Favorable Benefit-to-Risk Profile of Everolimus Upheld in Updated Safety Analyses

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The updated safety results of two studies have demonstrated a favorable benefit-to-risk profile of everolimus for progressive advanced neuroendocrine tumors. The findings are consistent with those of the initial safety analyses and the known safety profile of the drug in patients with cancer.

Everolimus is a mammalian target of rapamycin (mTOR) inhibitor that was studied in the RADIANT-2 and RADIANT-3 trials, two international, multicenter Phase 3 trials. In RADIANT-2, 429 adult patients with advanced neuroendocrine tumors with carcinoid syndrome were randomly assigned to treatment with octreotide LAR with either everolimus or placebo. In RADIANT-3, 410 patients with advanced neuroendocrine tumors of pancreatic origin were randomly assigned to best supportive care with either everolimus or placebo. The primary efficacy endpoint for both trials was progression-free survival (PFS). The results of the studies, which were reported in 2010, showed that the addition of everolimus led to significant increases in median PFS compared with placebo (16.4 months vs 11.3 months; p=0.026 in RADIANT-2; 11.0 months vs 4.6 months; p<0.0001 in RADIANT-3).

The updated safety analysis in each study represented an additional 3.1 months of follow-up compared with the initial analysis (median of 31.1 months [compared with 28 months] in RADIANT-2 and median of 20.1 months [compared with 17 months] in RADIANT-3). The safety population included 426 patients in RADIANT-2 (215 who received everolimus and 211 who received placebo) and 407 in RADIANT-3 (204 who received everolimus and 203 who received placebo).

Safety Analysis in RADIANT-2

David Gross, MD, Hadassah-Hebrew University Medical Center, Jerusalem, Israel, reported that the majority of treatment-related adverse events (AEs) in RADIANT-2 were grade 1 or 2. When considering AEs of all grades, stomatitis was the most common event (61.9%), followed by rash (37.2%) and fatigue (31.6%; Table 1). Other AEs included diarrhea (27.4%) and infections (20%). Pneumonitis was relatively infrequent, occurring in 9.3% in the everolimus + octreotide LAR group; 3 of these patients (1.4%) had grade 3 pneumonitis—this was modest compared with that reported in association with traditional cytotoxic chemotherapy.

The rate of grade 3 and 4 AEs was 40% and 5%, respectively, in the everolimus + octreotide LAR group, compared with 15% and 1% in the placebo + octreotide LAR group. The most common grade 3 AEs that were associated with everolimus were fatigue and stomatitis, each occurring in 7% (compared with 3% and 0% in the placebo groups). Diarrhea, infections, hyperglycemia, and thrombocytopenia also occurred in more than 3% of the everolimus + octreotide LAR group (Table 2).

Table 1. Updated Treatment-Related AEs (All Grades) in RADIANT-2 and RADIANT-3.

	Number of Patients (%) with AEs			
	RADIANT-2		RADIANT-3	
AE	EV + OC LAR	PL + OC LAR	EV + BSC	PL + BSC
Stomatitis	61.9	14.2	52.9	12.3
Rash	37.2	12.3	48.5	10.3
Fatigue	31.6	24.2	32.4	14.3
Diarrhea	27.4	15.6	34.3	10.3
Infections	20.0	7.1	24.0	5.9

EV=everolimus; OC=octreotide; PL=Placebo; BSC=Best Supportive Care.

Table 2. Updated Treatment-Related Grade 3 and 4 AEs Occurring in More than 3% of Patients in RADIANT-2.

	Number of Patients (%) with AEs			
	EV + OC LAR		PL + OC LAR	
AE	Grade 3	Grade 4	Grade 3	Grade 4
All	87 (40)	10 (5)	31 (15)	2 (1)
Fatigue	14 (7)	0	6 (3)	0
Stomatitis	14 (7)	0	0	0
Diarrhea	13 (6)	0	5 (2)	0
Infections	11 (5)	<1	<1	0
Hyperglycemia	11 (5)	0	1 (0.5)	0
Thrombocytopenia	9 (4)	1 (0.5)	0	0

EV=everolimus; OC=octreotide; PL=Placebo.

Overall, the AEs were modest compared with that reported in association with traditional cytotoxic chemotherapy. Most AEs were easily managed with dose modification or treatment interruptions, concomitant medication, or dietary interventions. Disease progression was the primary reason for treatment discontinuation in both groups. The rate of treatment-related AEs that led to discontinuation was 19.5% for the everolimus+octreotide LAR group compared with 3.8% for the placebo+octreotide LAR group.

Safety Analysis in RADIANT-3

Dieter Hörsch, MD, Klinik für Innere Medizin, ENETS Center of Excellence, Bad Berka, Germany, reported similar rates of treatment-related AEs in RADIANT-3. As in RADIANT-2, stomatitis, rash, fatigue, diarrhea, and infections were the most common events in RADIANT-3, although the rates of some events differed from those in RADIANT-2 (Table 1). Also similar was the infrequent occurrence of pneumonitis, which developed in 12.3% of patients who were treated with everolimus, 3 (1.4%) of whom had grade 3 pneumonitis.

Most AEs were manageable, resolving with dose modification or treatment interruptions or concomitant medication. The rate of treatment-related AEs that led to discontinuation was 13.7% for the everolimus group compared with 2.0% for the placebo group. Disease progression was the primary reason for treatment discontinuation in both groups.

The overall rate of grade 3 or 4 AEs in RADIANT-3 was also similar to that in RADIANT-2, affecting 41% and 5% of patients, respectively (Table 3). In addition, the rates of most AEs were similar to those in the other study, but the grade 3 events that occurred most frequently were different, with hyperglycemia being the most common (6%). Anemia was the second most common event (5%), followed by stomatitis (5%), thrombocytopenia (3%), and diarrhea (3%). The overall frequency of all treatment-related events (all grades) remained the same as in the initial safety analysis.

Table 3. Updated Treatment-Related Grade 3 and 4 AEs Occurring in More than 3% of Patients in RADIANT-3.

	Number of Patients (%) with AEs			
	EV + BSC		PL + BSC	
AE	Grade 3	Grade 4	Grade 3	Grade 4
All	84 (41)	10 (5)	26 (13)	3 (1)
Hyperglycemia	12 (6)	0	3 (1)	1(1)
Anemia	10 (5)	2 (1)	0	0
Stomatitis	10 (5)	0	0	0
Thrombocytopenia	7 (3)	1 (0.5)	0	0
Diarrhea	7 (3)	0	0	0

EV=everolimus; BSC=Best Supportive Care; PL=Placebo

Both Prof. Gross and Prof. Hörsch noted that the findings provide further evidence of the favorable risk-benefit profile of everolimus in patients with advanced neuroendocrine tumors and support the use of the drug as standard therapy in this setting. The findings of RADIANT-3 led to the United States Food and Drug Administration approval for the use of everolimus as treatment for progressive unresectable, locally advanced, or metastatic pancreatic neuroendocrine tumors in May 2010.