Incidence and risk of treatment-related mortality in cancer patients treated with the mammalian target of rapamycin inhibitors


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Background: Inhibition of the mammalian target of rapamycin (mTOR) is an established treatment for multiple malignancies. We carried out an up-to-date meta-analysis to determine the risk of fatal adverse events (FAEs) in cancer patients treated with mTOR inhibitors.

Patients and methods: PubMed, conferences and clinicaltrials.gov databases were searched for articles reported from January 1966 to June 2012. Eligible studies were limited to approved mTOR inhibitors (everolimus and

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The mammalian target of rapamycin (mTOR) is a kinase that plays a central role in cell growth, proliferation and metabolism [1]. Dysregulations of this pathway are thought to be present in several malignancies including renal cell carcinoma (RCC), refractory hormone-receptor-positive breast cancer (HR + BC) and others [2–4].

There are currently two agents approved that selectively target the mTOR pathway: everolimus (Afinito®, Novartis) and temsirolimus (Torisel®, Pfizer) both inhibit mTOR. Everolimus has been approved for the treatment of metastatic RCC in patients who failed prior sunitinib or sorafenib [5, 6], subependymal giant cell astrocytomas (SEGA) associated with tuberous sclerosis [7], advanced HR+, HER2-negative breast cancer in combination with second-line exemestane [8] and others [2–4]. Temsirolimus has only been FDA approved for the treatment of advanced RCC [10], though both the drugs continue to be evaluated in a much broader group of malignancies.

Fatal adverse events (FAEs) are defined as deaths that are at least possibly secondary to the use of a pharmaceutical agent. A recent analysis on serious adverse events of targeted anticancer agents showed that after a median of 4.3 years, 42% acquired one or more boxed warnings (the highest level of FDA alert) from pivotal phase III randomized, clinical trials (RCTs) [11].

The mTOR pathway plays a central role in normal cellular function, so mTOR inhibitors may have a variety of undesirable effects on healthy tissues. In fact, everolimus and temsirolimus have been associated with a set of adverse events including metabolic changes, gastrointestinal disturbances, infections and pneumonitis [12–14]. We set out to conduct the first study of peer-reviewed RCTs of everolimus and temsirolimus and their relationship to FAEs in patients with cancer.

**methods**

**study selection**

An independent review of the Pubmed and American Society of Clinical Oncology databases up to June 2012 was carried out. The search was conducted twice, once using the key terms ‘everolimus’, ‘afinitor’, ‘RAD-001’ and once using ‘temsirolimus’ ‘Torisel’, ‘CCI-779’, with both searches limited to human studies. Identified abstracts were then collected and independently coded by four investigators (T.K.C., M.D.K., G.S. and C.J.R.). Full texts of potentially relevant studies were then downloaded, with methods and results sections reviewed for trials design and reporting of study deaths. When specific data on FAEs could not be determined, efforts were made to contact the study authors/manufacturers for clarification. The most recent drug package insert was also scrutinized to include the most updated information.

The goal of this analysis was to evaluate any association between FAEs and exposure to mTOR inhibitors in cancer patients; to that end only RCTs comparing mTOR inhibitors against a placebo or control arm were used. Study quality was assessed using the Jadad scale [15] that includes assessment of study randomization, double-blinding practice and handling of withdrawals, a practice in agreement with other meta-analyses done in this context.

**statistical analysis**

The proportion of patients with FAEs and 95% CIs were derived from each study’s incidence and precision data. Inverse variance was used to pool the data across studies, in order to account for the expected heterogeneity of the comparisons across RCTs [16]. Any discrepancies between the reviewer’s classifications of publications were resolved by consensus.

**results**

**search results**

Our initial search yielded a total of 366 potentially relevant abstracts in Pubmed, 309 using the defined search criteria for everolimus and 57 for temsirolimus. Supplementary Figure S1,
available at Annals of Oncology online, outlines the selection process in detail. A total of eight RCTs, six phase III and two phase II trials were carefully reviewed for eligibility and selected for the analysis. These trials represent five studies with everolimus and three with temsirolimus. The characteristics of each trial are presented in Table 1.

patients
A total of 3193 patients were available for the meta-analysis, with 2236 patients from everolimus trials and 957 from temsirolimus trials. Patients included in those trials followed the eligibility criteria defined by each unique trial and generally included patients with good performance status and adequate organ function. Three trials were carried out in patients with RCC [6, 10, 20], two in patients with HR + BC, [8, 21] one with PNET [9], one with all types of neuroendocrine tumors (NETs) [22] and one with mantle cell lymphoma (MCL) [23]. (Table 1).

incidence and types of FAEs
The overall incidence of FAEs was 3.2% (95% CI, 2.1% to 4.8%) in the mTOR inhibitors arm (heterogeneity test: \( Q = 16.02; P < 0.001; I^2 = 56.3\% \)). When stratified by the drug type, the incidence of FAEs in everolimus trials was 3.2% (95% CI, 1.8% to 5.8%). In the temsirolimus trials, the incidence of FAEs was 2.7% (95% CI, 1.7% to 4.4%). For the placebo/control arm, the overall incidence was 1.2% (95% CI, 0.6% to 2.7%; heterogeneity test: \( Q = 12.83; P = 0.076; I^2 = 45.5\% \)).

Three of the included studies (two everolimus and one temsirolimus) did not specify the cause of death (unknown/unspecified cause) for the tallied FAEs, representing a total 61.4% of all reported FAEs [6, 10, 22]. Of the reported causes of FAEs, sepsis or infection was the most common cause of death, reported in four trials and representing a total of 11 deaths or 15.7% of all study deaths. Acute renal failure (alternatively reported as acute renal insufficiency) was the second most common cause of FAEs reported in four trials and represented 5.7% of all study deaths. Cardiac arrest or myocardial infarction occurred in two patients and represented 3% of all deaths. All other causes of deaths were infrequent and occurred in isolation. These included tumor hemorrhage, duodenal perforation, cerebral vascular accident, acute respiratory distress syndrome, hepatic failure, suicide, pulmonary embolism, hyperkalemia, sudden death and respiratory failure.

RR of FAEs and subgroup analysis
Among the 1930 patients treated with mTOR inhibitors, the RR of having an FAE was 2.20 (95% CI, 1.25–3.90; \( P = 0.006 \)). No significant heterogeneity was found among the studies of FAEs (\( Q = 4.35; P = 0.739; I^2 = 0.0\% \)) (Figure 1). From the five trials in which everolimus was the study drug (everolimus, \( n = 1315 \); placebo/control, \( n = 921 \)), there was a statistically significant increase in the RR of FAEs of 1.92 (95% CI, 1.04–3.57; \( P = 0.038 \)). Similarly from the three temsirolimus trials (temsirolimus, \( n = 615 \); placebo/control, \( n = 342 \)), a statistically significant increase in the RR of FAE was also observed, 4.74 (95% CI, 1.10–20.50; \( P = 0.04 \)). No significant differences were observed when comparing the RRs of the two mTOR inhibitors (\( P = 0.31 \)). Table 2 demonstrates the overall and stratified analysis.

To determine whether the tumor type had an influence on the RR of FAEs with mTOR inhibitors, we carried out a subgroup analysis of RCC, the most common tumor type versus all other tumor types (non-RCC). The RR of FAEs among patients with RCC treated with mTOR inhibitors (3 trials) was 1.60 (95% CI, 0.70–3.62; \( P = 0.263 \)) (heterogeneity test: \( Q = 1.87; P = 0.393; I^2 = 0.0\% \)). For non-RCC patients (five trials), the RR of FAEs was 2.98 (95% CI, 1.35–6.58; \( P = 0.007 \)) (heterogeneity test: \( Q = 1.32; P = 0.857; I^2 = 0.0\% \)). However, no significant difference between the RRs of these groups was observed (\( P = 0.32 \)). (Table 2).

study quality
Examination of individual trial design revealed that randomized treatment allocation sequences were generated in all included trials. All everolimus trials were placebo controlled, double-blinded and of high quality achieving the highest Jadad score of 5. None of the temsirolimus trials were blinded. The follow-up time was determined to be adequate in each trial. For patients enrolled in randomized, phase II trials (two studies, 439 patients), the RR of FAE was 2.59 (95% CI, 0.24–28.28; \( P = 0.436 \)). For those patients enrolled in randomized phase III trials (six studies, 2754 patients), the RR of FAE was 2.19 (95% CI, 1.22–3.92; \( P = 0.009 \)), with no significant difference in the RRs between both groups (\( P = 0.92 \)).

Finally, we attempted to see whether there is any impact of the mTOR inhibitor treatment duration on the incidence of FAEs, as patients who may stay longer on a treatment arm may be in theory more prone to develop events. When we compared the incidence of FAEs among studies with ‘short’ median time on therapy (defined as less than the median duration of all trials) versus the ones with ‘long’ median time on therapy (defined as greater than the median duration of all trials), no difference in the incidences of FAEs was found (\( P = 0.83 \)). When we analyzed treatment duration as a continuous variable in the meta-regression model, we again found that there was no statistically significant difference in incidences of FAEs (\( P = 0.586 \)).

publication bias
No evidence of publication bias was detected for incidence or RR of FAEs by either Begg’s or Egger’s test (for RR of FAEs, Begg’s \( P = 0.90 \) and Egger’s \( P = 0.11 \)).

discussion
To our knowledge, this is the first large study to demonstrate a significantly increased risk of death as a result of mTOR inhibitors. Despite the relatively low events rate, the risk of developing an FAE was more than twofold higher in patients treated with mTOR inhibitors. The process by which individual clinicians in trials determine whether a patient’s death was the result of a study drug, cancer progression or other unrelated causes does carry some subjectivity and is a potential source of bias. In this study, the large percentage of
### Table 1. Baseline characteristics of the included trials in final analysis

<table>
<thead>
<tr>
<th>Author, study</th>
<th>Phase</th>
<th>Histology</th>
<th>Patients enrolled</th>
<th>Treatment arms/dose</th>
<th>Median age (years) (range)</th>
<th>Median treatment duration (months) (range)</th>
<th>Median OS (months) (range)</th>
<th>Median PFS (independent/central review) (months) (range)</th>
<th>Patients for analysis</th>
<th>No. of deaths as a result of the study drug</th>
<th>Reported events</th>
<th>Quality</th>
</tr>
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<tbody>
<tr>
<td><strong>Everolimus</strong></td>
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<tr>
<td>Baselga et al. [8]</td>
<td>3</td>
<td>HR(+), BC</td>
<td>724</td>
<td>Everolimus 10 mg QD + exemestane 25 mg QD</td>
<td>62 (34–93)</td>
<td>6.0</td>
<td>Not reached</td>
<td>11 (9.7–15.0)</td>
<td>482</td>
<td>7</td>
<td>Sepsis, PNA, Hemorrhage, CVA, ARF, Suicide</td>
<td>5</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo + exemestane 25 mg QD</td>
<td>61 (28–90)</td>
<td>3.3</td>
<td>Not reached</td>
<td>4.1 (2.9–5.6)</td>
<td>238</td>
<td>1</td>
<td></td>
<td>5</td>
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<tr>
<td>Baselga et al. [21]</td>
<td>2</td>
<td>HR(+), BC</td>
<td>270</td>
<td>Everolimus 10 mg QD + letrozole 2.5 mg QD</td>
<td>69 (46–88)</td>
<td>Not reported</td>
<td>N/A</td>
<td>N/A</td>
<td>137</td>
<td>0</td>
<td>None</td>
<td>5</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo + letrozole 2.5 mg QD</td>
<td>67 (43–84)</td>
<td>Not reported</td>
<td>N/A</td>
<td>N/A</td>
<td>132</td>
<td>0</td>
<td>Sepsis, Candida PNA, Aspergillosis, MI</td>
<td>5</td>
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<tr>
<td>Motzer et al. [6]</td>
<td>3</td>
<td>RCC</td>
<td>416</td>
<td>Everolimus 10 mg QD</td>
<td>61 (27–85)</td>
<td>4.7 (0.6–15.0)</td>
<td>14.8</td>
<td>4.9 (4.0–5.5)</td>
<td>274</td>
<td>14</td>
<td></td>
<td>5</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>60 (29–79)</td>
<td>2 (0.7–9.8)</td>
<td>14.4</td>
<td>1.9 (1.8–1.9)</td>
<td>137</td>
<td>6</td>
<td></td>
<td>6</td>
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<tr>
<td>Pavel et al. [22]</td>
<td>3</td>
<td>NET</td>
<td>429</td>
<td>Everolimus 10 mg QD + octreotide 30 mg Q28D</td>
<td>60 (22–83)</td>
<td>9.2 (0.2–40.7)</td>
<td>Not reached</td>
<td>16.4 (13.7–21.2)</td>
<td>215</td>
<td>12</td>
<td>Not Specified</td>
<td>5</td>
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<td></td>
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<td></td>
<td></td>
<td>Placebo + octreotide 30 mg Q28D</td>
<td>60 (27–81)</td>
<td>9.1 (&lt;0.2–37.8)</td>
<td>Not reached</td>
<td>11.3 (8.4–14.6)</td>
<td>211</td>
<td>5</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Yao et al. [27]</td>
<td>3</td>
<td>PNET</td>
<td>410</td>
<td>Everolimus 10 mg QD</td>
<td>58 (23–87)</td>
<td>9.2</td>
<td>Not reached</td>
<td>13.7 (11.2–18.8)</td>
<td>207</td>
<td>7</td>
<td>ARDS, ARF, Cardiac Arrest, Hepatic Failure, PNA, Sepsis, PE</td>
<td>5</td>
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<td></td>
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<td>Placebo</td>
<td>57 (20–82)</td>
<td>4</td>
<td>Not reached</td>
<td>5.7 (5.4–8.3)</td>
<td>203</td>
<td>1</td>
<td></td>
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<tr>
<td><strong>Temsirolimus</strong></td>
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<tr>
<td>Hess et al. [23]</td>
<td>3</td>
<td>MCL</td>
<td>162</td>
<td>Temsirolimus 175 mg followed by 75 mg QW</td>
<td>68 (44–87)</td>
<td>3 (0.2–24.2)</td>
<td>12.8 (8.6–19.3)</td>
<td>4.8 (3.1–8.1)</td>
<td>54</td>
<td>2</td>
<td>Doudenal Perforation, Aspergillosis, Sepsis, ARF, Symptom Deterioration</td>
<td>3</td>
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<td>Temsirolimus 175 mg followed by 25 mg QW</td>
<td>68.5 (43–85)</td>
<td>3.5 (0.2–43)</td>
<td>10 (7.2–14.6)</td>
<td>3.4 (1.9–5.5)</td>
<td>54</td>
<td>3</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Investigator’s choice of therapy</td>
<td>64.5 (39–88)</td>
<td>1.2 (0.2–8.7)</td>
<td>9.7 (5.8–15.1)</td>
<td>1.9 (1.6–2.5)</td>
<td>53</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hudes et al. [10]</td>
<td>3</td>
<td>RCC</td>
<td>626</td>
<td>Temsirolimus 25 mg QW</td>
<td>58 (32–81)</td>
<td>3.8 (3.5–3.9)</td>
<td>10.9 (8.6–12.7)</td>
<td>5.5 (3.9–7.0)</td>
<td>209</td>
<td>2</td>
<td>Hyperkalemia, ARF</td>
<td>3</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>INF-a 3 mIU to 18 mIU TIW</td>
<td>60 (23–86)</td>
<td>1.9 (1.7–1.9)</td>
<td>7.3 (6.1–8.8)</td>
<td>3.1 (2.2–3.8)</td>
<td>207</td>
<td>1</td>
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<td></td>
<td>Temsirolimus 15 mg QW + INF-a 6 mIU TIW</td>
<td>59 (32–82)</td>
<td>2.5 (1.9–3.6)</td>
<td>8.4 (6.6–10.3)</td>
<td>4.7 (3.9–5.8)</td>
<td>210</td>
<td>7</td>
<td></td>
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</tr>
<tr>
<td>Negrier et al. [20]</td>
<td>2</td>
<td>RCC</td>
<td>171</td>
<td>Temsirolimus 25 mg QW + bevacizumab 10 mg/kg Q2W</td>
<td>62 (33–83)</td>
<td>5.1 (0–12)</td>
<td>Not reached</td>
<td>8.2 (7.0–9.6)</td>
<td>88</td>
<td>2</td>
<td>Sudden Death</td>
<td>3</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Temsirolimus 25 mg QW</td>
<td>61.2 (33–83)</td>
<td>10.4 (0.5–12)</td>
<td>Not reached</td>
<td>8.2 (5.5–11.7)</td>
<td>42</td>
<td>0</td>
<td>Respiratory</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>INF-a 9 mIU TIW + bevacizumab 10 mg/kg Q2W</td>
<td>61.9 (40–79)</td>
<td>7.2 (1.0–12)</td>
<td>Not reached</td>
<td>16.8 (6.0–26)</td>
<td>40</td>
<td>0</td>
<td>Failure</td>
<td></td>
</tr>
</tbody>
</table>

HR(+) BC: hormone receptor-positive breast cancer; RCC: renal cell cancer; NET: neuroendocrine tumor; PNET: pancreatic neuroendocrine tumor; MCL: mantle cell lymphoma; QD: once a day; QW: once a week; TIW: Three times a week; mIU: million International Units; Q2W: twice weekly; INF-a: interferon alpha; N/A: not applicable; OS: overall survival; PFS: progression-free survival; PNA: pneumonia; CVA: cerebral vascular accident; ARF: acute renal failure; MI: myocardial infarction; ARDS: acute respiratory distress syndrome; PE: pulmonary embolism.
reported FAEs that were not assigned a specific cause raise concern. We, however, do not believe that this played a significant role in our work, because all studies included in our analysis were randomized.

One of the most recognized adverse events with the use of mTOR inhibitors has been the development of non-infectious pneumonitis. While initially underreported in the registrational phase III trials [6, 10] dedicated independent radiologic review of the two RCC trials reported an incidence of 29% with temsirolimus [23] and 39% with everolimus [24]. However, only 10%–13% of patients would have respiratory symptoms suggestive of clinical pneumonitis, with the rest of patients having only radiographic findings. Our findings agree with these reports as fatal pneumonitis or respiratory disorders were rare. Furthermore, one report from our group showed that the development of pneumonitis may be a marker of therapeutic benefit and patients should not be taken off therapy, unless they become symptomatic [25]. Notably, the class-specific metabolic alterations (hyperlipidemia, hyperglycemia) were not directly associated with FAEs in our study.

Most frequently identified cause of an FAE in our analysis was infection, with a fair number of atypical or fungal infections occurring in this group. The factors underlying increased risk of infections with mTOR inhibitors include mucosal erosions, transient cytopenias (mainly lymphopenia), hyperglycemia, the use of corticosteroids and malnutrition [26–29]. At the cellular level, sirolimus, the active compound of temsirolimus, and everolimus form a complex with the FK-binding protein-12 (FKB-12). That complex inhibits mTOR-mediated pathways including IL-2 and IL-4 dependent proliferation of T and B cells leading to their cell-cycle arrest, and subsequent decreased immune response [30].

Despite the size of this meta-analysis, our study has some limitations. First, this is a meta-analysis conducted at a study level, and confounding variables at the patient level, such as co-morbidities, concomitant medications, specifc age and previous therapies could not be incorporated into the analysis. It is possible that some of the FAEs in the treatment arm could be deemed unrelated on subsequent follow up reports. Also all of the included studies were conducted in patients with adequate organ function at study entry, this would suggest that rates of FAEs could be higher in common practice. In fact, a recent analysis from the International mRCC Database Consortium suggested that patients ineligible for clinical trials due to one or more common exclusion criteria derive less benefit from targeted therapy than patients who meet all

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**Figure 1.** Relative risk (RR) of fatal adverse events associated with the mammalian target of rapamycin (mTOR) inhibitors.

**Table 2.** Incidence and relative risk (RR) of fatal adverse events (FAEs) due to the drug associated with mTOR inhibitors

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Events/Total No. of Patients</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mTOR Inhibitor</td>
<td>Control</td>
</tr>
<tr>
<td>Basega et al., 2012</td>
<td>7/482</td>
<td>1/238</td>
</tr>
<tr>
<td>Basega et al., 2009</td>
<td>0/137</td>
<td>0/132</td>
</tr>
<tr>
<td>Yao et al., 2011</td>
<td>7/207</td>
<td>1/203</td>
</tr>
<tr>
<td>Pavel et al., 2011</td>
<td>12/215</td>
<td>5/211</td>
</tr>
<tr>
<td>Motzer et al., 2010</td>
<td>14/247</td>
<td>6/137</td>
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<tr>
<td>Hudes et al., 2007</td>
<td>9/419</td>
<td>1/207</td>
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<tr>
<td>Hess et al., 2009</td>
<td>5/108</td>
<td>0/53</td>
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<tr>
<td>Negrier et al., 2011</td>
<td>2/88</td>
<td>0/82</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>56/1930</strong></td>
<td><strong>14/1263</strong></td>
</tr>
</tbody>
</table>

*Test for heterogeneity: Q=4.35, p=0.739, I-squared=0.0%
inclusion factors [31]. It is possible that the concomitant administration of other drugs (such as the combination of temsirolimus and interferon) in a few of the trials may have contributed to a higher risk of FAEs. Finally, the process by which investigators attribute FAE casually is a variable practice since FAEs were not the primary end point of any of the included studies.

In conclusion, the use of mTOR-inhibitor therapies are associated with a small, but significant increase in the risk of fatal drug-related events. Despite these findings, both everolimus and temsirolimus benefit the overall population of patients with clear FDA-approved indications. It is also important to recognize that as this class of drugs gains greater clinical use, practitioners must be aware of the risks associated with their use and must provide rigorous continuous monitoring, especially since the initial recognition of serious adverse effects can occur several years after a drug receives FDA approval [32].

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**disclosure**

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**references**