

Safety and Efficacy of Everolimus in Advanced Nonfunctional Neuroendocrine Tumors (NET) of Lung or Gastrointestinal (GI) Origin: Findings of the Randomized, Placebo-Controlled, Double-blind, Multicenter, Phase 3 RADIANT-4 Study

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Background: Everolimus (EVE), an oral mTOR inhibitor, is approved in advanced pancreatic NET. Advanced, nonfunctional NET of lung/GI origin however remains an area of significant unmet medical need. The RADIANT-4 study evaluated the efficacy and safety of EVE in this NET population.

Methods: Patients with advanced, progressive, well-differentiated, nonfunctional lung/GI NET were randomized (2:1) to EVE (10 mg/d) or placebo (PBO), both with best supportive care. Patients were stratified by tumor origin, WHO performance status (PS), and prior somatostatin analogue (SSA) treatment. Primary endpoint was progression free survival (PFS) assessed by central radiology review (modified RECIST 1.0). Secondary endpoints included overall survival (OS), objective response rate (ORR), disease control rate (DCR), and safety.

Results: 302 patients were randomized to EVE (n=205) or PBO (n=97); median age, 63 yrs; 53% females; G1/G2: 64%/35%; WHO PS: 0, 74% or 1, 26%; majority (76%) were Caucasian; most common tumor sites: lung (30%), ileum (24%). EVE demonstrated a statistically significant increase in median PFS of 7.1 months over placebo in this patient population (table). Subgroup analyses of PFS by stratification factors were consistent with the primary efficacy analysis. A preplanned interim OS analysis showed an HR of 0.64 (95% CI, 0.40–1.05; *P*=0.037) in favor of EVE although not statistical significant (threshold *P*-value for significance, 0.000213). Drug-related

adverse events (AEs) were mainly G1/2; most common AEs included stomatitis, diarrhea, fatigue, infections, rash and peripheral edema. Most frequent drug-related G3/4 AEs are listed below (table).

Conclusions: RADIANT-4, the first large, PBO-controlled, phase 3 study in patients with advanced, progressive, nonfunctional lung/GI NET, provided unequivocal evidence for the efficacy of EVE in this population. EVE demonstrated a statistically significant 52% risk reduction in progression or death along with clinically meaningful 7.1-month prolongation of PFS vs PBO. AEs were consistent with the known safety profile of EVE.

	EVE	PBO	HR (95% CI)	P-value
Prior therapies				
SSA therapy	53%	56%		
Chemotherapy	26%	24%		
Radiotherapy*	22%	20%		
	11%	10%		
Locoregional/Ablative**				
Median PFS Months (95% CI)	11.0 (9.2–	3.9	0.48	<i>P</i> <0.001
Central review	13.3)	(3.6–	(0.35–	<i>P</i> <0.001
Investigator review	14.0	7.4)	0.67)	
	(11.2–	5.5	0.39	
	17.7)	(3.7–	(0.28–	
		7.4)	0.54)	
ORR (All PR)	2%	1%		
DCR (PR + CR + SD)	82%	65%		
Progressive disease	9%	27%		
Grade 3/4 AEs (drug-related)				
Stomatitis	9%	0%		
Diarrhea	7%	2%		
Infections	7%	0%		
Anemia	4%	1%		
Fatigue	4%	1%		
Hyperglycemia	4%	0%		

*includes peptide receptor radionuclide therapy (PRRT)

**includes transarterial embolization (TAE), cryoablation or radiofrequency ablation.

Conflict of interest

James C. Yao: Consulting or Advisory Role – Ipsen, Lexicon, Novartis; Research Funding - Novartis (to institute)

Nicola Fazio: Honoraria – Ipsen, Novartis; Consulting or Advisory Role – Celgene, Ipsen, Lexicon, Novartis; Travel, Accommodations, Expenses - Ipsen, Novartis; Research Funding - Novartis (to institute)

Simron Singh: Honoraria – Novartis; Consulting or Advisory Role – Novartis; Research Funding -Novartis (to institute); Travel, Accommodations, Expenses – Novartis

Roberto Buzzoni: Research Funding - Italfarmaco (to institute), Novartis (to institute), Otsuka (to institute); Travel, Accommodations, Expenses - Ipsen; Italfarmaco; Novartis

Carlo Carnaghi: No Relationships to Disclose

Edward M. Wolin: Consulting or Advisory Role – Celgene, Ipsen, Novartis

Jiri Tomasek: Honoraria – Novartis; Research Funding - Novartis (to institute); Travel, Accommodations, Expenses – Novartis

Markus Raderer: Honoraria – Celgene, Ipsen, Novartis, Roche; Consulting or Advisory Role – Celgene, Ipsen, Novartis, Roche

Harald Lahner: Honoraria – Ipsen, Novartis, Pfizer; Consulting or Advisory Role – Novartis, Pfizer; Research Funding - Novartis (to institute); Travel, Accommodations, Expenses – Ipsen, Novartis, Pfizer

Maurizio Voi: Employment – Novartis; Stock and Other Ownership Interests – Novartis

Lida Pacaud: Employment – Novartis; Stock and Other Ownership Interests – Novartis

Nicolas Rouyrre: Employment – Novartis; Stock and Other Ownership Interests – Novartis

Carolin Sachs: Employment – Novartis; Stock and Other Ownership Interests – Novartis

Juan W. Valle: Honoraria – Novartis; Consulting or Advisory Role – Novartis; Research Funding -Novartis (to institute)

Gianfranco Delle Fave: Consulting or Advisory Role – Novartis; Research Funding – Novartis

Eric Van Cutsem: Research Funding - Novartis (to institute)

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