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The VEGF Pathway in Pancreatic Neuroendocrine Tumors: Prognostic and Predictive Capacity of Baseline Biomarker Levels on Efficacy of Everolimus Analyzed From the RADIANT-3 Study

James C. Yao[1]; Manisha Shah[2]; Ashok Panneerselvam[3]; David Chen[3]; Sotirios Stergiopoulos[3]; Tetsuhide Ito[4]; Marianne Pavel[5]

[1]The University of Texas MD Anderson Cancer Center, Houston, Texas, 77030, USA
[2]Ohio State University, Columbus, Ohio, 43210, USA
[3]Novartis Pharmaceuticals Corporation, Florham Park, New Jersey, 09732, USA
[4]Kyushu University, Fukuoka, 812-8581, Japan
[5]Charité Universitätsmedizin Berlin/Campus Virchow Klinikum, Berlin, 10117, Germany

Background: RADIANT-3, a phase III study, investigated the effect of the mTOR inhibitor everolimus on PFS in patients with advanced pancreatic neuroendocrine tumors. Everolimus significantly improved PFS compared with placebo (11 vs 4.6 months; HR=0.35; 95% CI, 0.27 to 0.45; *P*<.001). Here we investigate the predictive and prognostic effect of soluble VEGF pathway biomarkers among patients treated in this study.

Methods: Baseline plasma levels of VEGF-A, PlGF, sVEGFR1, and sVEGFR2 were determined by ELISA using multiplexed MSD platform. The optimal cutoffs for these markers were explored using the "survival tree analysis" method. Interaction of treatment and baseline marker status (< or ≥ cutoff) was analyzed using a Cox proportional hazards model to assess predictive effects of these markers. *P* values and hazard ratios for prognostic effects were obtained using stratified log rank test and Cox proportional hazards model, stratified by treatment.

Results: Significant improvement in PFS was observed in patients receiving everolimus compared with patients receiving placebo, regardless of baseline marker levels (*P*<.001, Table). Significantly longer PFS was seen in those with lower levels of VEGF-A, PlGF, and sVEGFR1, regardless of treatment. A trend for longer PFS was also observed for lower sVEGFR2 (Table).

Marker	**Cutoff** (pg/mL)	**Median PFS** (mts) <Cutoff vs ≥Cutoff	**Prognostic effect** HR [95% CI]; *P*	**Treatment effect;** *P*
VEGF-A	246.1	8.3 vs 5.5	1.50 [1.17-1.92]; <.001	<.001
PlGF	32.06	8.0 vs 4.2	1.52 [1.14-2.02]; .004	<.001
sVEGFR1	226.2	8.3 vs 5.5	1.62 [1.27-2.07]; <.001	<.001
sVEGFR2	24503.1	10.8 vs 5.7	1.30 [0.96-1.76]; .090	<.001

Conclusions: These exploratory analyses demonstrated consistent everolimus efficacy in all patients with advanced pNET irrespective of their baseline VEGF pathway biomarker levels, suggesting that the levels of the markers are not predictive of the efficacy of everolimus. Lower baseline levels of VEGF-A, PlGF, and sVEGFR1 are potential prognostic factors for pNET progression.

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