VOLUME 35 · NUMBER 13 · MAY 1, 2017

JOURNAL OF CLINICAL ONCOLOGY

CORRESPONDENCE

Reply to V. Amoroso et al

We thank Amoroso et al[1] for their discussion of our recent article entitled "Everolimus for the treatment of advanced pancreatic neuroendocrine tumors: Overall survival and circulating biomarkers from the randomized, phase III RADIANT-3 study."[2] The questions posed by Amoroso et al[1] concern the introduction of everolimus in earlier or later stages in the clinical history of pancreatic neuroendocrine tumors (pNET), treatments administered after progression on everolimus, and potential statistical interactions of the prognostic parameters with overall survival (OS).

RAD001 in Advanced Neuroendocrine Tumors, Third Trial (RADIANT-3) was a double-blind, randomized, placebo-controlled, multicenter phase III study, which met its primary end point of efficacy. In the RADIANT-3 study, crossover from placebo to open-label everolimus was permitted on disease progression. Patients continuing on study were unblinded after final progression-free survival (PFS) analysis and could transition to open-label everolimus at the investigator's discretion (extension phase). Of the 410 patients randomly assigned to everolimus or placebo, a total of 225 patients eventually received open-label everolimus: 172 patients (85%) who crossed over from the placebo arm and 53 patients (26%) who were randomly assigned initially to the everolimus arm.[2] The high crossover rate in the study allowed an indirect comparison of early versus delayed treatment with everolimus in advanced pNET. In view of that, although not statistically significant, the 6.3 months of improvement in median OS seems to favor the earlier introduction of everolimus in the clinical course of advanced, progressive pNET.

Although information regarding treatments administered after progression on everolimus was not specifically collected, data on treatments received postdiscontinuation of study drugs (after the open-label everolimus extension phase, if applicable) are available. The percentages of patients who started other antineoplastic therapies were similar between everolimus (63.7%) and placebo (57.1%). The most frequent antineoplastic therapies administered after discontinuation of the study drug were chemotherapy (29.4% and 29.1%) and targeted therapy (23% and 19.2%) in the everolimus and placebo arms, respectively. Both treatment arms were balanced with respect to the antineoplastic therapies administered postdiscontinuation of study treatment, and therefore no impact of post-study treatment on OS is anticipated.

On the basis of the study design of RADIANT-3, which included both therapy-naïve patients and patients who received prior therapies, everolimus can be used as first or later line of therapy; however, a definitive OS benefit of everolimus introduced early in the treatment algorithm has not been proven. Prognostic factors, such as higher tumor burden or higher proliferative activity, may have led to earlier use of systemic chemotherapy and may have impacted OS. The Randomized Open Label Study to Compare the Efficacy and Safety of Everolimus Followed by Chemotherapy With Streptozotocin-Fluorouracil Upon Progression or the Reverse Sequence, in Advanced Progressive Pancreatic NETs (SEQTOR) study (NCT02246127) is a prospective clinical trial investigating the optimal sequence of everolimus and chemotherapy in advanced, progressive pNET and aims to address the question whether starting everolimus or streptozotocin/fluorouracil followed by crossover on progression is superior with respect to disease control rate and OS.

Amoroso et al[1] also suggested that patients with more aggressive disease enrolled in the Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors (CLARINET) study may not have benefited with lanreotide, because PFS curves did not separate until after 9 months.[3] However, only nine (4%) patients from that study had progressive disease at entry, whereas the remaining 96% of patients had stable disease. Therefore, the study population of CLARINET was different from that of RADIANT-3, in which all patients must have had radiologic disease progression within 12 months before randomization. This is also reflected by the PFS in the placebo arms of both studies (12.1 months for the pNET subgroup in CLARINET *v* 5.4 months in RADIANT-3). On the basis of the data from the CLARINET study, lanreotide is mostly considered in patients with stable disease (or slowly growing tumors). Everolimus and sunitinib are approved targeted therapies available for advanced, progressive pNET, both having shown an improvement in PFS versus placebo. However, on the basis of early results favoring sunitinib in a randomized phase III study, the independent data monitoring committee recommended trial termination before the prespecified interim analysis.[4] This premature unplanned analysis may have led to an overestimation of the treatment effect of sunitinib.[3] A median OS of 38.6 months has been recently reported from the phase III study of sunitinib.[5] RADIANT-3 is the only phase III study that has demonstrated a statistically significant PFS benefit and an unprecedented median OS of 44 months in patients with advanced, progressive pNET.[6]

In addition, the correspondents have raised a query regarding the assessment of statistical interaction of prognostic parameters (circulating neuron-specific enolase, chromogranin A, and angiogenic biomarkers) with treatment arms. Elevated baseline levels of chromogranin A, neuron-specific enolase, placental growth factor, and soluble vascular endothelial growth factor receptor 1 were shown to be poor prognostic, but not predictive, factors for OS.[2] However, everolimus has demonstrated a consistent benefit among all subgroups analyzed on the basis these biomarkers.[2]

James C. Yao
University of Texas/MD Anderson Cancer Center, Houston, TX

Maurizio Voi
Novartis Pharmaceuticals Corporation, East Hanover, NJ

Jeremie Lincy
Novartis Pharmaceuticals AG, Basel, Switzerland

Marianne Pavel
Charité Universitätsmedizin Berlin, Berlin, Germany

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

ACKNOWLEDGMENT

Supported by Novartis Pharmaceuticals Corporation.
Clinical trial information: NCT00510068

REFERENCES

1. Amoroso V, Fazio N, Mosca A, et al: When should everolimus be administered in the natural history of pancreatic neuroendocrine tumors? J Clin Oncol 35: 1487-1488, 2017

2. Yao JC, Pavel M, Lombard-Bohas C, et al: Everolimus for the treatment of advanced pancreatic neuroendocrine tumors: Overall survival and circulating biomarkers from the randomized, phase III RADIANT-3 study. J Clin Oncol 34: 3906-3913, 2016

3. Caplin ME, Pavel M, Ćwikła JB, et al: Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med 371:224-233, 2014

4. Blumenthal GM, Cortazar P, Zhang JJ, et al: FDA approval summary: Sunitinib for the treatment of progressive well-differentiated locally advanced or metastatic pancreatic neuroendocrine tumors. Oncologist 17:1108-1113, 2012

5. Faivre S, Niccoli P, Castellano D, et al: Sunitinib in pancreatic neuroendocrine tumors: Updated progression-free survival and final overall survival from a phase III randomized study. Ann Oncol 2016 Nov 10 pii:mdw561. [Epub ahead of print]

6. Yao JC, Shah MH, Ito T, et al: Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med 364:514-523, 2011

DOI: 10.1200/JCO.2017.71.3875; published at jco.org on January 23, 2017.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Reply to V. Amoroso et al

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

James C. Yao
Consulting or Advisory Role: Novartis
Research Funding: Novartis (Inst)

Maurizio Voi
Employment: Novartis
Stock or Other Ownership: Novartis

Jeremie Lincy
Employment: Novartis

Marianne Pavel
Honoraria: Novartis/Ipsen, Lexicon
Consulting or Advisory Role: Novartis, Ipsen, Lexicon Pharmaceuticals
Research Funding: Novartis (Inst), Ipsen (Inst)