Relationship Between Metabolic Toxicity and Efficacy of Everolimus in Patients With Neuroendocrine Tumors (NETs): A Pooled Analysis From the Randomized, Phase 3 RADIANT-3 and RADIANT-4 Trials
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Introduction
• An improvement in progression-free survival (PFS) was observed with mammalian target of rapamycin (mTOR) inhibitors in patients with advanced renal cell carcinoma (RCC) who developed certain class-effect toxicities such as hyperglycemia, hypertriglyceridemia, and hypercholesterolemia.1
• Everolimus (mTOR inhibitor) therapy is an approved treatment for the management of patients with advanced gastrointestinal (GI) NETs, lung NETs, and pancreatic NETs (panNET).2–4

Methods
Study Design and Patient Population
• RADIANT-3 and RADIANT-4 were international, multicenter, randomized, double-blind, placebo-controlled phase 3 studies (Figure 1A and 1B).
  – In the RADIANT-3 trial, patients with advanced, low-, or intermediate-grade panNET received either oral everolimus 10 mg/day (N = 207) or placebo (N = 203).
  – In the RADIANT-4 trial, patients with advanced, low-, or intermediate-grade GI or lung NETs received either oral everolimus 10 mg/day (N = 205) or placebo (N = 97).
  – In both studies, treatment continued until disease progression, initiation of new cancer therapy, development of an intolerable AE, or withdrawal of consent. The dose reduction of everolimus to 5 mg/day was permitted in case of unacceptable toxicity.

Figure 1A. RADIANT-3 Study Design

Figure 1B. RADIANT-4 Study Design
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Methods (Contd.)

Assessments
• PFS in the overall pooled population was assessed as per central radiology review.
• Duration of exposure was calculated based on the first and last dose of study drug treatment received by the patients.

Statistical Analysis
• A landmark analysis of PFS according to central assessment was performed for patients treated for 16 weeks and according to occurrence of any grade hyperglycemia, hypertriglyceridemia, and hypercholesterolemia within the first 16 weeks of treatment.
• PFS was estimated using the Kaplan-Meier methods. Hazard ratios and associated 95% confidence intervals (CIs) were computed using a Cox proportional hazard model.
• The landmark analysis was used to correct bias inherent to the confounding effect of duration of exposure.
• Safety set was considered to describe safety, and the patients in full analysis set with at least 16 weeks of drug-exposure were considered for efficacy landmark analysis.

Results

Subgroup Population

Safety
• The incidence rates of hyperglycemia and hypercholesterolemia (regardless of study drug relationship) were slightly higher among panNET patients (RADIANT-3) than in non-panNET patients (RADIANT-4) treated with everolimus (Table 1).
• The number of patients with hypertriglyceridemia was too low to draw any meaningful conclusion.

Table 1. All Grade Adverse Events of Hyperglycemia and Hypercholesterolemia (Regardless of the Drug-Relationship) in Patients From RADIANT-3 and RADIANT-4

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>RADIANT-3</th>
<th>RADIANT-4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 204 All Grades, n (%)</td>
<td>N = 202 All Grades, n (%)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>39 (19.1)</td>
<td>24 (11.9)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>20 (9.8)</td>
<td>13 (6.4)</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>8 (3.9)</td>
<td>11 (5.4)</td>
</tr>
</tbody>
</table>

Duration of Exposure
• The duration of exposure to everolimus was longer in patients who developed hyperglycemia and hypercholesterolemia than in patients without these events.
  – The median treatment duration of everolimus was 48 weeks for patients with hyperglycemia vs 39.71 weeks for patients without hyperglycemia, and 66.43 weeks for patients with hypercholesterolemia vs 38.71 weeks for patients without hypercholesterolemia (Table 2).

Table 2. Median Duration of Exposure for the Overall Population

<table>
<thead>
<tr>
<th>Disease State</th>
<th>N = 406</th>
<th>Duration of Exposurea (Weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycemia, n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With</td>
<td>63</td>
<td>48 (2.1-110.6)</td>
</tr>
<tr>
<td>Without</td>
<td>342</td>
<td>39.71 (0.7-4286)</td>
</tr>
<tr>
<td>Hypercholesterolemia, n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With</td>
<td>33</td>
<td>66.43 (12.1-120.4)</td>
</tr>
<tr>
<td>Without</td>
<td>373</td>
<td>38.71 (0.7-4286)</td>
</tr>
</tbody>
</table>

*Data are presented as median (range). Duration of exposure (days) = (date of last administration of study treatment) – (date of first administration of study treatment) – 1. Duration of exposure was calculated on the safety set (based on the treatment received and not the randomized patients)

Progression-Free Survival in the Overall Pooled Population
• The improvement in PFS with everolimus in the pooled analysis was consistent with the findings of the individual RADIANT-3 and RADIANT-4 trials.
  – A total of 412 patients randomized, (RADIANT-3, n = 207; RADIANT-4, n = 205) treated with everolimus were included in the pooled analysis.
  – The median PFS (95% CI) with everolimus was 11.37 months (11.01–13.93) in the pooled analysis; 13.67 months (11.17–18.79) in RADIANT-3, and 11.01 months (9.23–13.31) in RADIANT-4 (Figure 2-following slide).
Results (Contd.)

Figure 2. Kaplan-Meier Plot of PFS Per Central Review in Everolimus-Treated Patients; Full Analysis Set

- The development of hyperglycemia and hypercholesterolemia on treatment with everolimus were not significantly associated with improvements in PFS.
- A total of 308 patients were exposed to the treatment for at least 16 weeks (with/without: hyperglycemia \( n = 39/269 \) and hypercholesterolemia \( n = 20/288 \)).
- The median PFS (95% CI) was 18.79 months (11.20–not estimable [NE]) and 14.09 months (11.37–17.41) among everolimus-treated patients who did and did not develop hyperglycemia, respectively (Figure 3A).
- PFS was 14.09 months (8.35–NE) and 14.75 months (11.73–17.71) for those who did and did not develop hypercholesterolemia, respectively (Figure 3B).
- The median PFS was comparatively higher in patients who develop hyperglycemia than the overall population; this effect might be due to a longer duration of drug exposure in patients who develop hyperglycemia vs overall population.

Figure 3. Kaplan-Meier Plot of PFS (Central Review) in Everolimus-Treated Patients With/Without (A) Hyperglycemia (B) Hypercholesterolemia – Landmark 16 weeks

- The median PFS was comparatively higher in patients who develop hyperglycemia than the overall population; this effect might be due to a longer duration of drug exposure in patients who develop hyperglycemia vs overall population.
Conclusions

- The results of this exploratory analysis showed no correlation between the metabolic toxicities (hyperglycemia and hypercholesterolemia) and PFS.
  - There was a trend towards improved PFS among patients who developed hyperglycemia, however the numbers of events were very low and it remains unclear if any meaningful conclusions can be drawn from this observation.
- A cause-effect relationship was observed between the duration of drug exposure and development of hyperglycemia and hypercholesterolemia.
- These results suggest that development of metabolic toxicity had no significant impact on PFS or duration of treatment among patients receiving everolimus in the RADIANT-3 and RADIANT-4 trials.
  - An increase of glucose and/or cholesterol levels may not be useful as a predictor of efficacy during treatment with everolimus in patients with NETs.
- However, these findings warrant further investigation in future prospective studies.

References


Disclosures

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