.

Treatment-related outcomes and dose adjustment of everolimus in previous studies

Study, (year)	n	Regimen (n)	Treatment duration, median	Reasons of discontinuation		Dose adjustment of Eve		Dose intensity of Eve, median (mg/day)	Eve-related mortality
				AEs	Disease progression	Reduction (R)	Interruption (I)		
Phase I-III studies									
RADIANT-1, phase II; Yao *et al* (2008)[20]	60	Eve + Oct	-	5%	-	13%	-	-	-
RADIANT-2, phase III; Pavel *et al* (2011)[21]	216	Eve + Oct	9.2 mo	19%	44%	65% (R+I)		8.3	0%
RADIANT-3, phase III; Yao *et al* (2011)[22]	207	Eve	8.8 mo	17%	44%	59% (R+I)			<1% [a]
Sub-analysis Yao *et al* (2016)[65]	225	Eve (open label)	44 wk	24%	55%	-	-	-	0%
RADIANT-4, phase III; Yao *et al* (2016)[23]	205	Eve	40.4 wk	12%	37%	67% (R+I)		-	1% [b]
Phase II; Yao *et al* (2010)[72]	115 45	Eve Eve + Oct	- -	- -	- -	- -	- -	9.9 9.4	- -
Phase II; Bajetta *et al* (2014)[73]	50	Eve + Oct	74 wk	16%	-	26%	0%	9.4	0%
COOPERATE-2, phase II; Kulke *et al* (2017)[75]	79 81	Eve + Pas Eve	49.4 wk 48.3 wk	23% 21%	40% 43%	53% 36%	65% 56%	7.8 9.8	3% [c] 1% [c]
LUNA, Phase II; Ferolla *et al* (2015)[76]	42 41	Eve Eve + Pas	-	35% 32%	17% 24%	67% (R+I) 54% (R+I)		9.4 8.4	2% [d] 5% [d]
Phase I; Chan *et al* (2012)[77]	22	Eve + Pas	6 cycles (4-wk)	5%	36%	14%	-	-	0%
Phase II; Salazar *et al* (2017)[86]	31	Eve	39.4 wk	16%	-	-	-	-	0%
Phase I/II; Chan *et al* (2013)[83]	43	Eve + temozolomide	8.5 cycles (4-wk)	21%	49%	-	-	-	0%
Phase I; Chan *et al* (2013)[84]	21	Eve + sorafenib	4 cycles (4-wk)	14%	57%	14%	-	-	0%
Phase I; Dasari *et al* (2015)[78]	19	Eve + Oct + cixutumumab	10 cycles (3-wk)	21%	42%	-	-	-	0%
NETTLE, Phase I; Claringbold *et al* (2015)[85]	16	Eve + PRRT	24 wk (Eve) + 4 cycles of PRRT (8-wk)	-	0%	100% (R+I) in 10mg cohort		8.3, 8.0, 4.8 in 5mg, 7.5mg, 10mg cohort	0%
Prospective /retrospective studies									
Yao *et al* (2015)[96]	39	BV or Eve	-	-	-	25% (R+I)		-	0%

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Study, (year)	n	Regimen (n)	Treatment duration, median	Reasons of discontinuation		Dose adjustment of Eve		Dose intensity of Eve, median (mg/day)	Eve-related mortality
				AEs	Disease progression	Reduction (R)	Interruption (I)		
		→ Bv + Eve							
Pavel *et al* (2016) [166]	123 117	Eve (PANNET) Eve (non PANNET)	12.1 wk 24 wk	17% 25%	- -	39% (R+I) 53% (R+I)		- -	0% 0%
Panzuto *et al* [91]	169	Eve	6 mo	9%	50%	17%	63%	-	0%
Berardi *et al* (2017)[92]	116	Eve	-	-	-	22%	66%	-	0%
Capdevila *et al* (2015) [100]	73	Eve + lanreotide	4.7mo	14%	32%	-	-	-	-
Liu *et al* (2016) [93]	53	Eve	-	6%	51%	-	-	-	2% [e]
Lee *et al* (2017) [94]	47	Eve	50 wk	34%	43%	-	-	-	0%
Lee *et al* (2017) [95]	40	Eve	8 mo	5%	-	-	-	-	0%
Angelousi *et al* (2017)[98]	20 11	Eve (1st line) Eve (2nd line)	13.6 mo 7 mo	10% 9%	90% 63%	- -	- -	- -	0% 0%
Kamp *et al* (2013) [97]	24	Eve	10.2 mo	17%	29%	17%	29%	-	0%
Yoo *et al* (2017) [99]	17	Eve	-	24%	-	29%	-	-	0%

AEs, adverse events; Bv,bevacizumab; Eve, everolimus; Plt, platelet; panNET, pancreatic NET; Oct,octreotide; Pas, pasireotide; PRRT, peptide receptor radionuclide therapy .

[a] Included acute respiratory distress syndrome (n=1).

[b] Included respiratory failure (n=1), septic shock (n=1), and cardiac failure (n=1).

[c] Included ketoacidosis (n=1) and sepsis (n=1) in combination arm; pulmonary embolism (n=1) in Eve arm.

[d] Included acute kidney injury associated with diarrhea(n=1) in Eve arm; diarrhea and urinary sepsis (n=1), acute renal failure and respiratory failure (n=1) in combination arm.

[e] Included interstitial pneumonitis (n=1).