

Relationship Between Metabolic Toxicity and Efficacy of Everolimus in Patients With Neuroendocrine Tumors (NETs): A Pooled Analysis From the Randomized, Phase 3 RADIANT-3 and RADIANT-4 Trials

Nicola Fazio,¹ Carlo Carnaghi,² Roberto Buzzoni,³ Juan W Valle,⁴ Fabian Herbst,⁵ Antonia Ridolfi,⁶ Jonathan Strosberg,⁷ Matthew H Kulke,⁸ Marianne Pavel,⁹ James C Yao¹⁰

¹IEO, European Institute of Oncology IRCCS, Milan, Italy; ²IRCCS Istituto Clinico Humanitas, Rozzano, Italy; ³Fondazione IRCCS, Istituto Nazionale dei Tumori, Milano, Italy; ⁴Division of Cancer Sciences, University of Manchester, The Christie NHS Foundation Trust, Manchester, United Kingdom; ⁵Novartis Pharma AG, Basel, Switzerland; ⁶Novartis Pharma S.A.S., Rueil-Malmaison, France; ⁷Moffitt Cancer Center, Tampa, Florida, USA; ⁸Dana-Farber Cancer Institute, Boston, Massachusetts, USA; ⁹University of Erlangen-Nuremberg, Erlangen, Germany; ¹⁰University of Texas MD Anderson Cancer Center, Houston, Texas, USA

CLICK TO GO
BACK TO KIOSK
MENU

Introduction

- An improvement in progression-free survival (PFS) was observed with mammalian target of rapamycin (mTOR) inhibitors in patients with advanced renal cell carcinoma (RCC) who developed certain class-effect toxicities such as hyperglycemia, hypertriglyceridemia, and hypercholesterolemia.¹
- Everolimus (mTOR inhibitor) therapy is an approved treatment for the management of patients with advanced gastrointestinal (GI) NETs, lung NETs, and pancreatic NETs (panNET).
 - Pantano et al reported the data from a real-word analysis conducted in 177 patients wherein, a significant association between metabolic events and the clinical outcomes with everolimus was observed in patients with metastatic RCC.²
 - In a pooled subgroup analysis from the RECORD-1 and REACT trials in metastatic RCC, PFS improved in 12% and 20% of patients (in RECORD-1) and 6% and 1% of patients (in REACT) who reported to have hyperglycemia and hypercholesterolemia, respectively.³
 - When compared with placebo, everolimus significantly improved the median PFS and risk of disease progression/death in patients with advanced panNET (6.4 months and 65% in RADIANT-3) and GI/lung NETs (7.1 months and 52% in RADIANT-4).^{4,5}
- The objective of this pooled analysis of data from RADIANT-3 and RADIANT-4 trials was to assess the impact of treatment-related hyperglycemia, hypertriglyceridemia, and hypercholesterolemia as reported from the adverse events (AEs) on the efficacy of everolimus among patients with NETs.

Methods

Study Design and Patient Population

- RADIANT-3 and RADIANT-4 were international, multicenter, randomized, double-blind, placebo-controlled phase 3 studies (**Figure 1A** and **1B**).
 - In the RADIANT-3 trial, patients with advanced, low-, or intermediate-grade panNET received either oral everolimus 10 mg/day (N = 207) or placebo (N = 203).
 - In the RADIANT-4 trial, patients with advanced, low-, or intermediate-grade GI or lung NETs received either oral everolimus 10 mg/day (N = 205) or placebo (N = 97).
 - In both studies, treatment continued until disease progression, initiation of new cancer therapy, development of an intolerable AE, or withdrawal of consent. The dose reduction of everolimus to 5 mg/day was permitted in case of unacceptable toxicity.

Figure 1A. RADIANT-3 Study Design

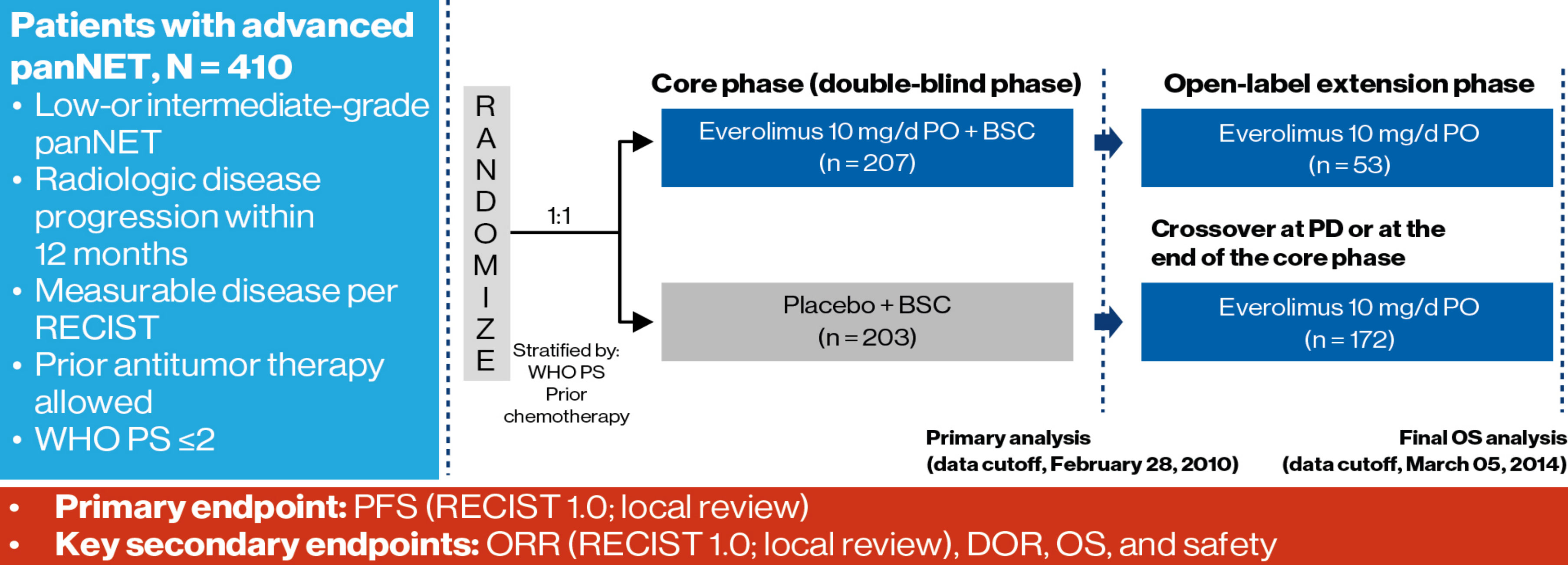
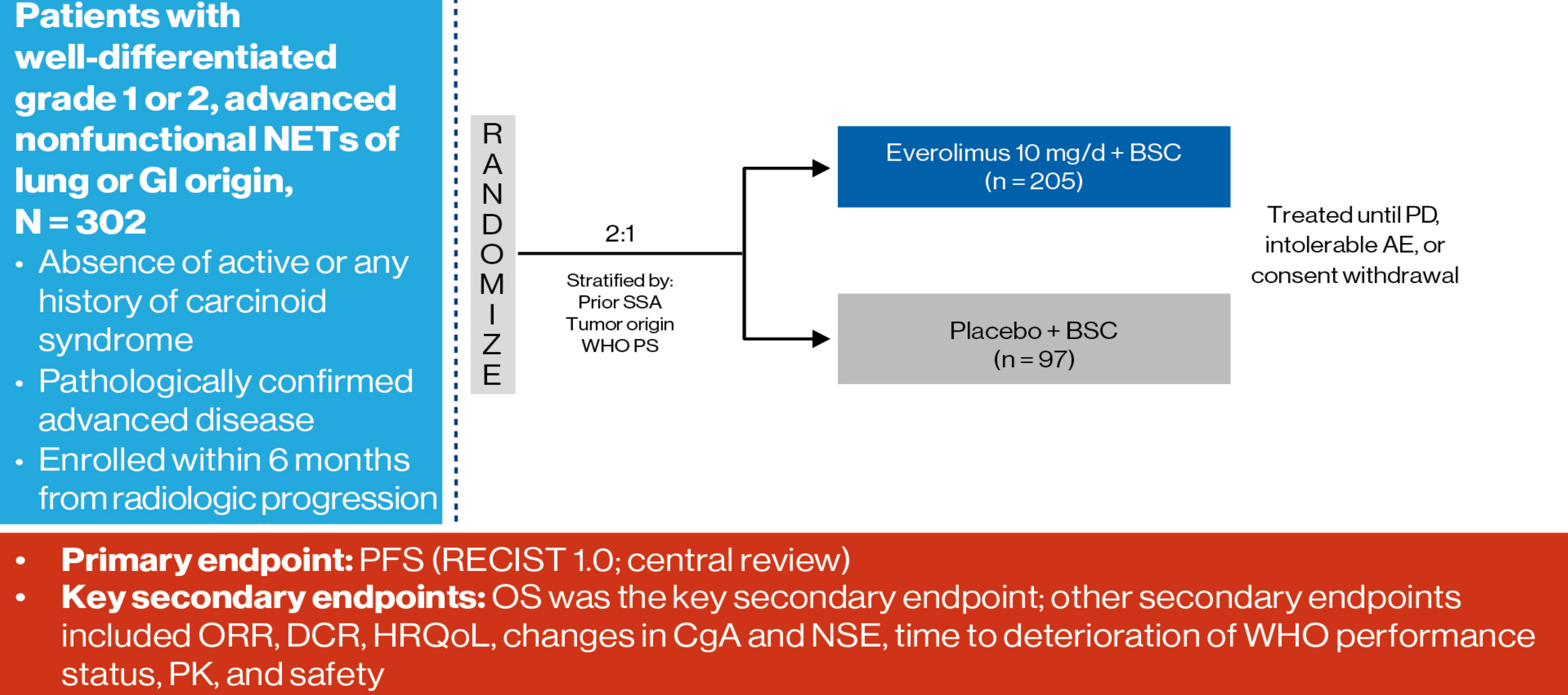


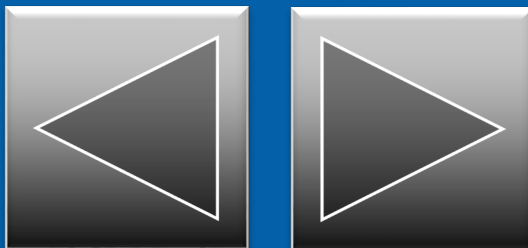
Figure 1B. RADIANT-4 Study Design



Relationship Between Metabolic Toxicity and Efficacy of Everolimus in Patients With Neuroendocrine Tumors (NETs): A Pooled Analysis From the Randomized, Phase 3 RADIANT-3 and RADIANT-4 Trials

Nicola Fazio,¹ Carlo Carnaghi,² Roberto Buzzoni,³ Juan W Valle,⁴ Fabian Herbst,⁵ Antonia Ridolfi,⁶ Jonathan Strosberg,⁷ Matthew H Kulke,⁸ Marianne Pavel,⁹ James C Yao¹⁰

¹European Institute of Oncology, Milan, Italy; ²IRCCS Istituto Clinico Humanitas, Rozzano, Italy; ³Fondazione IRCCS, Istituto Nazionale dei Tumori, Milano, Italy; ⁴Division of Cancer Sciences, University of Manchester, The Christie NHS Foundation Trust, Manchester, United Kingdom; ⁵Novartis Pharma AG, Basel, Switzerland; ⁶Novartis Pharma S.A.S., Rueil-Malmaison, France; ⁷Moffitt Cancer Center, Tampa, Florida, USA; ⁸Dana-Farber Cancer Institute, Boston, Massachusetts, USA; ⁹University of Erlangen-Nuremberg, Erlangen, Germany; ¹⁰University of Texas MD Anderson Cancer Center, Houston, Texas, USA



Methods (Contd.)

Assessments

- PFS in the overall pooled population was assessed as per central radiology review.
- Duration of exposure was calculated based on the first and last dose of study drug treatment received by the patients.

Statistical Analysis

- A landmark analysis of PFS according to central assessment was performed for patients treated for 16 weeks and according to occurrence of any grade hyperglycemia, hypertriglyceridemia, and hypercholesterolemia within the first 16 weeks of treatment.
- PFS was estimated using the Kaplan-Meier methods. Hazard ratios and associated 95% confidence intervals (CIs) were computed using a Cox proportional hazard model.
- The landmark analysis was used to correct bias inherent to the confounding effect of duration of exposure.
- Safety set was considered to describe safety, and the patients in full analysis set with at least 16 weeks of drug-exposure were considered for efficacy landmark analysis.

Results

Subgroup Population

Safety

- The incidence rates of hyperglycemia and hypercholesterolemia (regardless of study drug relationship) were slightly higher among panNET patients (RADIANT-3) than in non-panNET patients (RADIANT-4) treated with everolimus (**Table 1**).
- The number of patients with hypertriglyceridemia was too low to draw any meaningful conclusion.

Table 1. All Grade Adverse Events of Hyperglycemia and Hypercholesterolemia (Regardless of the Drug-Relationship) in Patients From RADIANT-3 and RADIANT-4

Adverse Event	RADIANT-3 N = 204	RADIANT-4 N = 202
	All Grades, n (%)	All Grades, n (%)
Hyperglycemia	39 (19.1)	24 (11.9)
Hypercholesterolemia	20 (9.8)	13 (6.4)
Hypertriglyceridemia	8 (3.9)	11 (5.4)

Duration of Exposure

- The duration of exposure to everolimus was longer in patients who developed hyperglycemia and hypercholesterolemia than in patients without these events.
 - The median treatment duration of everolimus was 48 weeks for patients with hyperglycemia vs 39.71 weeks for patients without hyperglycemia, and 66.43 weeks for patients with hypercholesterolemia vs 38.71 weeks for patients without hypercholesterolemia (**Table 2**).

Table 2. Median Duration of Exposure for the Overall Population

Disease State	N = 406	Duration of Exposure ^a (Weeks)
Hyperglycemia, n		
With	63	48 (2.1-110.6)
Without	342	39.71 (0.7-4286)
Hypercholesterolemia, n		
With	33	66.43 (12.1-120.4)
Without	373	38.71 (0.7-4286)

^aData are presented as median (range). Duration of exposure (days) = (date of last administration of study treatment) – (date of first administration of study treatment) + 1. Duration of exposure was calculated on the safety set (based on the treatment received and not the randomized patients)

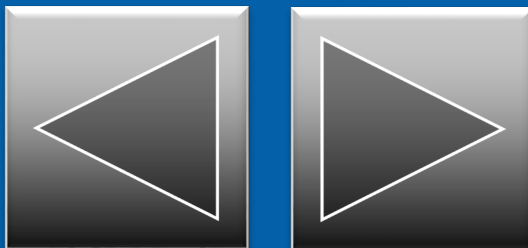
Progression-Free Survival in the Overall Pooled Population

- The improvement in PFS with everolimus in the pooled analysis was consistent with the findings of the individual RADIANT-3 and RADIANT-4 trials.
 - A total of 412 patients randomized, (RADIANT-3, n = 207; RADIANT-4, n = 205) treated with everolimus were included in the pooled analysis.
 - The median PFS (95% CI) with everolimus was 11.37 months (11.01–13.93) in the pooled analysis; 13.67 months (11.17–18.79) in RADIANT-3, and 11.01 months (9.23–13.31) in RADIANT-4 (**Figure 2-following slide**).

Relationship Between Metabolic Toxicity and Efficacy of Everolimus in Patients With Neuroendocrine Tumors (NETs): A Pooled Analysis From the Randomized, Phase 3 RADIANT-3 and RADIANT-4 Trials

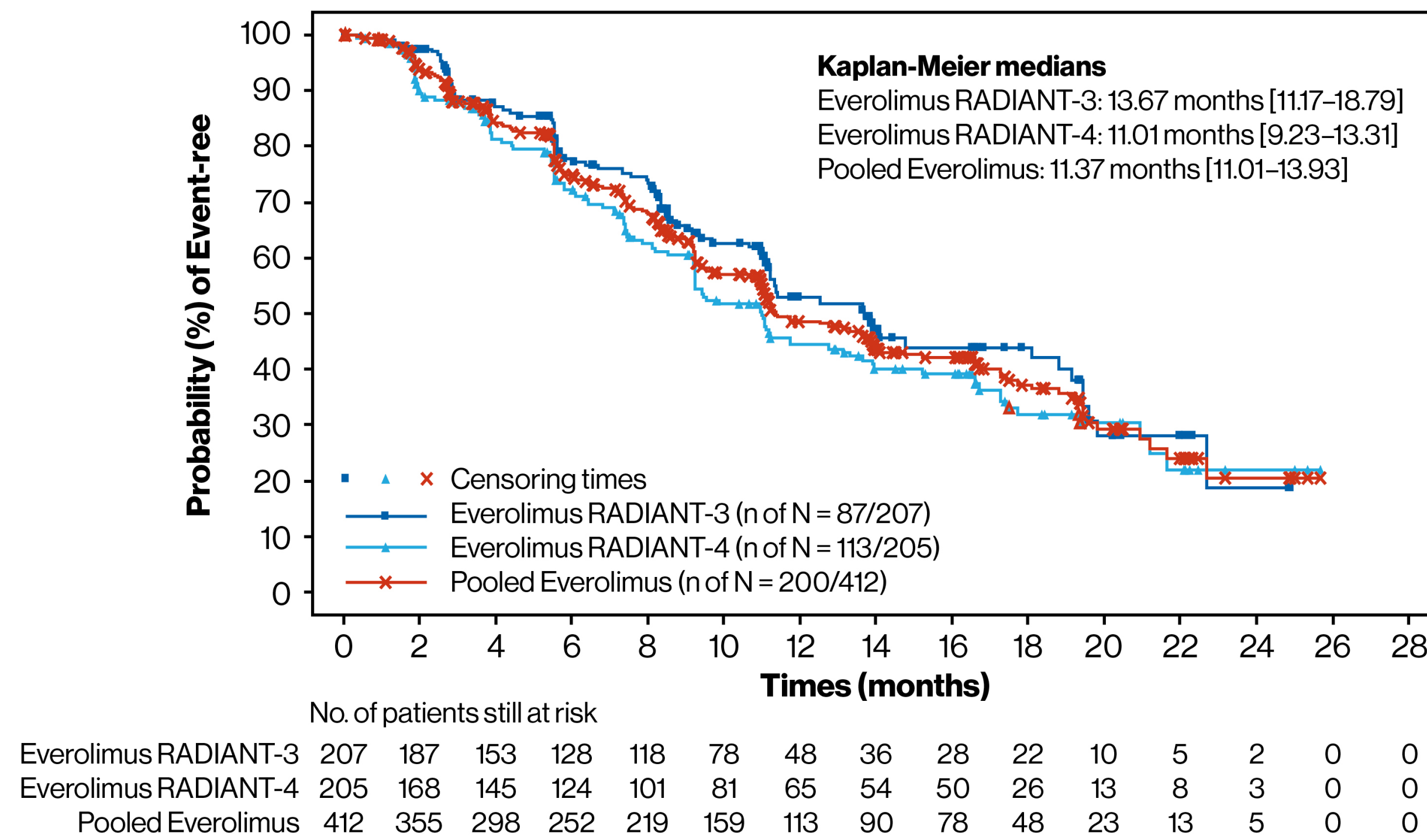
Nicola Fazio,¹ Carlo Carnaghi,² Roberto Buzzoni,³ Juan W Valle,⁴ Fabian Herbst,⁵ Antonia Ridolfi,⁶ Jonathan Strosberg,⁷ Matthew H Kulke,⁸ Marianne Pavel,⁹ James C Yao¹⁰

¹European Institute of Oncology, Milan, Italy; ²IRCCS Istituto Clinico Humanitas, Rozzano, Italy; ³Fondazione IRCCS, Istituto Nazionale dei Tumori, Milano, Italy; ⁴Division of Cancer Sciences, University of Manchester, The Christie NHS Foundation Trust, Manchester, United Kingdom; ⁵Novartis Pharma AG, Basel, Switzerland; ⁶Novartis Pharma S.A.S., Rueil-Malmaison, France; ⁷Moffitt Cancer Center, Tampa, Florida, USA; ⁸Dana-Farber Cancer Institute, Boston, Massachusetts, USA; ⁹University of Erlangen-Nuremberg, Erlangen, Germany; ¹⁰University of Texas MD Anderson Cancer Center, Houston, Texas, USA



Results (Contd.)

Figure 2. Kaplan-Meier Plot of PFS Per Central Review in Everolimus-Treated Patients; Full Analysis Set

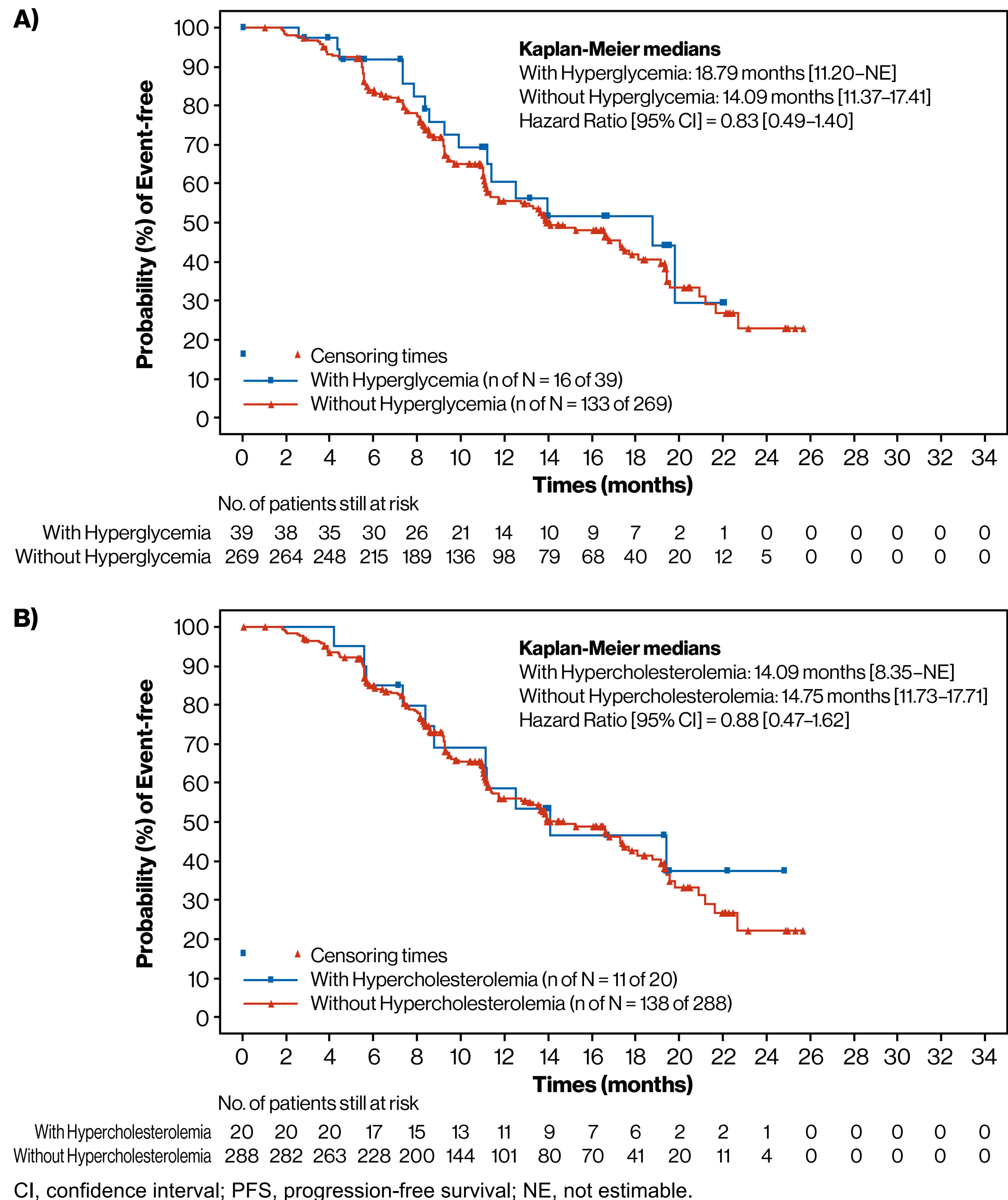


PFS, progression-free survival.

PFS Landmark Analysis in Patients With and Without AE

- The development of hyperglycemia and hypercholesterolemia on treatment with everolimus were not significantly associated with improvements in PFS.
- A total of 308 patients were exposed to the treatment for at least 16 weeks (with/without: hyperglycemia [n = 39/269] and hypercholesterolemia [n = 20/288]).
- The median PFS (95% CI) was 18.79 months (11.20–not estimable [NE]) and 14.09 months (11.37–17.41) among everolimus-treated patients who did and did not develop hyperglycemia, respectively (**Figure 3A**).
- PFS was 14.09 months (8.35–NE) and 14.75 months (11.73–17.71) for those who did and did not develop hypercholesterolemia, respectively (**Figure 3B**).
 - The median PFS was comparatively higher in patients who develop hyperglycemia than the overall population; this effect might be due to a longer duration of drug exposure in patients who develop hyperglycemia vs overall population.

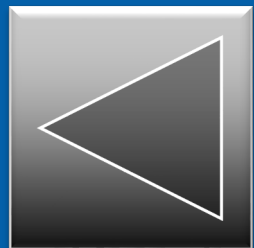
Figure 3. Kaplan-Meier Plot of PFS (Central Review) in Everolimus-Treated Patients With/Without (A) Hyperglycemia (B) Hypercholesterolemia – Landmark 16 weeks



Relationship Between Metabolic Toxicity and Efficacy of Everolimus in Patients With Neuroendocrine Tumors (NETs): A Pooled Analysis From the Randomized, Phase 3 RADIANT-3 and RADIANT-4 Trials

Nicola Fazio,¹ Carlo Carnaghi,² Roberto Buzzoni,³ Juan W Valle,⁴ Fabian Herbst,⁵ Antonia Ridolfi,⁶ Jonathan Strosberg,⁷ Matthew H Kulke,⁸ Marianne Pavel,⁹ James C Yao¹⁰

¹European Institute of Oncology, Milan, Italy; ²IRCCS Istituto Clinico Humanitas, Rozzano, Italy; ³Fondazione IRCCS, Istituto Nazionale dei Tumori, Milano, Italy; ⁴Division of Cancer Sciences, University of Manchester, The Christie NHS Foundation Trust, Manchester, United Kingdom; ⁵Novartis Pharma AG, Basel, Switzerland; ⁶Novartis Pharma S.A.S., Rueil-Malmaison, France; ⁷Moffitt Cancer Center, Tampa, Florida, USA; ⁸Dana-Farber Cancer Institute, Boston, Massachusetts, USA; ⁹University of Erlangen-Nuremberg, Erlangen, Germany; ¹⁰University of Texas MD Anderson Cancer Center, Houston, Texas, USA



Conclusions

- The results of this exploratory analysis showed no correlation between the metabolic toxicities (hyperglycemia and hypercholesterolemia) and PFS.
 - There was a trend towards improved PFS among patients who developed hyperglycemia, however the numbers of events were very low and it remains unclear if any meaningful conclusions can be drawn from this observation.
- A cause-effect relationship was observed between the duration of drug exposure and development of hyperglycemia and hypercholesterolemia.
- These results suggest that development of metabolic toxicity had no significant impact on PFS or duration of treatment among patients receiving everolimus in the RADIANT-3 and RADIANT-4 trials.
 - An increase of glucose and/or cholesterol levels may not be useful as a predictor of efficacy during treatment with everolimus in patients with NETs.
- However, these findings warrant further investigation in future prospective studies.

References

1. Ravaud A. <i>The Oncologist</i> 2011;16:32-44.	4. Yao JC, et al. <i>N Engl J Med</i> 2011;364:514-523.
2. Pantano F, et al. <i>PLoS One</i> 2015;10:e0120427.	5. Yao JC, et al. <i>Lancet</i> . 2016;387:968-977.
3. Petri Bono SO, et al. <i>Clin Genitourin Cancer</i> 2016;14:406-414.	

Disclosures

NF reports consultation fee from Novartis, Ipsen, Pfizer, Merck Serono and AAA; and research funds from Novartis and Merck Serono. J WV reports grants and personal fee from Novartis. JS reports personal fee from Novartis. JCY reports consultation fee from Novartis and Ipsen. MHK reports consultation fee from Lexicon, Novartis, and Ipsen. MP reports grants and personal fee from Novartis and Ipsen, and personal fee from Pfizer and Lexicon. CC and RB has nothing to disclose. FH and AR are employees of Novartis.

Acknowledgments

The study was sponsored by Novartis Pharmaceuticals Corporation. We thank the patients and investigators for their participation in the study; we also thank the worldwide network of research nurses, trial coordinators, and operations staff for their contributions. In addition, we would like to thank Anamika Gulati of Novartis Healthcare Pvt Ltd for medical editorial assistance with this poster.

Presented at NANETS Annual Multidisciplinary NET Disease Symposium, Seattle, Washington; 4-6 October 2018

Previously presented at 15th Annual ENETS Conference, Barcelona, Spain; 7-9 March 2018

Text: Q63212

To: 8NOVA (86682) US Only
+18324604729 North, Central and South Americas; Caribbean; China
+447860024038 UK, Europe & Russia
+46737494608 Sweden, Europe

Visit the web at:

<http://novartis.medicalcongressposters.com/Default.aspx?doc=63212>

Copies of this poster obtained through Quick Response (QR) code are for personal use only and may not be reproduced without written permission of the authors

Scan this QR code



Corresponding author:
nicola.fazio@ieo.it