Adverse event management in patients with advanced cancer receiving oral everolimus: focus on breast cancer

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Background: Everolimus, an orally administered rapamycin analogue, inhibits the mammalian target of rapamycin (mTOR), a highly conserved intracellular serine–threonine kinase that is a central node in a network of signaling pathways controlling cellular metabolism, growth, survival, proliferation, angiogenesis, and immune function. Everolimus has demonstrated substantial clinical benefit in randomized, controlled, phase III studies leading to approval for the treatment of advanced renal cell carcinoma, advanced neuroendocrine tumors of pancreatic origin, renal angiomyolipoma and subependymal giant-cell astrocitoma associated with tuberous sclerosis complex, as well as advanced hormone-receptor-positive (HR+) and human epidermal growth factor receptor-2-negative advanced breast cancer.

Materials and methods: We discuss clinically relevant everolimus-related adverse events from the phase III studies, including stomatitis, noninfectious pneumonitis, rash, selected metabolic abnormalities, and infections, with focus on appropriate clinical management of these events and specific considerations in patients with breast cancer.

Results: The majority of adverse events experienced during everolimus therapy are of mild to moderate severity. The safety profile and protocols for toxicity management are well established. The class-effect adverse event profile observed with everolimus plus endocrine therapy in breast cancer is (as expected) distinct from that of endocrine therapy alone, but is similar to that observed with everolimus in other solid tumors. Information gained from the experience in other carcinomas on prompt diagnosis and treatments to optimize drug exposure, treatment outcomes, and patients’ quality of life also applies to the patient population with advanced breast cancer.

Conclusions: As with all orally administered agents, education of both physicians and patients in the management of adverse events for patients receiving everolimus is critical to achieving optimal exposure and clinical benefit. Active monitoring for early identification of everolimus-related adverse events combined with aggressive and appropriate intervention should lead to a reduction in the severity and duration of the event.

Key words: everolimus, stomatitis, pneumonitis, metabolic abnormality, infections, rash

introduction

Everolimus has an established role in the treatment of solid tumors, including advanced renal cell cancer (RCC), neuroendocrine tumors of pancreatic origin (pNET), and renal angiomyolipoma and tuberous sclerosis complex (TSC) including pediatric and adult patients with TSC who have subependymal giant cell astrocitoma (SEGA) [1, 2]. Most recently, everolimus (in combination with oral exemestane) was approved for the treatment of postmenopausal patients with hormone-receptor-positive (HR+), human epidermal growth factor-2-negative (HER2−) advanced breast cancer recurring or progressing during/after nonsteroidal aromatase inhibitor treatment [2]. Overall, continuous daily dosing with 10-mg oral everolimus is adequately tolerated, and no evidence of cumulative toxicity has been observed in clinical trials over median treatment durations of 20–52 weeks [2, 3]. While initiating everolimus treatment at a dose of 5 mg may decrease the proportion of patients with grade
3/4 adverse events, more complete inhibition of eukaryotic initiation factor 4E binding protein 1 (4E-BP1) and pS6K phosphorylation occurs at the 10-mg dose. This dose has proven clinical benefit in RCC, pNET and HR⁺, HER2⁻ advanced breast cancers [4–6].

Class-effect toxicities during mammalian target of rapamycin (mTOR) inhibitor therapy are well characterized [7]. Extensive clinical experience with everolimus, particularly in patients with RCC, has advanced our understanding of its safety profile [8, 9]. In the phase III BOLERO-2 study of everolimus plus exemestane in patients with HR⁺ breast cancer progressing after prior non-steroidal aromatase inhibitor therapy, the incidence and severity of class-effect adverse events was comparable with that of phase III studies of everolimus monotherapy in patients with RCC and pNET, and no new or unexpected safety signals were identified.

Because everolimus is a new drug class in the breast cancer arena, many physicians treating such patients may be unfamiliar with its adverse event profile and appropriate management [10]. In clinical practice, the threshold for change in therapy because of adverse events may be lower in breast cancer compared with other malignancies because of the availability of multiple approved treatment options with which physicians have more experience [11]. As with any drug, the optimal use of everolimus in breast cancer is contingent upon adequate management of adverse events, to maximize treatment exposure and facilitate optimal outcomes. This article reviews the clinical management and monitoring guidelines for class-effect adverse events of everolimus, focusing on the data from HR⁺ advanced breast cancer. Practical guidance is also provided, based on clinical experience across approved oncology indications.

**everolimus safety profile: class-effect toxicities**

Adverse events observed in patients undergoing systemic treatment with mTOR inhibitors include epithelia-cutaneous events (stomatitis, rash), pulmonary dysfunction (noninfectious pneumonitis), toxicities related to metabolic dysfunction (elevated blood levels of glucose and lipids), and immune suppression (infections) [10]. Metabolic and immune-related adverse events are clearly associated with on-target effects of mTOR inhibition [12]. However, skin-cutaneous effects may have a less direct association with mTOR inhibition; inhibition of mTOR-mediated growth and tissue repair and/or immune dysregulation may be a factor in mucosal epithelia with high turnover (Figure 1) [13, 14].

In general, the incidences of class-effect adverse events in the large phase III trials of everolimus in RCC (RECORD-1), pNET (RADIANT-3), and HR⁺, HER2⁻ advanced breast cancer (BOLERO-2) were comparable (Table 1) [5, 6, 8, 15]. Therefore, the addition of exemestane did not alter the adverse event...
profile compared with everolimus monotherapy. However, rates of treatment discontinuations and dose modifications in BOLERO-2 were slightly higher than that observed in the other phase III trials of everolimus monotherapy, which may in part be related to the novelty of everolimus and its safety profile to clinicians and patients. The median duration of everolimus treatment was 20.1 weeks in patients with RCC [8], 37.7 weeks in patients with pNET [6], and 23.9 weeks in HR+ advanced breast cancer [16].

Most class-effect adverse events are manageable and resolve without the need for treatment discontinuation. However, active monitoring and early identification can reduce the rate and severity of specific adverse events. Clinical management information and guidelines for adverse events during mTOR therapy have been published, detailing the strategies for each type of event [2, 17–25]. In both the RCC and pNET phase III trials, 13% of patients discontinued everolimus treatment because of an adverse event [6, 8]. In patients with pNET, the most common adverse events resulting in treatment discontinuation were pneumonitis, fatigue, and interstitial lung disease. In patients with RCC, these adverse events were pneumonitis, dyspnea, lung disorders, and fatigue [9]. In patients with HR+ advanced breast cancer, 26% discontinued treatment of one or both study drugs in the everolimus group because of an adverse event [16]; the most common events were pneumonitis, stomatitis, dyspnea, rash, and fatigue.

stomatitis

Stomatitis is an adverse event term that encompasses inflammation and ulceration of the oral mucosal lining. Oral mucositis is the more specific, preferred term used to describe oral inflammation/ulceration observed on nonkeratinized mucosal surfaces. Preferred terms that are included in stomatitis and related events include stomatitis, mouth ulceration, aphthous stomatitis, glossodynia, gingival pain, lip ulceration, and glossitis. In general, the onset of stomatitis with mTOR inhibition is rapid and occurs within a few weeks of treatment initiation [22, 24]. In patients receiving everolimus plus exemestane for advanced breast cancer in BOLERO-2, more than a third of stomatitis and related events (grade ≥2) were reported in the first 2 weeks after starting treatment. Furthermore, these events began to plateau at 6 weeks (Figure 2A) [16, 26]. A similar trend was noted in patients receiving everolimus monotherapy for RCC in RECORD-1 [20]. After the initial 2-month treatment period, the probability of stomatitis occurring in patients who have not already experienced this adverse event is low [20].

The clinical presentation of stomatitis in patients receiving mTOR inhibitors is distinct from that induced by chemotherapy in that it is characterized by discrete, superficial, well-demarcated, aphthous-like ulcers with a grayish-white pseudomembrane [22]. Recent reviews note that the average incidence of stomatitis during everolimus treatment is 44% [22, 24], making it the most common treatment-related adverse event.

In phase III studies, the incidence of all-grade stomatitis (preferred term) in the everolimus plus exemestane group of the BOLERO-2 study (advanced HR+ breast cancer) was 59%, similar to that observed in the everolimus-treated patients with RCC (44%) and pNET (64%) (Table 1) [6, 8, 15]. The incidence of grade 3/4 stomatitis was 8% in patients with breast cancer, 4% in patients with RCC, and 7% in patients with pNET [6, 8, 16]. No dose modifications are required for managing grade 1 stomatitis (Table 2) [2, 20, 21]. For stomatitis events of grade 2 or 3, treatment interruption is recommended until resolution to grade ≤1. The median time to resolution from grade 3 to ≤1 stomatitis following everolimus dose interruption/reduction was 3.1 weeks in 97% of patients with breast cancer (complete resolution occurred in 82% of patients after a median of 7.4 weeks) [16].

In general, patients should be advised on good oral hygiene, and to avoid spicy foods and mouthwashes containing debriding agents such as peroxide upon onset of stomatitis. Topical analgesics can alleviate symptoms such as oral pain. However, patients should be cautioned regarding the use of topical analgesics and ingestion of hot foods, as there is an increased likelihood of mouth burns from the inability to sense food temperature. Mouth pain, dysgeusia, and dysphagia in the absence of clinically apparent lesions may be useful symptoms to monitor to allow for

### Table 1. Incidence of key class-effect toxicities from phase III studies of everolimus in advanced solid tumors

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Everolimus + best supportive care</td>
<td>Everolimus (n = 204), %</td>
<td>Everolimus + exemestane (n = 482), %</td>
</tr>
<tr>
<td></td>
<td>(n = 274), %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Grades</td>
<td>Grade 3/grade 4</td>
<td>All grades</td>
<td>Grade 3/grade 4</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>44/1/0</td>
<td>64/7</td>
<td>59/8/0</td>
</tr>
<tr>
<td>Rash</td>
<td>29/1/0</td>
<td>49/1/0</td>
<td>39/1/0</td>
</tr>
<tr>
<td>Noninfectious pneumonia</td>
<td>14/4/0</td>
<td>17/2</td>
<td>16/3/0</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>57b/15/1&lt;1b</td>
<td>13/5</td>
<td>14c/5/1&lt;1</td>
</tr>
<tr>
<td>Infections</td>
<td>37/7/3</td>
<td>23/2</td>
<td>50c/4/1&lt;1</td>
</tr>
</tbody>
</table>

*Breakdown by grade 3 and 4 not reported.
^Based on laboratory values.
Based on investigator-reported adverse events.
Incidence based on system organ class (SOC); includes all infections.
Data from Afinitor prescribing information [2].
Figure 2. Cumulative incidence of grade ≥2 (A) stomatitis, (B) noninfectious pneumonitis, and (C) infections in patients with advanced breast cancer (BOLERO-2). Infections included all infections and infestations. EVE, everolimus; EXE, exemestane; PBO, placebo. Parts (A) and (B) reprinted with permission from Rugo et al., OUP, on behalf of the European Society for Medical Oncology [16]. Part (C) reprinted with permission from Rugo et al. [26].
## Table 2. Recommendations for clinical management of key adverse events by symptom severity

<table>
<thead>
<tr>
<th>Grade</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stomatitis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms/description</td>
<td>Minimal symptoms (normal diet)</td>
<td>Symptomatic (able to eat and swallow modified diet)</td>
<td>Symptomatic (unable to properly eat/drink)</td>
<td>Symptoms may be associated with life-threatening consequences</td>
</tr>
<tr>
<td>Treatment</td>
<td>• Alcohol-free mouthwash or saline several times per day</td>
<td>• Topical oral treatments Dobendan Strepsils® Dolo lozenges</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Cooling with ice, frozen pineapple chunks, or balls of frozen pineapple juice</td>
<td>Lidocaine-containing denture adhesive for denture wearers</td>
<td>Mouthwash with local anesthetic (e.g. benzocaine 15 ml q3h), with or without steroids</td>
<td>Rinse with supersaturated calcium phosphate solution (moistsens mouth and makes it slippery)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gelclair® oral gel (3 × daily, or as needed ≥1 h before next food/drink intake), undiluted or diluted (15 ml + 40 ml water); rinse mouth thoroughly for ≥1 min</td>
<td>Rinse with ‘magic mouthwash’ containing analgesic or anesthetic Ketamine oral rinse (ketamine 20 mg in 5 ml saliva replacement fluid or isotonic saline) q4h for stomatitis pain</td>
<td></td>
</tr>
<tr>
<td>Everolimus dose adjustment*</td>
<td>• None</td>
<td>• Temporary interruption until recovery to grade ≤1; restart at same dose</td>
<td>• Topical corticosteroids</td>
<td>• Discontinue everolimus</td>
</tr>
<tr>
<td></td>
<td>• If grade 2 stomatitis recurs, interrupt dose until recovery to grade ≤1; restart at reduced dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pneumonitis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms/description</td>
<td>Asymptomatic; radiographic findings only</td>
<td>Symptomatic; no impairment of ADL</td>
<td>Symptomatic; impairment of ADL, supplemental oxygen required</td>
<td>Life-threatening; strong impairment of ADL, mechanical ventilation required</td>
</tr>
<tr>
<td>Treatment</td>
<td>• Observation</td>
<td>Depending on symptom severity:</td>
<td>Consult pulmonologist</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Consult pulmonologist</td>
<td>• Diagnostics to rule out infection</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Consider diagnostics to rule out infection</td>
<td>• Corticosteroids if infectious cause excluded</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Consider corticosteroids until symptoms improve to grade ≤1</td>
<td>• For impending respiratory distress: concomitant antibiotics and corticosteroids are recommended</td>
<td></td>
</tr>
<tr>
<td>Everolimus dose adjustment*</td>
<td>• None</td>
<td>• Temporary interruption; restart at reduced dose</td>
<td>• Temporary interruption until recovery to grade ≤1; restart at reduced dose</td>
<td>• Discontinue everolimus</td>
</tr>
<tr>
<td></td>
<td>• Discontinue everolimus if failure to recover within 4 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hyperglycemia</strong></td>
<td></td>
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</tr>
<tr>
<td>Glucose level</td>
<td>&gt;ULN–160 mg/dl (8.9 mmol/l)</td>
<td>160–250 mg/dl (&gt;8.9–13.9 mmol/l)</td>
<td>250–500 mg/dl (&gt;13.9–27.8 mmol/l)</td>
<td>&gt;500 mg/dl (&gt;27.8 mmol/l)</td>
</tr>
<tr>
<td>Treatment</td>
<td>• None*</td>
<td>• Patient self-monitoring of blood glucose</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Patient self-monitoring of blood glucose</td>
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*Continued*
early implementation of preventive measures. In a recent report, 87% of patients had resolution of stomatitis following local or systemic treatment with corticosteroid therapy [27]. Accordingly, an ongoing study, BOLERO-4, will assess the effectiveness of treating stomatitis using a 0.5-mg/5-ml dexamethasone mouth rinse [28].

The use of antiseptic and sodium bicarbonate mouth rinses for using a sodium bicarbonate mouth rinse and a mouth rinse with one center was successful in minimizing the rate of stomatitis [29]. Ongoing study, BOLERO-4, will assess the effectiveness of treating stomatitis using a sodium bicarbonate mouth rinse and a mouth rinse with Benadryl*, tetracycline, hydrocortisone, and nystatin [30].

**noninfectious pneumonitis**

Noninfectious pneumonitis is a nonmalignant inflammatory infiltration of the lungs that is associated with the use of rapamycin derivatives (e.g. current mTOR inhibitors) [20, 25]. The time to onset for noninfectious pneumonitis has a wide range over several months [20]. The median time to onset in advanced breast cancer (BOLERO-2) was not reported, although approximately half of all events (grade ≥2) occurred within the first 24 weeks of treatment initiation. Cumulative risks of pneumonitis and related events (grade ≥2) in the everolimus plus exemestane arm were 10% and 16% at weeks 24 and 48, respectively (Figure 2B) [6, 8, 16]. In patients with advanced RCC, the median times to onset varied between 65 and 108 days in a retrospective review of patients treated in clinical practice and phase III trials, respectively [8, 25, 32]. This range is consistent with previous experience where most cases of noninfectious pneumonitis were observed within 6 months of treatment initiation [17]. The incidence of pneumonitis may also reflect the variation in the duration of everolimus exposure (20.1–37.7 weeks) across the tumor types.

Patients with noninfectious pneumonitis may be asymptomatic or present with nonspecific respiratory symptoms such as cough, shortness of breath/dyspnea, pleural effusion, or hypoxia. Radiologic changes such as ground glass opacities and focal consolidation may be evident (Figure 3) [33]. Occasionally, patients may present with systemic symptoms such as fatigue and fever [17, 20, 25]. Pathologic features of noninfectious pneumonitis may include nonspecific interstitial pneumonitis, bronchiolitis obliterans organizing pneumonia, alveolar hemorrhage, desquamative interstitial pneumonia, and vasculitis. Appropriate differential diagnosis to exclude alternative causes, including infection, is needed to identify noninfectious pneumonitis.

The incidence of any-grade (16%) and grade 3/4 (3%) noninfectious pneumonitis (preferred term) in advanced breast cancer was similar to that of patients with RCC or pNET (Table 1) [6, 8, 15]. Radiologic review of everolimus-treated patients in the RCC study shows that many patients with changes consistent with pneumonitis (39%) did not exhibit clinical symptoms consistent with pneumonitis during the trial [25], highlighting the importance of consulting an experienced radiologist. In an analysis of five everolimus studies in breast cancer, the overall rate of noninfectious pneumonitis was 41% in pretreated metastatic disease, although 35% represented grade 1/2 and included patients without clinical symptoms [34]. Of the patients with advanced breast cancer enrolled in BOLERO-2 who developed grade 3 noninfectious pneumonitis or related events (includes interstitial lung disease, lung infiltration, organizing pneumonia, and pulmonary fibrosis), the majority (75%) had complete resolution at a median of 5.4 weeks, typically after dose adjustments [16]. Similarly, 60% of patients with RCC and grade 3 noninfectious pneumonitis had complete resolution following dose adjustments/discontinuation and/or corticosteroid therapy [20].

Before initiating everolimus therapy, clinicians should evaluate pulmonary history, educate patients on the symptoms of this potentially serious complication, and caution patients with pre-existing conditions (e.g. chronic obstructive pulmonary disease) regarding the potential emergence of noninfectious pneumonitis. Patients should be encouraged to seek medical attention if they develop new or unexplained cough and/or dyspnea. To facilitate diagnoses, a baseline pretreatment chest X-ray or preferably, a computed tomography (CT) scan, is helpful to distinguish onset of drug-associated noninfectious pneumonitis on subsequent examinations. If the patient presents with clinical symptoms during treatment with everolimus, prompt referral to a pulmonologist is recommended, as symptoms (e.g. from grade 3 to 4) may rapidly worsen. In such instances, timely imaging is needed to exclude differential diagnoses such as tumor progression or pleural effusion (Table 2) [2, 20, 21]. Bronchoalveolar lavage is recommended to eliminate the possibility of respiratory

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**Table 2. Continued**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Everolimus dose adjustment*</th>
<th>None</th>
<th>If intolerable, temporary interruption until recovery to grade ≤1, then restart at same dose</th>
<th>Temporary interruption; restart at reduced dose</th>
<th>Discontinue everolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>None</td>
<td></td>
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</table>

*Apply more vigorous monitoring strategy.
*If dose reduction is required, the suggested dose is ~50% lower than the dose previously administered.

Data from Afinitor prescribing information [2], Porta et al. [20], and Nathan et al. [21].

ADA, American Diabetes Association; ADL, activities of daily living; EASD, European Association for the Study of Diabetes; HSV, herpes simplex virus; q3h, every 3 h; q4h, every 4 h; ULN, upper limit of normal.
infection that could not otherwise be diagnosed and may also be useful in differentiation from neoplastic lymphangitis. The subsequent monitoring schedule depends on the grade and clinical course, and has been reviewed in detail [10, 17]. Treatment with corticosteroids and everolimus dose adjustments, if necessary, is presented in Table 2.

Infections
The immunosuppressive properties of mTOR inhibitors may predispose patients to localized and systemic infections such as candidiasis, pneumonia, other bacterial infections, and invasive fungal infections [20]. In phase III studies of everolimus, infection rates are generally similar across the entire treatment period [8, 20], and in patients with advanced breast cancer (BOLERO-2), the incidence of infections grade ≥2 had no noticeable plateau (Figure 2C) [26]. The most common types of infections reported for patients with advanced breast cancer were nasopharyngitis (10%), urinary tract infection (10%), upper respiratory tract infection (6%), and pneumonia (4%) [2]. In patients with RCC, the infections included pneumonia, sepsis, and fungal infections, and in some populations, reactivation of latent hepatitis viral infections [20]. No cases of tuberculosis reactivation in everolimus-treated patients have been reported.

The incidence of overall infections was higher in patients with advanced breast cancer (50%) [2] compared with RCC (37%) [8] and pNET (23%) [6]; however, the incidence of infections in the advanced breast cancer placebo group was also higher (25%) compared with RCC (18%) and pNET (6%). Thus, rates of all-grade infections could vary by setting, potentially because of differences in the background infection rates in control arms and possibly from differences in reporting. The proportion of patients with infections and longer everolimus exposure (pNET) was lower (23%) compared with that of patients who had a shorter exposure (RCC; 37%), suggesting that risk of infection does not directly correlate with treatment duration. Overall, the incidence rates of grade 3/4 infection are low (~6%), and infections were not reported as being a major cause for dose adjustments or discontinuations across these phase III studies [26].

All infections require prompt diagnosis and treatment with antibiotic, antifungal, or antiviral agents, and interruption or discontinuation of everolimus therapy should be considered [1, 2, 20]. Consideration of drug interactions with everolimus should be taken into account when treating infections; several drugs are CYP3A4 inhibitors or inducers to various degrees necessitating an everolimus dose adjustment, and concomitant strong inhibitors of CYP3A4 should not be used (Table 3) [2]. For grade 2 or 3 infections, treatment with everolimus should be interrupted until improvement to grade ≤1; treatment may be reinitiated at the same dose for grade 2 events and at a lower dose for grade 3 events.

The importance of hygiene should be stressed, and patients should be encouraged to seek medical attention for infection-related signs and symptoms (e.g. fever, cough, etc.) [18]. Overall, vigilance for infections is standard practice during chemotherapy for metastatic breast cancer (because of potential myelosuppressive effects), and this should be incorporated as a component of patient care during everolimus-based treatment. In areas with a high prevalence of hepatitis, physicians may consider a comprehensive baseline medical history that includes an antibody immune status (hepatitis B virus) to identify high-risk patients (see Supplementary Appendix, available at Annals of Oncology online for details) [20].

Metabolic adverse events
Hyperglycemia and hyperlipidemia are potential metabolic dysfunctions that can arise from mTOR inhibition [13]. In muscle tissue, mTOR inhibition can lead to a reduction in glucose uptake and contribute to systemic glucose intolerance. In the liver, inhibition of the PI3K/Akt/mTOR pathway promotes gluconeogenesis, thus contributing to hyperglycemia. In adipose tissue, mTOR inhibition can reduce lipid uptake, leading to

**Figure 3.** Radiographic scans of (A) pneumonitis and (B) improvement. This patient had metastatic renal cell carcinoma in the lower right lobe. After 8 weeks of everolimus treatment, the chest X-ray shows patch consolidation and ground glass opacity (A). Everolimus was discontinued; 2 weeks later, improvement was noted on the follow-up X-ray (B). Reprinted with permission from Lee et al. [33].
hyperglycemia. Hyperglycemia is well defined by elevated blood glucose levels [36]. Patients with uncontrolled diabetes (fasting serum glucose >1.5× upper limit of normal [ULN]) should not receive everolimus therapy. Although the time to onset of hyperglycemia or new-onset diabetes was not reported for advanced breast cancer, approximately half of these events (grade ≥2) occurred within the first 6 weeks of treatment initiation [16]. Median time to onset of hyperglycemia was also not reported for RCC and pNET.

The incidence of hyperglycemia (preferred term) in advanced breast cancer was 14%, with a similar rate reported in pNET (13%) [6]. The incidence of hyperglycemia traditionally defined as an adverse event was 8% in RCC, and there was one case of new-onset diabetes [20]. However, the incidence of hyperglycemia in RCC reported on the basis of laboratory tests was 57% (Table 1) [6, 8, 15, 20].

Among the patients with advanced breast cancer who had grade 3/4 hyperglycemia or new-onset diabetes mellitus, 46% experienced resolution to grade ≤1 after a median of 29.1 weeks. During the study, more patients (5%) in the everolimus arm used insulin or its analogues compared with the control (exemestane only) arm (2%) [16]. In patients with pre-existing dysfunction in sugar metabolism, it is necessary to monitor fasting serum glucose levels and manage the patient to optimal glycemic control before initiating everolimus (see Supplementary Appendix, available at *Annals of Oncology* online for details) [2, 37].

Hyperlipidemia. Hyperlipidemia is also well defined by elevated blood cholesterol and/or triglyceride levels [38]. Before initiating everolimus therapy, patients should have a fasting serum cholesterol ≤300 mg/dl or 7.75 mmol/l and fasting triglycerides ≤2.5× ULN (data in Baselga et al., Supplementary Appendix, available at *Annals of Oncology* online [5]). If one or both of these thresholds are exceeded, adequate control should be achieved before initiation of therapy. The time to onset of hyperlipidemia was not reported in phase III everolimus studies.

The incidences of elevated cholesterol and triglyceride levels were 24–44% higher in patients treated with everolimus compared with the respective control arms of the phase III oncology trials [2]. As with hyperglycemia, patients with elevated lipids at baseline should have their lipid panels screened frequently and managed to stable levels. However, intervention for elevated lipid levels should be adapted to the overall concern for the extent of cancer disease, the individual’s cardiovascular risk factor, and the expected survival (which may exceed 2 years in advanced breast cancer) [39]. In individual cases, it may be acceptable to tolerate lipid elevations to grade 1 and perhaps even grade 2 because lipid abnormalities do not have the same clinical impact as hyperglycemia.

Hyperlipidemia can also be treated per guidelines [20, 38, 40, 41], with monitoring for possible interactions between statins and CYP3A4 enzymes. High triglyceride levels (≥500 mg/dl) should be lowered promptly with fibrates because of the risk of acute pancreatitis [20, 23, 37, 42].

### Rash

Rash is a typical class-effect of mTOR inhibitors, and usually manifests as an acneiform dermatitis that starts as an inflammatory lesion (papule or pustule), with comedones (blackheads) sometimes appearing thereafter [43, 44]. Similar to stomatitis, rash usually develops soon after initiating everolimus treatment. This rash is distinguished by its wide and unusual distribution—typically found in areas not acne prone such as the upper extremities or neck [43, 44].

The incidence of rash in the phase III trials of everolimus monotherapy ranged from 29% to 49% [6, 8]. The incidence of rash for everolimus plus exemestane in BOLERO-2 was 39% [26]. A meta-analysis of rash incidence in 13 everolimus trials (N = 2242) reported an all-grade incidence of 29% and a grade 3/4 incidence of 1% [45].

Because there are so few high-grade events, the majority of rash events typically resolve without therapeutic intervention. Topical application of cortisone creams and moisturizers may

### Table 3. Known drug interactions with everolimus

<table>
<thead>
<tr>
<th>Reason for interaction</th>
<th>Increased everolimus concentration</th>
<th>Decreased everolimus concentration</th>
<th>Increased drug concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ketoconazole, itraconazole, voriconazole</td>
<td>Strong CYP3A4 inhibitor&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Midazolam Sensitive CYP3A4 substrate</td>
</tr>
<tr>
<td></td>
<td>Clarithromycin, telithromycin</td>
<td>Strong CYP3A4 inhibitor&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Atazanavir, saquinavir, ritonavir, indinavir, nelfinavir</td>
<td>Strong CYP3A4 inhibitor&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nefazodone</td>
<td>Strong CYP3A4 inhibitor&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluconazole</td>
<td>Moderate CYP3A4 inhibitor and/or PgP inhibitor&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Erythromycin</td>
<td>Moderate CYP3A4 inhibitor and/or PgP inhibitor&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amprenavir, fosamprenavir</td>
<td>Moderate CYP3A4 inhibitor and/or PgP inhibitor&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Verapamil</td>
<td>Moderate CYP3A4 inhibitor and/or PgP inhibitor&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Aprepitant</td>
<td>Moderate CYP3A4 inhibitor and/or PgP inhibitor&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Diltiazem</td>
<td>Moderate CYP3A4 inhibitor and/or PgP inhibitor&lt;sup&gt;b&lt;/sup&gt;</td>
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<td></td>
<td>Rifampin</td>
<td>Strong CYP3A4 inducer&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
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<td>Rifabutin, rifapentine</td>
<td>Strong CYP3A4 inducer&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>Phenytoin</td>
<td>Strong CYP3A4 inducer&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>Phenoobarbital</td>
<td>Strong CYP3A4 inducer&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Carbamazepine</td>
<td>Strong CYP3A4 inducer&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

Data from Afinitor prescribing information [2].
<sup>a</sup>Concomitant strong inhibitors of CYP3A4 should not be used.
<sup>b</sup>If alternative treatment cannot be administered, reduce the everolimus dose up to 2.5 mg daily.
<sup>c</sup>If alternative treatment cannot be administered, increase the everolimus dose up to 20 mg daily using 5-mg increments.

### References


[Annals of Oncology](https://www.sciencedirect.com/journal/annals-of-oncology)
provide symptomatic relief, although caution is recommended for symptomatic treatment of rash with steroids in patients prone to infection and/or hyperglycemia [46].

**specific considerations for management of everolimus-related adverse events in patients with breast cancer**

While large phase III trials have established that there are no significant differences in the safety profile of everolimus across various indications, there are issues specific to population, disease, and concomitant treatment that are particularly relevant in patients with breast cancer. For breast cancer, everolimus has a specific indication in combination with exemestane [1, 2]; consequently, patients with advanced breast cancer who receive everolimus will be postmenopausal and possibly already experienced or will be at risk for certain adverse events. In one database review of patients with breast cancer (N = 64,034) who were diagnosed at a median age of 75 years, 42% had one or more comorbid conditions, often diabetes and/or chronic obstructive pulmonary disease [47]. Correspondingly, concurrent medications for the comorbid conditions should be reviewed for the potential to influence the risk of adverse events such as immunosuppression and resulting infections, as well as for drug interactions (Table 3).

Patients with advanced breast cancer who receive everolimus may also have received other prior therapies, the effects of which may influence patient perception of everolimus. For example the safety profile of everolimus may be favorably perceived by the patient after receiving intravenous chemotherapy. In contrast, patients who have only received prior hormonal therapy will need education on the benefit-to-risk ratio of everolimus and adverse event management. Adherence to defined thresholds for dose reductions per management guidelines is critical to maximize treatment exposure and clinical benefit. Patient education on class-effects of mTOR inhibitors is, therefore, also critical. Further, physicians may also have a low threshold for opting to change treatment because of potential increases in adverse event incidence or severity versus prior hormonal therapies. For example in BOLERO-2, study treatment was discontinued for grade 1/2 pneumonitis in 18 patients (3.7%) and for grade 1/2 stomatitis in 9 patients (1.9%) [26].

Many patients will receive bone-conserving therapies (e.g. bisphosphonates or denosumab) to prevent skeletal-related events or to treat osteoporosis related to the use of an aromatase inhibitor. Although relatively infrequent, certain adverse events during bone-conserving therapy, including renal impairment and osteonecrosis of the jaw (ONJ), may present additional management/monitoring considerations in patients with breast cancer. For example grade 3/4 creatinine increase was observed in ~2% of patients with breast cancer receiving everolimus therapy, and this may affect the usage of bisphosphonates or denosumab. In theory, ONJ is part of the differential diagnosis at the presentation of a stomatitis event. Although the denuded bone area is easily distinguished from superficial mucosal lesions on the gum, preliminary symptoms such as pain are observed in both clinical conditions. Preventive measures and patient education are critical to reduce rates of ONJ and stomatitis.

Special consideration/monitoring for metabolic abnormalities may be required for perimenopausal women. Recent oophorectomy or use of luteinizing hormone-releasing hormone agonists may predispose them to metabolic dysfunction [48]. Accordingly, the metabolic profile of these patients needs to be monitored regularly to minimize the risk of adverse events associated with severe metabolic dysfunction.

Finally, all patients with cough or dyspnea should seek medical attention to rule out noninfectious pneumonitis. Notably, 24% and 21% of patients enrolled in BOLERO-2 had cough and dyspnea, respectively (all-grade) [2]. In particular, patients with breast cancer who have had prior radiation therapy should have a baseline CT scan or X-ray to evaluate for pre-existing radiographic pneumonitis resulting from radiotherapy.

**conclusions**

The adverse event profile of everolimus is broadly similar across various approved indications, and no new safety signals were observed in combining everolimus with hormonal therapy in patients with breast cancer. Clinical management protocols for everolimus-related adverse events are well established and applicable across all oncology settings. Many adverse events begin as minor issues, and patient education may encourage early reporting, which allows for prompt intervention and mitigation of the adverse event’s severity and duration. It may be advisable to see or contact the patients after 2 weeks of treatment in order to elicit signs/symptoms of early toxicity. Overall, everolimus is an effective treatment option, with manageable toxicity, among patients with HR+ advanced breast cancer who have recurring or progressing disease during/after nonsteroidal aromatase inhibitor therapy.

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consultant with Novartis and GSK; has been a member on an advisory committee for Roche, Pfizer, Novartis, and GSK; has received honoraria or been part of speaker’s bureaus from Roche, Novartis, GSK, and Amgen. KP acted as a consultant and/or speaker for Novartis, Pfizer, GSK, Bayer-Schering, Astellas, Aven, and Boehringer-Ingelheim; he also received research grants from Novartis and Bayer-Schering. KP is a consultant with sanofi-aventis, AstraZeneca, Roche, Pfizer, Novartis, Abrisax, Amgen, and GSK; has received research funding either directly through per-case funding for studies or indirectly through the National Cancer Institute of Canada Clinical Trials Group; contracted with pharmaceutical companies including AstraZeneca, Bristol-Myers Squibb, sanofi-aventis, Amgen, Pfizer, Novartis, and GSK; has received honoraria or been part of speaker’s bureaus from sanofi-aventis, AstraZeneca, Pfizer, Roche, Novartis, GSK, and Amgen; has given paid expert testimony for sanofi-aventis, AstraZeneca, and GSK; and has been a member on an advisory committee for sanofi-aventis, AstraZeneca, Roche, Pfizer, Novartis, GSK, and Amgen. AR is a member of Global, European, and/or French advisory boards in renal cell cancer for Pfizer, Novartis, Bayer-Schering, GSK, Astellas, Aven, and Bristol-Myers Squibb; has received institutional grant support from Pfizer, Novartis, and Roche; has been an international principal investigator for trials sponsored by Novartis and Pfizer; and has been a member of steering committees of trials for Pfizer, Novartis, and Bristol-Myers Squibb; and has received travel and housing support for meetings from Novartis and Pfizer.

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Present and future breast cancer management—bench to bedside and back: a positioning paper of academia, regulatory authorities and pharmaceutical industry

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Insights into tumour biology of breast cancer have led the path towards the introduction of targeted treatment approaches; still, breast cancer-related mortality remains relatively high. Efforts in the field of basic research revealed new druggable targets which now await validation within the context of clinical trials. Therefore, questions concerning the optimal design of future studies are becoming even more pertinent. Aspects such as the ideal end point, availability of predictive markers to identify the optimal cohort for drug testing, or potential mechanisms of resistance need to be resolved. An expert panel representing the academic community, the pharmaceutical industry, as well as European Regulatory

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