

Everolimus + Octreotide LAR vs Placebo + Octreotide LAR in Patients With Advanced Neuroendocrine Tumors (NET): Updated Results of a Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase III Trial (RADIANT-2)

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BACKGROUND

- Most patients with neuroendocrine tumors (NET) have advanced disease at the time of diagnosis, and 65% die within the first 5 years after diagnosis¹
- There are no approved therapies for controlling NET disease progression, and only a limited number of large phase III trials have enrolled patients with advanced NET
- The pathogenesis of NET has been linked to the overactivation of mammalian target of rapamycin (mTOR), a serine-threonine kinase that stimulates cell growth, proliferation, metabolism, and angiogenesis²
- Everolimus, an oral inhibitor of mTOR, demonstrated promising antitumor activity in patients with advanced NET as a single agent and in combination with octreotide long-acting repeatable (LAR) in two phase II studies^{3,4}
- Octreotide downregulates insulin-like growth factor-1, an upstream activator of the PI3K/AKT/mTOR pathway⁵
- Octreotide LAR, historically used for symptom control, prolongs the time to disease progression⁶
- Everolimus with octreotide LAR, through the dual inhibition of mTOR and growth factors, is a rational treatment approach for patients with advanced NET

OBJECTIVE

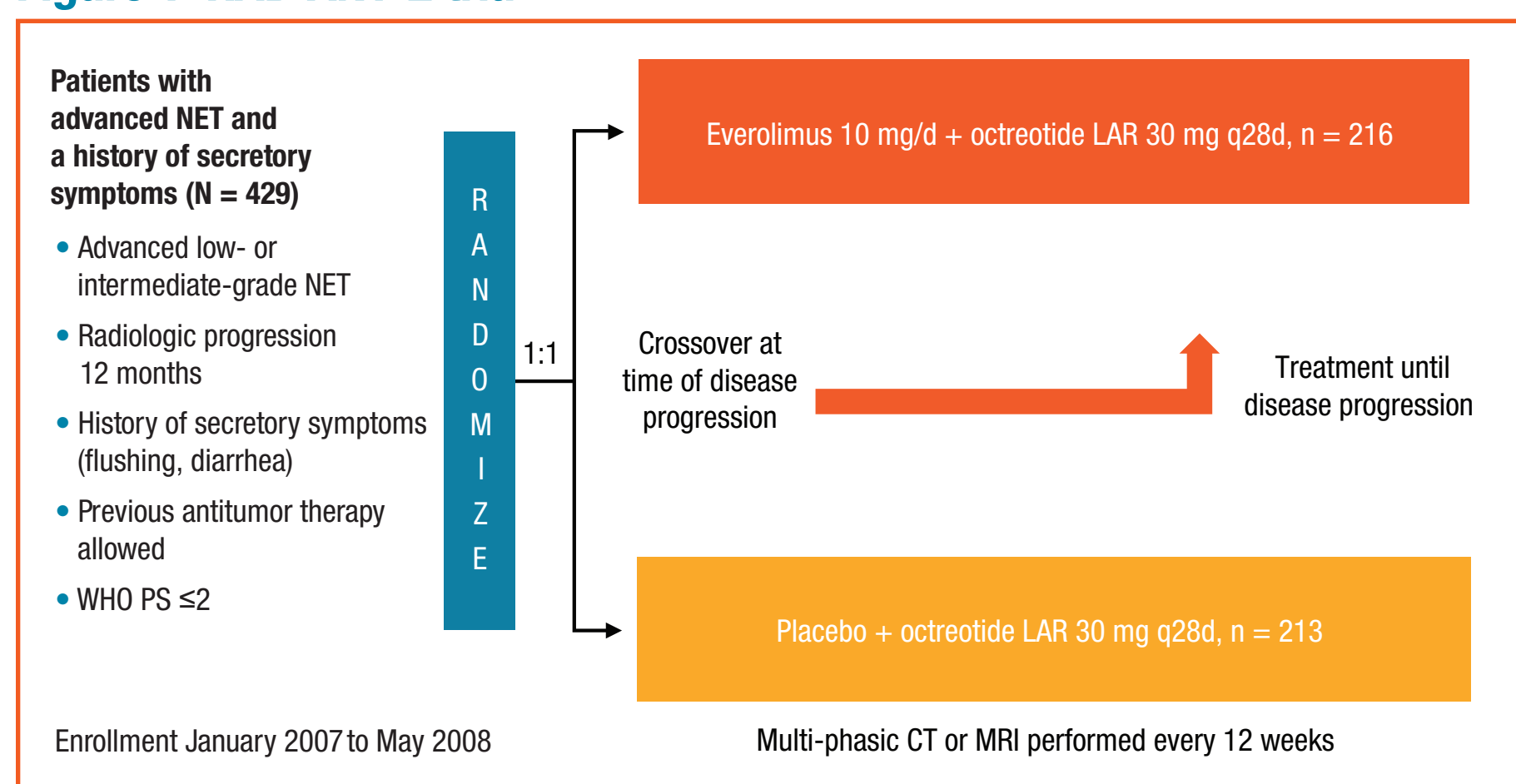
- To evaluate everolimus in combination with octreotide LAR in the treatment of patients with advanced NET in a randomized, double-blind, placebo-controlled, phase III study

METHODS

Study Design and Patient Population

- RADIANT-2 was an international, multicenter, double-blind, placebo-controlled, phase III study (Figure 1)

Figure 1. RADIANT-2 trial.



- Patients received oral everolimus 10 mg/d or matching placebo; each was administered in conjunction with intramuscular octreotide LAR 30 mg every 28 days
- Treatment continued until progression of disease, development of unacceptable toxic effects, or withdrawal of consent
- Dose adjustments were permitted for patients unable to tolerate the protocol-specified dosing schedule
- Patients randomly assigned to placebo + octreotide LAR were permitted to cross over to open-label everolimus + octreotide LAR upon disease progression
- Primary endpoint was progression-free survival (PFS) by adjudicated central review (RECIST version 1.0)
- Secondary endpoints included confirmed objective response rate, overall survival, and safety

Demographics and Disease Characteristics

- A total of 429 patients with advanced NET were randomly assigned to everolimus + octreotide LAR (216 patients) or placebo + octreotide LAR (213 patients)
- Important prognostic baseline characteristics (lung as the primary site, WHO performance status, and previous chemotherapy) were imbalanced (Table 1)

Table 1. Baseline Demographics and Disease Characteristics

	Everolimus + Octreotide LAR n = 216	Placebo + Octreotide LAR n = 213
Median age, y (range)	60 (22–83)	60 (27–81)
Sex, %		
Male	45	58
Female	55	42
WHO performance status, %		
0	55	66
1/2*	39/6	29/5
Primary site of cancer, %		
Small intestine	51	53
Lung ^a	15	5
Colon	6	7
Pancreas	5	7
Liver	3	5
Histologic grade, %		
Well differentiated	77	82
Moderately differentiated	18	14
Poorly differentiated	1	1
Unknown/missing	5	3
Previous long-acting somatostatin analog, %	80	78
Other previous systemic antitumor therapy, %	46	39
Chemotherapy ^b	35	26
Immunotherapy	13	9
Targeted therapy	7	8
Other	10	13

*Statistically significant for imbalance ($P < 0.05$).

- Median follow-up was 28 months; median (range) duration of treatment was 37 (1–163) weeks in the everolimus + octreotide LAR arm and 37 (0–152) weeks in the placebo + octreotide LAR arm (Table 2)
- Primary reasons for treatment discontinuation were disease progression and adverse events (Table 2)

Table 2. Patient Disposition

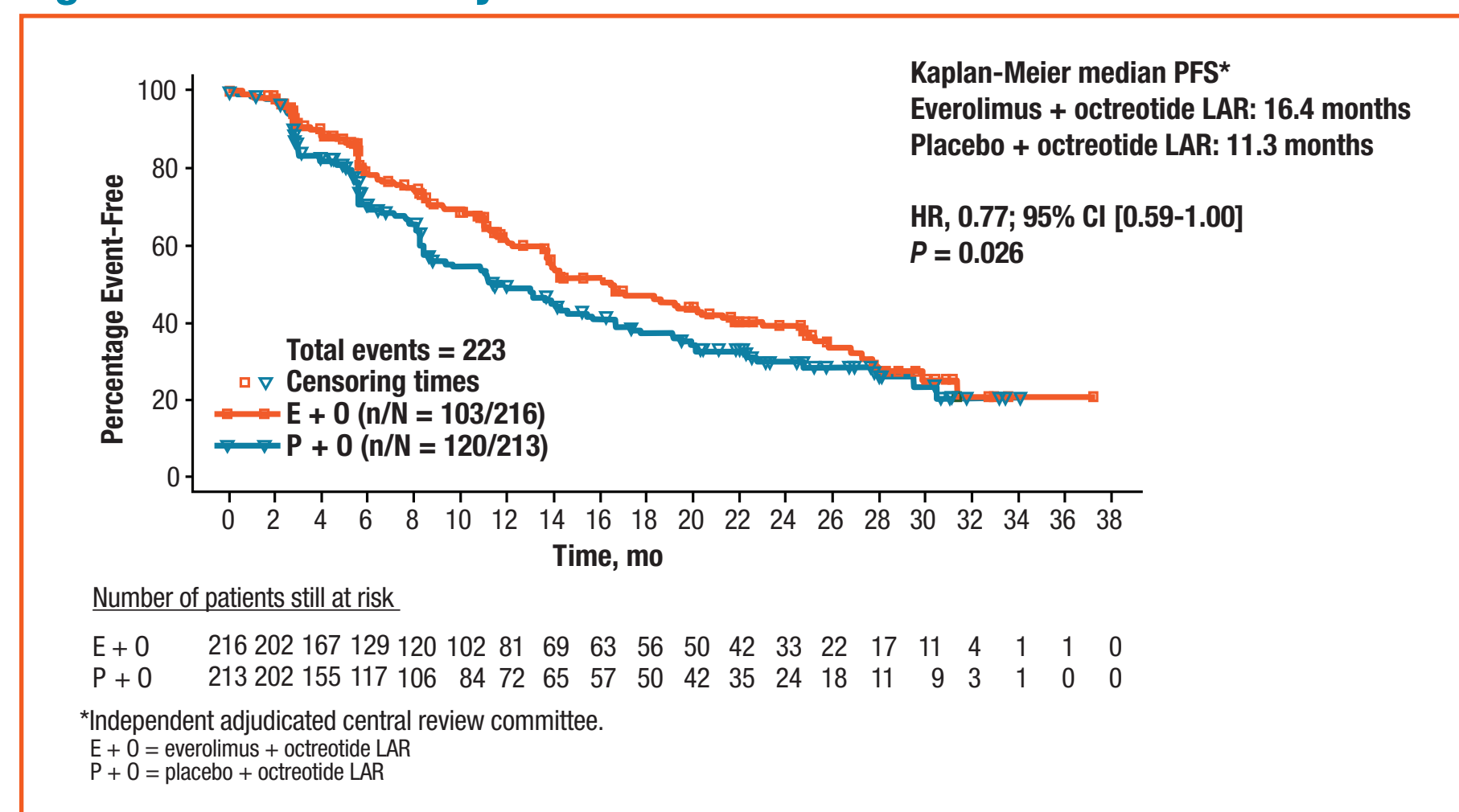
	Everolimus + Octreotide LAR n = 216	Placebo + Octreotide LAR n = 213
Median duration of exposure, wks (range)	37.0 (1–163)	36.6 (0–152)
Treatment ongoing, n (%)	37 (17.1)	34 (16.0)
Discontinuation, n (%)	179 (82.9)	179 (84.0)
Disease progression	95 (44.0)	146 (68.5)
AEs	57 (26.4)	14 (6.6)
Withdrawal of consent	17 (7.9)	11 (5.2)
Death	6 (2.8)	2 (0.9)
Protocol violation	3 (1.4)	4 (1.9)
New cancer therapy	1 (0.5)	1 (0.5)
Lost to follow-up	0 (0)	1 (0.5)
Crossover to everolimus, n (%)	—	123 (58)

RESULTS

Progression-Free Survival by Central Review

- The primary endpoint was PFS assessed by independent adjudicated central review committee using RECIST v1.0 criteria
- Everolimus + octreotide LAR provided clinically meaningful 5.1-month improvement in median PFS compared with placebo + octreotide LAR (Figure 2)
- There was a 23% reduction in the relative risk of progression (HR = 0.77; 95% confidence interval [CI], 0.59–1.00; $P = 0.026$)
 - The predefined statistical boundary was 0.0246
- Sustained benefit was demonstrated for everolimus + octreotide LAR versus placebo + octreotide LAR (Figure 2)
 - 12-month PFS rates: 95% CI, 60.6% (52.6–67.6) versus 48.7% (41.0–56.0), respectively
 - 18-month PFS rates: 95% CI, 47.2% (38.9–55.1) versus 37.4 (29.9–44.9), respectively

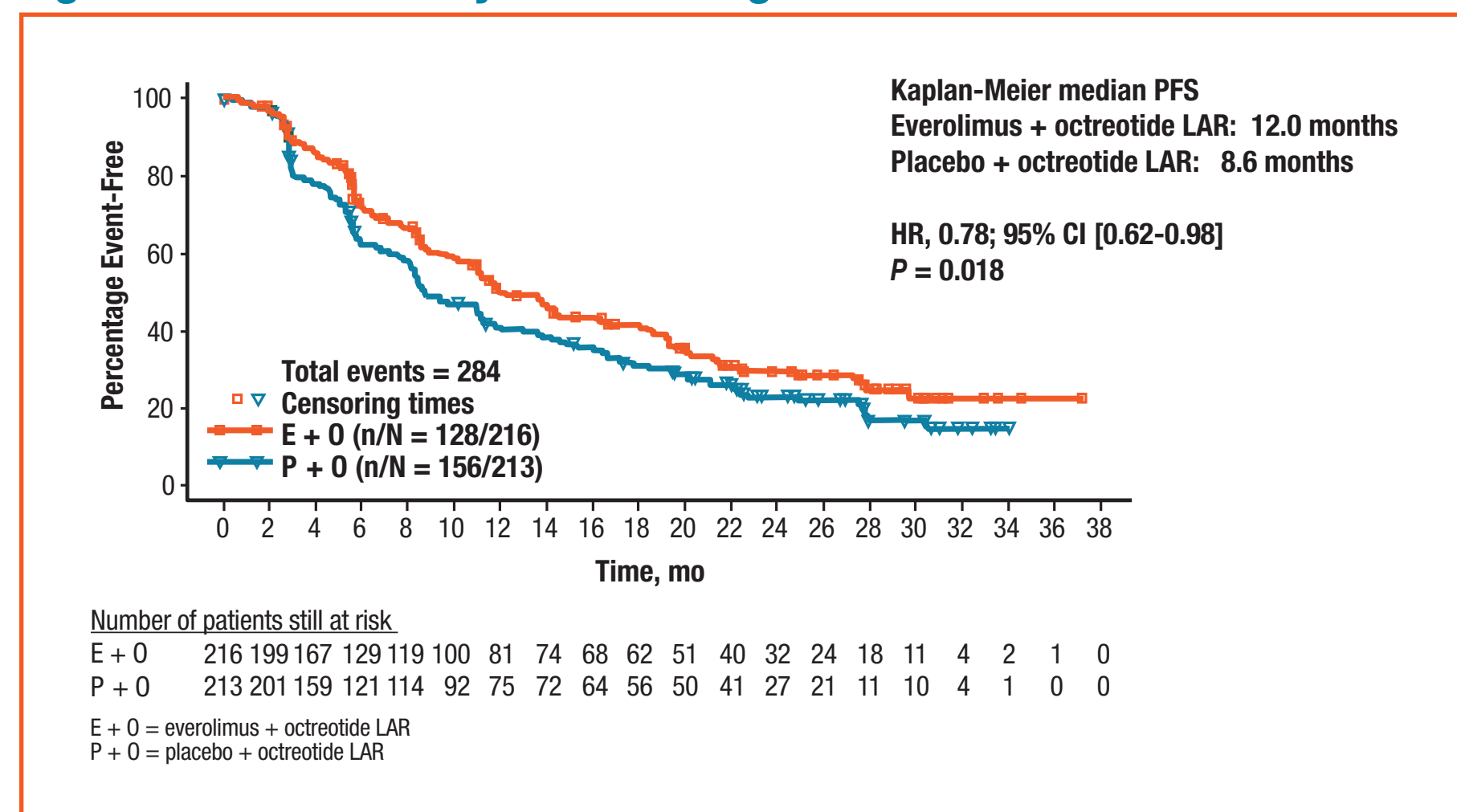
Figure 2. Median PFS by central review.



Progression-Free Survival by Local Investigator Review

- Hazard ratios (HRs) were similar in the local investigator review and the central review, but more PFS events were captured in the local investigator review, resulting in a lower P value ($P = 0.018$) crossing the significance threshold (Figure 3)
- The 22% reduction in risk of progression in the local investigator review supports the efficacy of everolimus + octreotide LAR (Figure 3)

Figure 3. Median PFS by local investigator review.



Inverse Probability of Censoring Weights Analysis

- Inverse probability of censoring weights (IPCW) is a well-established and validated methodology applied to adjust for informative censoring in clinical trials (Table 3)
- IPCW has been applied to other large phase 3 trials (BIG1-98⁷ and ACTG-021[HIV]⁸)
- Informative censoring in this trial resulted in a loss of PFS events (Table 3)

Table 3. PFS Comparison Including IPCW Analysis

	Hazard Ratio (95% CI)	P	Median PFS, mo	
			Everolimus + Octreotide LAR	Placebo + Octreotide LAR
Central review ^a 223 events	0.77 (0.59-1.00)	0.026	16.4	11.3
Local investigator review 284 events	0.78 (0.62-0.98)	0.018	12.0	8.6
IPCW	0.60 (0.44-0.84)	0.0014	13.8	8.3

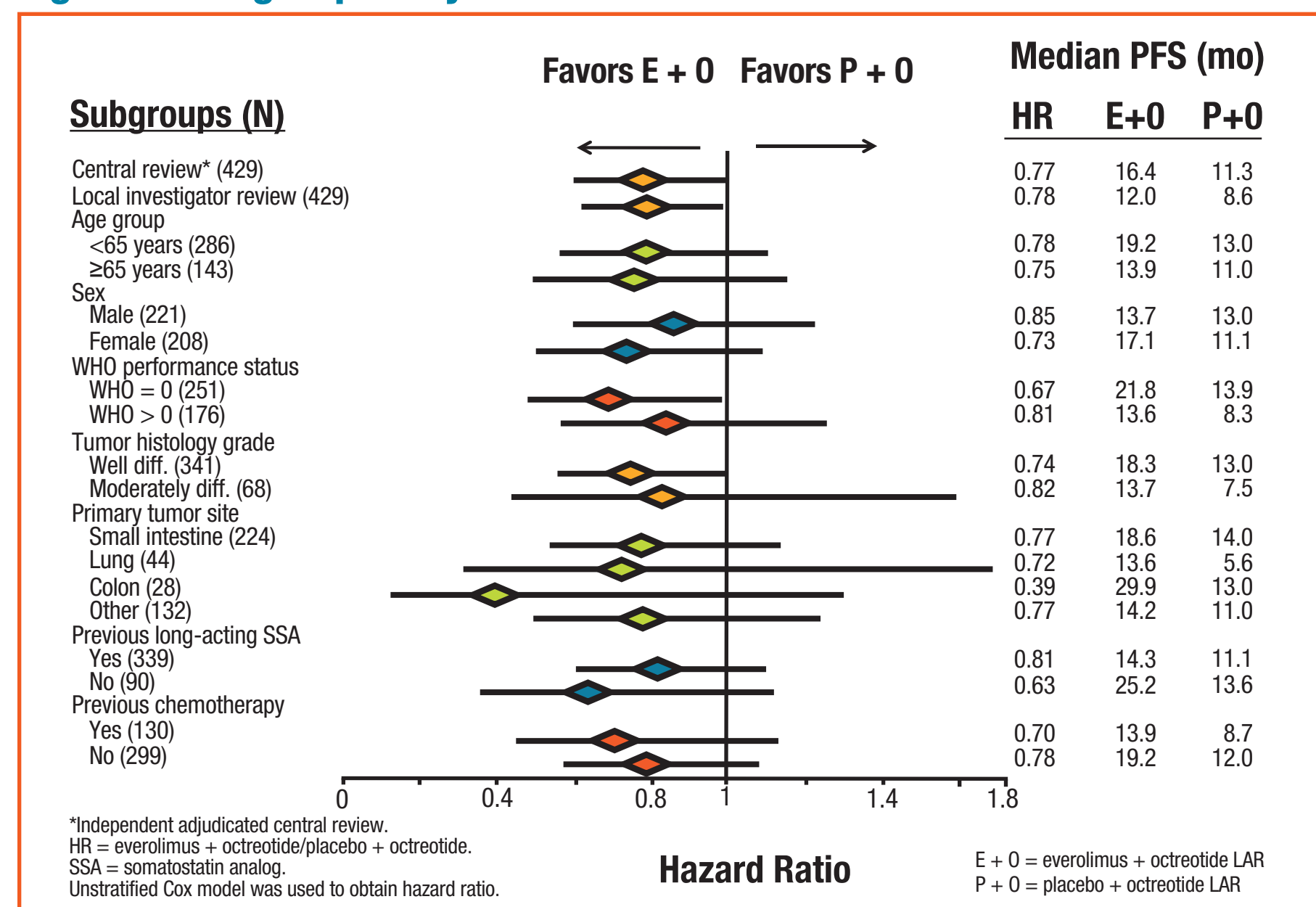
^aIndependent adjudicated central review committee.

- The IPCW model assigns weights based on the assessed probability of censorship for each patient during each time segment and provides a corrected treatment effect estimate of PFS
- IPCW analysis corrected for the bias introduced by informative censoring and imbalances of prognostic baseline patient characteristics, further supporting the benefit of everolimus + octreotide LAR compared with placebo + octreotide LAR (HR, 0.60; 95% CI, 0.44–0.84; $P = 0.0014$) (Table 3)

Subgroup Analysis of Progression-Free Survival

- Benefit of everolimus + octreotide LAR was demonstrated by consistent improvement in PFS across all patient subgroups (Figure 4)
- A benefit of everolimus + octreotide LAR was evident regardless of previous use of chemotherapy of somatostatin analog therapy, WHO performance status, age, sex, tumor grade, and primary tumor site (Figure 4)

Figure 4. Subgroup analysis of PFS.



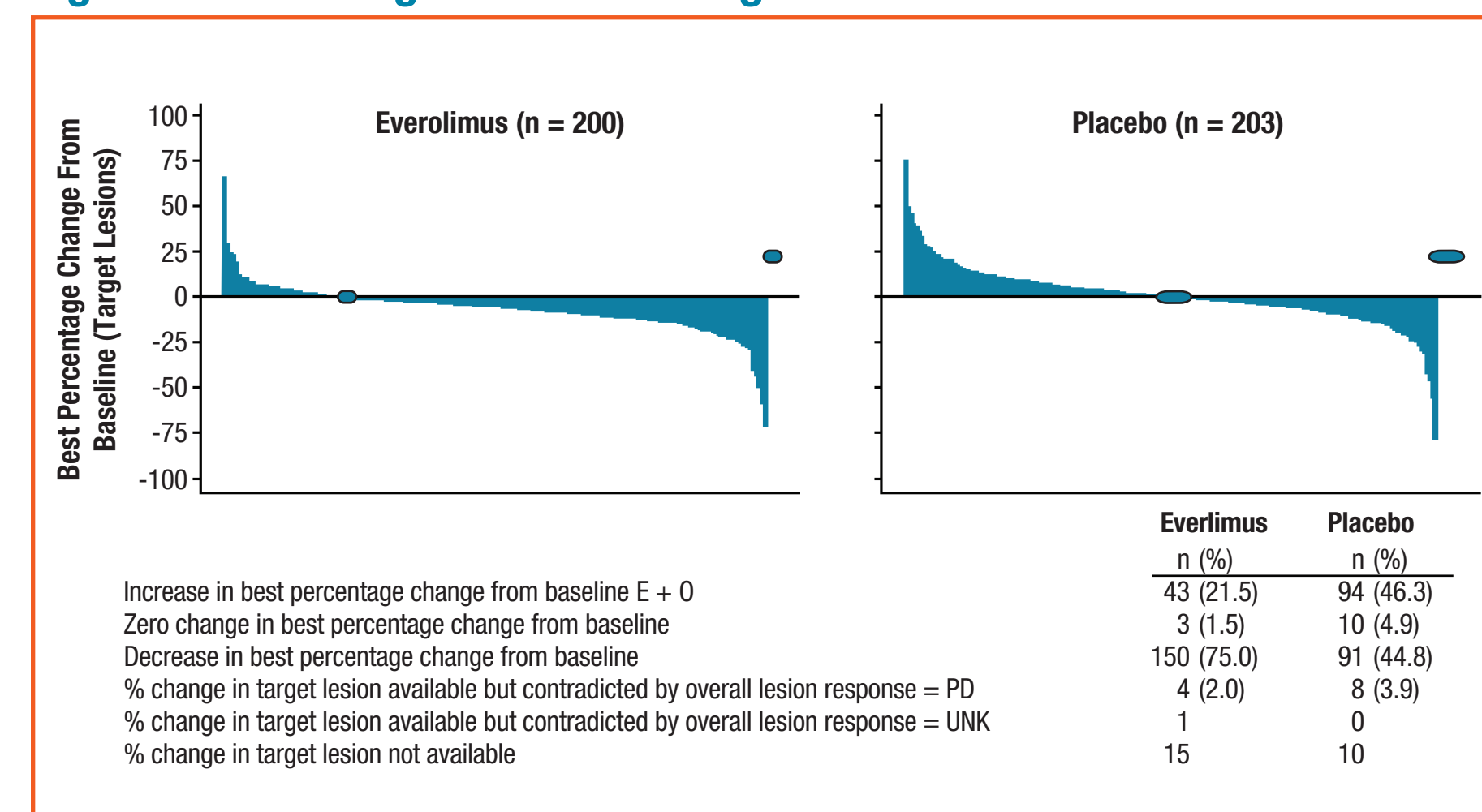
Tumor Shrinkage

- Objective responses were assessed by RECIST version 1.0 criteria (Table 4)
- Benefit from everolimus + octreotide LAR, compared with placebo + octreotide LAR, resulted primarily from tumor shrinkage not meeting the criteria for objective response and in the lower incidence of progressive disease (Figure 5)

Table 4. Confirmed Objective Responses

	Everolimus + Octreotide LAR n = 216	Placebo + Octreotide LAR n = 213
Partial response, n (%)	5 (2.3)	4 (1.9)
Stable disease, n (%)	182 (84.3)	172 (80.8)
Progressive disease, n (%)	9 (4.2)	26 (12.2)

Figure 5. Percentage tumor shrinkage from baseline.



Overall Survival

- A total of 123 patients (58%) in the placebo + octreotide LAR arm crossed over to open-label everolimus + octreotide LAR at the time of disease progression
- At the time of this analysis, 185 patients had died; the final overall survival analysis will be conducted after 252 deaths have occurred

Table 5. Kaplan-Meier Estimates of Overall Survival

Kaplan-Meier Estimate, mo	Everolimus + Octreotide LAR n = 216 (95% CI)	Placebo + Octreotide LAR n = 213 (95% CI)
6	91.1 (86.4, 94.2)	92.4 (87.9, 95.3)
12	80.9 (74.9, 85.6)	81.8 (75.8, 86.4)
18	70.6 (63.9, 76.3)	73.5 (66.9, 79.0)
24	57.1 (49.9, 63.6)	63.3 (56.2, 69.5)

Adverse Events

- Most frequently reported AEs related to everolimus + octreotide LAR treatment included stomatitis, rash, fatigue, diarrhea, nausea, and infection (Table 6)

Table 6. Treatment-Related AEs Occurring in ≥10% of Patients

	Everolimus + Octreotide LAR n = 215		Placebo + Octreotide LAR n = 211	
	All Grades, %	Grade 3/4, %	All Grades, %	Grade 3/4, %
Stomatitis ^a	62	7	14	0
Rash	37	1	12	0
Fatigue	31	7	23	3
Diarrhea	27	6	16	2
Nausea	20	1	16	1
Infections ^b	20	5	6	1
Dysgeusia	17	1	3	0
Anemia	15	1	5	0
Decreased weight	15	1	3	0
Thrombocytopenia	14	5	0	0
Decreased appetite	14	0	6	0
Peripheral edema	13	0	3	0
Hyperglycemia	12	5	2	1
Dyspnea	12	2	1	0
Pulmonary ^c	12	2	0	0
Vomiting	11	1	5	1
Pruritus	11	0	4	0
Asthma	10	1	7	1

^aIncludes stomatitis, aphthous stomatitis, mouth ulceration, and tongue ulceration.

^bIncludes all infections.

^cIncludes pneumonitis, interstitial lung disease, lung infiltration, and pulmonary fibrosis.

- Most commonly reported AEs leading to discontinuation of everolimus + octreotide LAR therapy were fatigue (2.3% of patients), diarrhea, general physical health deterioration, interstitial lung disease, and pneumonia (1.9% of patients in each arm)
- Safety profiles and discontinuation rates were similar to the known safety profile of everolimus + octreotide LAR

CONCLUSIONS

- In this pivotal large, randomized, double-blind, placebo-controlled, phase III trial, everolimus + octreotide LAR compared with placebo + octreotide LAR demonstrated a clinically meaningful 5.1-month improvement of median PFS by adjudicated central review
- Local investigator review and IPCW analysis supported the PFS benefit of everolimus + octreotide LAR
- Everolimus + octreotide LAR demonstrated PFS benefit across all patient subgroups
- Everolimus + octreotide LAR treatment was associated with tumor shrinkage in 75% of patients, in contrast to 45% of those who received placebo
- The safety profile of everolimus + octreotide LAR was manageable, and AEs were consistent with the agents
- Together with the findings from the RADIANT-3 trial, which demonstrated a significant 6.4-month improvement in PFS with everolimus therapy in patients with pNET, these results support the efficacy of everolimus in patients with advanced NET

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