

**Correlation of Progression-Free Survival (PFS)
with Early Response of Biomarkers
Chromogranin A (CgA) and 5-
Hydroxyindoleacetic Acid (5-HIAA) Levels in
Patients with Advanced Neuroendocrine
Tumors: Phase III RADIANT-2 Study Results**

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Background: In RADIANT-2, everolimus 10 mg/d (an oral mTOR inhibitor) + octreotide LAR 30 mg IM q28 days (E+O) demonstrated a clinically meaningful 5.1-mo increase in median progression-free survival (PFS) compared with placebo + octreotide LAR (P+O) in patients with low- or intermediate-grade advanced neuroendocrine tumors (NET) and a history of flushing/diarrhea. Chromogranin A (CgA) and 5-hydroxyindoleacetic acid (5-HIAA) are NET biomarkers correlating with tumor burden or symptoms. The effects of early CgA and 5-HIAA response on PFS were analyzed.

Materials: 429 patients were randomized to E+O (n=216) or P+O (n=213). Serum CgA and 24-h urinary 5-HIAA were collected at baseline and, if elevated (>ULN), on day 1 of each monthly cycle. Relationship between early CgA and 5-HIAA responses ($\geq 30\%$ reductions on the first day of cycle 2 after 4 weeks of treatment compared to baseline values) with PFS were assessed using Kaplan-Meier and Cox-proportional hazard modeling.

Results: Significantly more E+O patients had early CgA (36.3% vs 23.1%) and 5-HIAA (37.1% vs 24.3%) responses than P+O patients. Median PFS was significantly longer in early CgA responders (20.0 vs 10.8 months; HR, 0.49; P<0.001) than in nonresponders, and was longer in patients with early 5-HIAA response than those without (17.1 vs 12.0 months; HR, 0.76; P=0.193) [table].

Conclusion: In RADIANT-2, E+O was associated with significantly more early CgA and 5-HIAA responses than P+O. Early CgA responses were associated with significant improvement in PFS regardless of treatment. A smaller, non-significant trend was seen for early 5-HIAA responses.

Table. Median PFS by early biomarker response.

	Biomarker Responders	Biomarker Nonresponders
	CgA Responders n=77	CgA Nonresponders n=179
Median PFS (95% CI)	20.0 months (13.8-27.8)	10.8 months (8.3-11.7)
HR (95% CI)	0.49 (0.33-0.72) P<0.001	
	5-HIAA Responders n=61	5-HIAA Nonresponders n=139
Median PFS (95% CI)	17.1 months (11.3-25.9)	12.0 months (8.4-14.3)
HR (95% CI)	0.76 (0.51-1.15) P=0.193	