Everolimus treatment for neuroendocrine tumors: latest results and clinical potential

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Sara Pusceddu, Elena Verzoni, Natalie Prinzi, Alessia Mennitto, Daniela Femia, Paolo Grassi, Laura Concas, Claudio Vernieri, Giuseppe Lo Russo and Giuseppe Procopio

***Abstract*:** Neuroendocrine tumors (NETs) are a heterogeneous class of diseases characterized by challenging management. Preclinical evidence shows that the PI3K/AKT/mTOR signaling pathway plays a central role in the pathogenesis and progression of NETs. Everolimus is a direct inhibitor of this pathway, and therefore this molecule appears to be a well-grounded strategy for the treatment of NETs, capable of changing clinical practice. The efficacy and safety of everolimus was demonstrated in the RADIANT trials. In this work, we comment on the results of the RADIANT trials, and other recent key evidence from fully published clinical trials on everolimus, and we discuss the current role of everolimus in the treatment of NETs.

Keywords: everolimus, neuroendocrine tumors, RADIANT trials

Introduction

Neuroendocrine tumors (NETs) are a heterogeneous class of neoplasms with increasing incidence worldwide [Fraenkel *et al*. 2012]. Tumor behavior and patient survival largely depend upon a number of different factors such as tumor histology, primary site, staging and proliferative index [Panzuto *et al*. 2014].

The management of NETs is challenging, and therefore effective and safe therapeutic options for the treatment of these tumors are actively pursued in clinical research. In particular, targeted therapies such as sunitinib and everolimus have shown promising results and have thus entered clinical practice [Barbieri *et al*. 2014; Kulke *et al*. 2008; Raymond *et al*. 2011; Ito *et al*. 2013; Yao *et al*. 2008, 2010; Pavel *et al*. 2011; Yao *et al*. 2011, 2016].

A bulk of preclinical evidence has shown that the PI3K/AKT/mTOR signaling pathway plays a central role in the pathogenesis and progression of NETs [Manfredi *et al*. 2015; Yao *et al*. 2008; Pusceddu *et al*. 2016a; Procopio *et al*. 2012; Pusceddu *et al*. 2016]. Everolimus is a direct inhibitor of this pathway, and therefore this molecule appear to be a well-grounded strategy for the treatment of NETs, capable of changing clinical practice. The efficacy and safety of everolimus was demonstrated in the RADIANT trials [Yao *et al*. 2010; Pavel *et al*. 2011; Yao *et al*. 2011, 2015]. In this work, we comment on the results of the RADIANT trials, and other recent key evidence from fully published clinical trials on everolimus, and we discuss the current role of everolimus in the treatment of NETs.

Everolimus in patients with pancreatic NETs

The open-label, phase II RADIANT 1 trial has assessed the efficacy and safety of everolimus in patients with metastatic pancreatic NET (pNET) who have progressed on prior chemotherapy [Yao *et al*. 2010]. Patients were stratified according to the use of everolimus 10 mg/day only (n = 115), or everolimus 10 mg/day + octreotide long-acting release (LAR) (n = 45). At central analysis, the rate of partial response was 9.6% with everolimus only and 4.4% with everolimus + octreotide LAR; the incidence of stable disease was 67.8% and 80.0%, respectively. Median progression-free survival (PFS) was 9.7 months with everolimus only and 16.7 months with the combination strategy. On this basis, it was suggested that everolimus 10 mg/day, with or without concomitant octreotide LAR, presents a degree of antitumor activity in patients with advanced pNETs who have failed prior chemotherapy.

Correspondence to:
Giuseppe Procopio, MD
Medical Oncology, Istituto Nazionale Tumori, Via Venezian 1, 20100, Milan, Italy
giuseppe.procopio@istitutotumori.mi.it

Sara Pusceddu, MD
Elena Verzoni, MD
Natalie Prinzi, MD
Alessia Mennitto, MD
Daniela Femia, MD
Paolo Grassi, MD
Laura Concas, MS
Claudio Vernieri, MD
Giuseppe Lo Russo, MD
Medical Oncology, Istituto Nazionale Tumori, Milan, Italy

Further to the RADIANT 1 trial, the international randomized, placebo-controlled, phase III RADIANT 3 trial has evaluated patients with advanced pNET (low or intermediate-grade) who showed radiologic progression within the previous 12 months before inclusion [Yao *et al*. 2012]. It is the largest study ever conducted in the setting of NETs. Patients were randomly assigned to either everolimus 10 mg/day (n = 207) + best supportive care or placebo (n = 203). Of note, patients assigned to placebo who showed radiological progression during the study (73%) were offered open-label everolimus. Median PFS was longer in the everolimus group, compared with placebo [11.0 *versus* 4.6 months; hazard ratio (HR), 0.35; 95% confidence interval (CI), 0.27–0.45; $p < 0.001$]. Statistical analysis showed that the estimated proportion of patients free from progression at 18 months was 34% (95% CI, 26–43) with everolimus and 9% (4–16) with placebo. Remarkably, the PFS advantage shown with everolimus was consistent in all the subgroups analyzed, independently from age, sex, ethnicity, prior exposure to somatostatin analogues (SSAs), performance status, and tumor differentiation. These findings suggest that everolimus is effective in all patients with well-differentiated or moderately-differentiated pNET, without any parameter which may suggest exclusion from treatment. On the other hand, overall survival was similar in the two groups (HR, 1.05; 95% CI, 0.71–1.55), most likely due to the high number of patients who were switched to everolimus from placebo.

Interestingly, the impact of previous chemotherapy on the efficacy of everolimus was evaluated in a recent subanalysis of the RADIANT 3 trial [Lombard-Bohas *et al*. 2015]. Among enrolled patients, 204 (50%) were chemo-naïve. Everolimus prolonged PFS regardless of prior chemotherapy (prior chemotherapy group: 11.0 months with everolimus and 3.2 months with placebo; HR, 0.34; 95% CI, 0.25–0.48; $p < 0.0001$; chemo-naïve group: 11.4 *versus* 5.4 months; HR, 0.42; 95% CI, 0.29–0.60; $p < 0.0001$).

Everolimus in patients with NET and carcinoid syndrome: the RADIANT 2 trial

The randomized, double-blind, placebo-controlled phase III RADIANT 2 has evaluated the combination of everolimus 10 mg/day and octreotide LAR compared with octreotide LAR alone in 429 patients who presented low or intermediate-grade NET and carcinoid syndrome [Pavel *et al*. 2011]. Median PFS by central review, the primary endpoint of the trial, was 16.4 months in the combination arm and 11.3 months with octreotide LAR only. The HR for progression between the two groups did not reach statistical significance (0.77, 95% CI, 0.59–1.00). Those findings did not match those reported at the local review of PFS, which suggested a benefit for everolimus (12.0 months *versus* 8.6; HR, 0.78, 95% CI, 0.62–0.98). Moreover, it should be noted that World Health Organization performance status was poorer in the combination arm compared with the octreotide-only group. Moreover, patients assigned to the combination therapy presented a higher incidence of pulmonary primary tumors and bone involvement, had higher chromogranin A (CgA) values at baseline, and were more heavily pretreated. Those imbalances have contributed to the lack of statistical differences between the two groups in terms of PFS, as also shown at a dedicated multivariate analysis [Pusceddu *et al*. 2016; Yao *et al*. 2012].

The results of the RADIANT 2 study have led to several subanalyses. First, a subanalysis including only patients with pulmonary NET (everolimus + octreotide LAR, n = 33; octreotide LAR only, n = 11) showed a 2.4-fold longer PFS in the combination arm, associated with a 28% reduction in the risk of progression (13.6 *versus* 5.6 months; HR, 0.72; 95% CI, 0.31–1.68) [Fazio *et al*. 2013]. In this same analysis, tumor shrinkage was reported by a >2-fold proportion of patients on everolimus + octreotide, compared with those assigned to octreotide LAR only (67% *versus* 27%).

Another subgroup analysis of patients with colorectal NET led to overall similar results [Castellano *et al*. 2013]. In more details, the 19 patients on everolimus + octreotide LAR had a 4-fold prolonged PFS than the 20 patients assigned to octreotide monotherapy (29.9 *versus* 6.6; HR, 0.34; 95% CI, 0.13–0.89; p = 0.011). Moreover, tumor shrinkage was more frequent with combination treatment (67% *versus* 37%).

Another recent subanalysis of the RADIANT 2 trial has assessed the impact of previous treatment with SSAs on the efficacy of everolimus treatment [Anthony *et al*. 2015]. The 339 patients treated with everolimus and octreotide LAR had longer median PFS, regardless of previous SSA exposure (with prior exposure: PFS 14.3 months, 95% CI, 12.0–20.1; without prior exposure: 25.2

months, 95% CI, 12.0–not recorded) compared with those assigned to octreotide LAR only (with: 11.1 months, 95% CI, 8.4–14.6; without: 13.6 months, 95% CI, 8.2–22.7).

Everolimus in patients with pulmonary or gastrointestinal NETs

A phase II trial of everolimus + octreotide LAR as first-line treatment for patients with previously untreated, well-differentiated gastroenteropancreatic NETs and NETs of lung origin, both functioning and not functioning, demonstrated an overall response rate of 18% [2% complete response and 16% partial response], with a disease control rate of 92%; the responses obtained were generally durable (>6 months) [Bajetta *et al.* 2014].

The efficacy of everolimus in patients with well-differentiated (G1 or G2) advanced NET of gastrointestinal (GI) or lung origin was also evaluated in the landmark RADIANT 4 trial, a prospective, multicenter, randomized, double-blind, placebo-controlled, phase III study [Yao *et al.* 2016]. Patients received everolimus 10 mg/day (n = 205) or placebo (n = 97) plus best supportive care. In total, 175 patients had GI NETs and 90 had lung disease.

According to centralized analysis, patients on everolimus showed an almost 3-fold longer median PFS than those assigned to the control group (11.0 *versus* 3.9 months, HR, 0.48; 95% CI, 0.35–0.67; $p < 0.00001$). These findings were confirmed at the local evaluation (14.0 *versus* 5.5 months) and were observed in all the analyzed subgroups, including those with pulmonary disease and patients with GI NETs. However, when patients with better prognoses (appendix, caecum, jejunum, ileum, duodenum, and NETs of unknown primary) are compared with those with worse prognoses (lung, stomach, rectum, and colon except caecum), a better HR for progression or death was observed for patients with worse prognosis (0.43 for everolimus *versus* placebo) and in those with moderately-differentiated NETs G2 patients (0.49 for everolimus *versus* placebo). On the other hand, HR for progression or death in the 'better prognosis' subgroup was 0.63 for everolimus *versus* placebo, and HR in patients with well-differentiated NETs G1 was 0.57.

The rate of tumor shrinkage was 64% in the everolimus group and 26% in the placebo group. Disease control rate, assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.0, was 82.4% and 64.9%, respectively.

Implications for clinical practice

In our opinion, everolimus does represent a major advance in the therapy of NETs. In fact, according to the results of well-conducted clinical trials, the efficacy of everolimus has been consistently shown in well-differentiated NETs from all origins. With respect to safety, the tolerability profile of everolimus has been consistent in all studies, with most adverse events being of mild or moderate severity; the onset of grade 3/4 anemia and hyperglycemia (both with a rate of about 5%) must however be noticed.

In the next paragraphs, we will discuss the role of everolimus in the different types of NETs.

pNETs

Everolimus undoubtedly represents one of the most effective treatments in pNET patients. However, its role within the therapeutic sequence (e.g. in the first-line setting or at later treatment lines) remains unclear also due to the number of effective options in these patients with confirmed efficacy or under evaluation [sunitinib, SSAs, chemotherapy, peptide receptor radionuclide therapy (PRRT), and pazopanib]. Of note, the subgroup analysis of the RADIANT 3 study showed no differences in PFS between pretreated and naïve patients [Lombard-Bohas *et al.* 2015]. The use of everolimus in the frontline setting is also supported by a smaller study in a heterogeneous population of patients with NETs of different origin [Bajetta *et al.* 2014].

Given the lack of results from well-conducted head-to-head trials, we believe that everolimus might be a particularly suitable first-line treatment for G2 pNET patients who show rapidly-evolving disease and high disease burden, given the antiproliferative efficacy and tolerability profile of this molecule. On the other hand, everolimus may be more useful as a second-line therapy in patients with G1 pNET, who frequently show low tumor burden and indolent disease, and as such may be effectively treated with SSAs.

Pulmonary NETs

The RADIANT 4 trial was the first randomized study to show that everolimus is effective in patients with pulmonary NETs, a class of disease

for which no treatment is established. In this setting, everolimus may be particularly suitable as a first-line therapy for patients who present with aggressive disease, including those with atypical carcinoids. Moreover, data on second-line everolimus are even stronger, also when compared with those for chemotherapy and PRRT, which were reported in small retrospective or noncontrolled, heterogeneous series of patients.

Gastrointestinal NETs

The RADIANT 4 trial showed the efficacy of everolimus in patients with well-differentiated, advanced, progressive, nonfunctional GI NETs. Overall, its findings suggest that worse grade of differentiation and worse prognosis might be associated with higher efficacy of everolimus, although specific studies appear necessary to further evaluate those findings.

Therefore, we believe that the use of everolimus may be limited in the upfront setting for 'better prognosis' patients with appendix, caecum, jejunum, ileum, duodenum (midgut) NETs, also because several other treatment options are available. On the other hand, everolimus may become of paramount importance for the treatment of less indolent GI carcinoids, due to the lack of effective therapeutic opportunities other than SSAs.

Future perspectives

Research on everolimus in the treatment of NETs is particularly active and at present a number of studies are ongoing or are awaiting their final results. In addition, everolimus is being investigated within different combination regimens with other targeted therapies including sorafenib and bevacizumab, temozolomide or pasireotide. An intriguing strategy, actively pursued by our group, is the combination of everolimus with metformin, due to the potential antiproliferative effect of this small molecule and its ability to control hyperglycemia [Pusceddu *et al*. 2014b; Pusceddu *et al*. 2016b]. The METNET1 study is investigating this combination [ClinicalTrials.gov identifier: NCT02294006]. In addition, also the combination of everolimus and SSAs or everolimus and PRRT is currently being explored, (e.g. in the ongoing Luna trial [Ferolla, 2014]), while the combination of first-line everolimus and temozolomide is being investigated in another study [ClinicalTrials.gov identifier: NCT02248012]. Another interesting pilot study is evaluating everolimus with external beam radiotherapy for the treatment of NET liver metastasis [Clinical Trials.gov identifier: NCT02205515].

Noteworthy, given the high heterogeneity of NETs we believe that clinical trials on everolimus in this setting should focus on single disease entities, in order to provide more specific results. Interestingly, the efficacy of everolimus is being tested also in poorly-differentiated NETs (neuroendocrine carcinomas (NEC) [ClinicalTrials.gov identifier:NCT02687958]. Moreover, the correct place of everolimus in the therapeutic algorithm (e.g. frontline or second-line) requires further investigation: some hints to this respect will be provided by the ongoing SEQTOR trial [ClinicalTrials.gov identifier: NCT02246127]. This trial investigates which sequence of streptozotocin-based chemotherapy and everolimus gives better results in terms of second PFS in well-differentiated and advanced pNETs. At the same time, research should focus on the identification of clinical and biological biomarkers capable of discriminating between patients eligible to upfront treatment and those who may be treated with everolimus at a later therapy line.

Conclusion

Treatment of NETs remains challenging, mostly because they represent a highly heterogeneous group of tumors. The international RADIANT trial showed the marked efficacy of everolimus in thousands of patients with different NET subtypes, likely permitting to improve therapeutic management and providing new evidence to develop therapeutic algorithms. However, the identification of the optimal treatment sequence and the selection of patients are still to be investigated in controlled clinical trials.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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