Toxicity of mTOR inhibitors

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Approved mTOR inhibitors in cancer

- **EVEROLIMUS**
  - HR+ BC after an AI in combination with EXE
  - RCC after failure to an VEGFR inhibitor
  - Neuroendocrine pancreatic cancer

- **TEMSIROLIMUS**
  - RCC
  - Mantle Lymphoma
mTOR functions

Metabolic side effects

Secondary to protein synthesis
Immune side effects
Most common side effects

**EVEROLIMUS**
- HR+ BC
  - stomatitis (67%)
  - infections (50%)
  - rash (39%)
  - fatigue (36%)
  - diarrhea (33%)
  - decreased appetite (30%)

- RCC
  - stomatitis (44%)
  - infections (37%)
  - asthenia (33%)
  - fatigue (31%)
  - cough (30%)
  - diarrhea (30%)

**PNET**
- stomatitis (70%)
- rash (59%)
- diarrhea (50%)
- fatigue (45%)
- edema (39%)
- abdominal pain (36%)
- nausea (32%)
- fever (31%)
- headache (30%)
- decreased appetite (30%)

**TEMsiROLIMUS**
- skin rash (47%)
- Fatigue (51%)
- mucositis (41%)
- Nausea (37%)
- Edema (35%)
- loss of appetite (32%)

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https://www.afinitor.com

http://www.pfizerpro.com/hcp/torisel/home
Most common Grade 3/4 side effects

**EVEROLIMUS**

**HR+ BC**
- stomatitis (67%)
- infections (50%)
- rash (39%)
- fatigue (36%)
- diarrhea (33%)
- decreased appetite (30%)

**RCC**
- stomatitis (44%)
- infections (37%)
- asthenia (33%)
- fatigue (31%)
- cough (30%)
- diarrhea (30%)

**PNET**
- stomatitis (70%)
- rash (59%)
- diarrhea (50%)
- fatigue (45%)
- edema (39%)
- abdominal pain (36%)
- nausea (32%)
- fever (31%)
- headache (30%)
- decreased appetite (30%)

**TEMSIROLIMUS**
- skin rash (47%)
- Fatigue (51%)
- mucositis (41%)
- Nausea (37%)
- Edema (35%)
- loss of appetite (32%)

**stomatitis (8%), dyspnea (7%), diarrhea (5.5%), infections (5%), hyperglycemia (5%), and fatigue (5%)**

[https://www.afinitor.com](https://www.afinitor.com)  [http://www.pfizerpro.com/hcp/torisel/home](http://www.pfizerpro.com/hcp/torisel/home)
Most common laboratory abnormalities

**EVEROLIMUS**
- HR+ BC
  - hypercholesterolemia (70%)
  - hyperglycemia (69%)
  - increased AST (69%)
  - anemia (68%)
  - leukopenia (58%)
  - thrombocytopenia (54%)
  - lymphopenia (54%)
  - increased ALT (51%)
  - hypertriglyceridermia (50%)

**RCC**
- anemia (92%)
- lymphocytopenia (51%)
- hypercholesterolemia (77%)
- hypertriglyceridermia (73%)
- hyperglycemia (57%)
- increased creatinine (50%)

**PNET**
- anemia (86%)
- decreased bicarbonate (56%)
- hyperglycemia (75%)
- increased ALP (74%)
- hypercholesterolemia (66%)
- increased AST (56%)

**TEMSIROLIMUS**
- anemia (94%)
- hyperglycemia (89%)
- hyperlipemia (87%)
- hypertriglyceridermia (83%)
- elevated ALP (68%)
- elevated creatinine (57%)
- lymphopenia (53%)
- hypophosphatemia (49%)
- thrombocytopenia (40%)
- elevated AST (38%)
- leukopenia (32%)

Anemia, hypercholesterolemia, hypertriglyceridermia, hyperglycemia
Stomatitis
Etiology and incidence

The etiology is multifactorial. Role of immune deregulation. Several potential mechanisms described: antibody-dependent cell mediated cytotoxicity; autoimmune and cross-reactions between a microbial antigen and a peptide within the oral epithelium.

Incidence ranging from 44% to 86%
Grade 3/4 stomatitis 4% to 9% of patients

ARCC
incidence in 42%; mostly (39%) mild-to-moderate stomatitis that resolved within 3 days. 10% required dose modification or treatment interruption.

<table>
<thead>
<tr>
<th>Stomatitis and Related Events</th>
<th>EVE+ EXE n = 482</th>
<th>PBO+ EXE n = 238</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose interruptions, % (n)</td>
<td>24% (118)</td>
<td>1% (3)</td>
</tr>
<tr>
<td>Median time for complete resolution of grade 2 stomatitis and related events; % (n) of patients</td>
<td>16 days; 98% (118 of 121)</td>
<td>8 days; 80% (4 of 5)</td>
</tr>
<tr>
<td>Treatment discontinuation stomatitis, % (n)</td>
<td>3% (14)</td>
<td>&lt; 1% (1)</td>
</tr>
</tbody>
</table>

HR+ Breast Cancer
**Difference between mucositis and stomatitis**

**Oral mucositis**: describes inflammation of oral mucosa resulting from chemotherapeutic agents or ionizing radiation. Typically manifests as erythema or ulcerations and may be exacerbated by local factors, like secondary infections and trauma.

![Mucositis](image)

**Mucositis**
**Stomatitis:** is a less specific term that refers more generally to any inflammatory condition of oral tissues.
Stomatitis: Clinical presentation

• Ulceration of mucosal surfaces involved includes non-keratinized oral tissues such as labial and buccal mucosa and the ventral surface of the tongue and floor of the mouth

• Presents with discrete aphthous-like ulcerations

• They can be very painful and limit food intake

Stomatitis: Clinical presentation

“...I got 2 horrendous mouth sores and some smaller ones on my tongue and throat about 8-10 days after starting A/A. They took about 3-4 weeks to go away and I have not gotten any since; however I do occasionally have a feeling of one coming on (sore spot but not open)”

http://community.breastcancer.org/forum/8/topic/800156

### Stomatitis: Management

<table>
<thead>
<tr>
<th>Grade</th>
<th>Symptoms</th>
<th>Treatment and Management</th>
<th>Everolimus Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Minimal; can maintain normal diet</td>
<td>• Nonalcoholic or 0.9% salt water mouthwash several times daily</td>
<td>• No change</td>
</tr>
</tbody>
</table>
| 2     | Symptomatic but can eat and swallow modified diet | • Topical analgesic mouth treatments with or without topical corticosteroids  
• Avoid agents containing hydrogen peroxide, iodine, and thyme derivatives | • Temporarily interrupt dose until recovery to grade ≤ 1, then restart at same dose  
• If stomatitis recurs at grade 2, then temporarily interrupt dose until recovery to grade ≤ 1, and restart at reduced dose |
| 3     | Symptomatic and unable to adequately aliment or hydrate orally | • Topical analgesic mouth treatments with or without topical corticosteroids  
• Avoid agents containing hydrogen peroxide, iodine, and thyme derivatives | • Temporarily interrupt dose until recovery to grade ≤ 1, then restart at reduced dose |
| 4     | Associated with life-threatening consequences | • Treat with appropriate medical therapy | • Discontinue treatment |

Stomatitis: Patient education

- **Patient awareness and early intervention** are important
- Consider evaluation for herpesvirus or fungal infection

- **Oral hygiene:** Educate patients about good oral hygiene
  - Rinse with nonalcoholic mouthwash and floss after each meal
  - Use mild toothpaste and soft-bristled toothbrush
  - Avoid agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives
  - Preventive treatment with sodium bicarbonate-based mouthwash ineffective

- **Avoid foods that are spicy/acidic/salty**

- **Prompt reporting:**
  - > 3 lesions
  - Lesions lasting > 3 days
  - Lesions interfering with eating and drinking

"I read somewhere that if you put the pill in a small marshmallow to take it, you won't get the sores as it has something to do with the coating on the pill...."
Non-infectious Pneumonitis (NIP)
mTOR inhibitors may bind directly to tissue proteins evoking an autoimmune-like inflammatory response, mediated by CD4 cells in the absence of infection. Proinflammatory properties of mTOR inhibitors have also been described in various experimental models.

Reported in up to 19% of patients treated with everolimus. The incidence of grade 3/4 was up to 4.0% and up to 0.2%, respectively. Fatal outcomes have been observed.
NIP: Clinical presentation

- Appearance around 2 to 6 months after starting treatment with mTOR inhibitor
- Symptomatology includes from absence of any symptoms to dyspnea, coughing, hypoxia, fever, pleural effusion
- Diagnosis usually by exclusion

8 cases of pneumonitis in renal transplanted patients during sirolimus treatment

Clinically: bilateral interstitial infiltrates, marked general symptoms

BAL: alveolitis with moderate to marked alveolar lymphocytosis. In three cases, flow cytometry demonstrated presence of T cells (mostly CD4+) with few eosinophils and mast cells.

Negativity for bacteria, mycobacteria, fungi, parasites and viruses

Negativity for CMV antigenemia and serology for Legionella, Mycoplasma and Aspergillus

Transbronchial biopsies in 2 cases: histological features consisting of bronchiolitis obliterans with organized pneumonia, interstitial lymphocytic infiltrates and nonnecrotizing macrophagic granuloma

All results compatible with the diagnosis of hypersensitivity pneumonitis
Radiological findings

• Ground glass opacity

• Airspace consolidation
## NIP: Management

<table>
<thead>
<tr>
<th>Grade</th>
<th>Symptoms</th>
<th>Treatment and Management</th>
<th>Everolimus Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Asymptomatic; radiographic</td>
<td>• Initiate appropriate monitoring</td>
<td>• No change</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Life threatening, ventilatory support indicated</td>
<td>• Perform diagnostic tests for infectious causes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Consider treatment with corticosteroids</td>
<td></td>
</tr>
</tbody>
</table>

Cases of interstitial lung disease, some resulting in death, have occurred. Some patients were asymptomatic or had minimal symptoms. Patients should undergo baseline radiography prior to temsirolimus therapy and periodically thereafter, even in the absence of clinical respiratory symptoms.

NIP: Risk evaluation

Obtain complete pulmonary history

- No evidence of compromised lung function
  - CT scan and lung function tests at physician’s discretion
    - Diffusion capacity <20%: use mTOR inhibitor with caution
      - TLCO <40%, hold mTOR inhibitor until lung function normalized

- Respiratory symptoms, or
  - Multiple lung metastases
    - CT scan
    - Lung function tests

- Significant fibrosis, or
  - Severe COPD
    - Avoid mTOR inhibitor therapy

Abbreviations: COPD, chronic pulmonary obstructive disease; CT, computed tomography; TLCO, single breath transfer factor lung volume for carbon monoxide.
“... I, too, am concerned about discussions disappearing about respiratory problems caused by Afinitor. I'm not sure I'll use it since from the beginning my mets have been in the lung pleura. I'm afraid it will take lots of convincing before I will be willing to try it. My onc said he would do xrays periodically to check for streaking in the lung. I'm still not convinced it would be the right drug for me ...”
Metabolic side effects
mTORC1 acts as a signal integrator for four major regulatory inputs: nutrients, growth factors, energy and stress.

mTORC1 controls the activity of several transcription factors that are implicated in lipid synthesis and mitochondrial metabolism.
Hypertension: Management

- One of the most common Grade 3/4 side effects for all types of tumors
- Check on glucose levels regularly before starting treatment and afterwards during treatment

<table>
<thead>
<tr>
<th>Grade</th>
<th>Laboratory values</th>
<th>Treatment</th>
<th>Dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Glucose: &gt;ULN-160 mg/dL</td>
<td>• None</td>
<td>• No changes</td>
</tr>
<tr>
<td>2</td>
<td>Glucose: &gt;160-250 mg/dL</td>
<td>• Adequate treatment according to the guidelines of the American Diabetes Association and the European Association for the Study of Diabetes</td>
<td>• No dose adjustment</td>
</tr>
<tr>
<td>3</td>
<td>Glucose: &gt;250-500 mg/dL</td>
<td>• Restart treatment at a lower dose</td>
<td>• Temporary interrupt the treatment until recovery to grade ≤1</td>
</tr>
<tr>
<td>4</td>
<td>Glucose: &gt;500 mg/dL</td>
<td></td>
<td>• Stop mTOR inhibitor definitively</td>
</tr>
</tbody>
</table>

## Hyperlipidemia: Management

<table>
<thead>
<tr>
<th>Grade</th>
<th>Laboratory values</th>
<th>Treatment</th>
<th>Dose modification</th>
</tr>
</thead>
</table>
| 1     | - Colesterol: >ULN-300 mg/dL  
- Triglicerids: >ULN-2.5 × ULN | - None | - No dose modification |
| 2     | - Colesterol: >300-400 mg/dL  
- Triglicerids: >2.5-5.0 × ULN | - Treat hyperlipidemia following standard guidelines  
- Triglicerid levels ≥500 mg/dL increase the risk of pancreatitis; it is recommended the use of fibrates | - Maintain dose level if good tolerance  
- If the patient has problems tolerating the dose, dose interruption until recovery of grade ≤1; then restart at the same dose |
| 3     | - Colesterol: >400-500 mg/dL  
- Triglicerids: >5.0-10 × ULN | | - Dose interruption until recovery to grade ≤1; then restart the treatment with dose reduction o permanently stop the therapy according to medical criteria |
| 4     | - Colesterol: >500 mg/dL  
- Triglicerids: >10 × ULN | | - Definitively stop mTOR inhibitor |

Metabolic side effects: Patients’ awareness

“… Sweets are still my weakness. At the moment it's oatmeal cookies, banana bread and ice cream...”

http://community.breastcancer.org/forum/8/topic/800156
Infections
Infections: Incidence

- Infection is a common AE reported in patients treated with mTOR inhibitors
- The immunosuppressive properties predispose patients to bacterial, fungal, viral or protozoal infections including pneumonia, sepsis, mycobacterial infections, aspergillosis, candidiasis, and reactivation of Hepatitis B

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Everolimus+ exemestane (n=482), %</th>
<th>Placebo+ exemestane (n=238), %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>56</td>
<td>8</td>
</tr>
<tr>
<td>Infection^a</td>
<td>44</td>
<td>4</td>
</tr>
<tr>
<td>Rash</td>
<td>36</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>33</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>30</td>
<td>2</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>18</td>
<td>4</td>
</tr>
<tr>
<td>Anemia</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>11</td>
<td>3</td>
</tr>
</tbody>
</table>

Peterson et al, Support Care Cancer 2013; 21: 2341-49
Infections: Recommendations

- Full medical history of prior infection including fungal, hepatitis, HIV, tuberculosis and other opportunistic infections
- Live vaccinations and close contact with those who received live vaccines should be avoided

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Intervention</th>
<th>Everolimus dose adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>• Institute adequate treatment of infection with antibiotics, as appropriate</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Perform culture and be aware of atypical infections</td>
<td>• If toxicity is tolerable, no dose adjustment required</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• In patients who test positive for hepatitis B surface antigen, consider prophylaxis with entecavir or tenofovir</td>
<td>• Initiate appropriate medical therapy and monitor</td>
</tr>
<tr>
<td>2</td>
<td>Localized infection, with local intervention indicated</td>
<td>• In patients who test positive for hepatitis B surface antigen, consider prophylaxis with entecavir or tenofovir</td>
<td>• If toxicity is tolerable, no dose adjustment required</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Provide IV antibiotic, antifungal*, or antiviral therapy; institute additional interventions as for grade 1</td>
<td>• Initiate appropriate medical therapy and monitor</td>
</tr>
<tr>
<td>3</td>
<td>IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or surgery indicated</td>
<td>• Provide IV antibiotic, antifungal*, or antiviral therapy; institute additional interventions as for grade 1</td>
<td>• If toxicity becomes intolerable, temporary dose interruption until recovery to grade ≤1. Reinitiate everolimus at the same dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• If toxicity occurs at grade 2, interrupt everolimus until recovery to grade ≤1. Reinitiate everolimus at a lower dose</td>
</tr>
<tr>
<td>4</td>
<td>Life-threatening consequences such as septic shock, hypotension, acidosis, or necrosis</td>
<td>• Provide appropriate standard therapy, as for grade 1</td>
<td>• Temporary dose interruption until recovery to grade ≥1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Initiate appropriate medical therapy and monitor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Consider reinitiating everolimus at a lower dose. If toxicity recurs at grade 3, consider discontinuation</td>
</tr>
</tbody>
</table>

* If diagnosis of invasive systemic fungal infection is made, everolimus therapy should be promptly and permanently discontinued. Avoid coadministration of everolimus with strong cytochrome 3A4 inhibitors

Peterson et al, Support Care Cancer 2013; 21: 2341-49
“... can't eat anything uncooked because I'm always immunosuppressed (...) I almost died from either a salad at a restaurant, strawberries from our garden, or a cantaloupe from a store. I had an abcess in my brain and had to have brain surgery and 6 weeks in the hospital on antibiotics. My leg and arm were affected by the abcess and my leg never did return to normal. Not something I want to repeat. Be careful everyone...”
Fatigue
Fatigue: clinical presentation and etiology

- Cancer-related fatigue is defined as a distressing, persistent and subjective sense of tiredness and exhaustion related to cancer or cancer treatment

- Not proportional to recent activity and interferes with usual functioning

- **Multifactorial**
  - Cancer
  - Pain
  - Anemia
  - Hipotiroidisme
  - Insuficiencia renal
  - Depression
  - Sleep deprivation

Fatigue: management

- The ONS and NCCN identify exercise as a key intervention for preventing and treating cancer-related fatigue

- Treatment of other any underlying causes (anemia)

- Other measures:
  - Nutrition consultation
  - Sleep therapy
  - Stimulus control therapy
  - Strategies to reduce cognitive-emotional arousal
  - Muscle relaxation training (yoga, Tai-chi)
“...I RECENTLY TRIED THE A/A THERAPY, (...) I NEVER DID GET MOUTH SORES. HOWEVER, I NEVER BECAME SO RUN DOWN IN MY LIFE, SO FATIQUED I SPENT ALOT OF TIME SLEEPING MOST DAYS, TO TIRED I COULDN'T FUNCTION...”
General points
QoL

Health-Related Quality of Life of Patients With Advanced Breast Cancer Treated With Everolimus Plus Exemestane Versus Placebo Plus Exemestane in the Phase 3, Randomized, Controlled, BOLERO-2 Trial

Time-to-definitive deterioration

TABLE 1. ECOG Performance Status

<table>
<thead>
<tr>
<th>Score</th>
<th>EVE+EXE, % (n = 485)</th>
<th>PBO+EXE, % (n = 239)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>60</td>
<td>59</td>
</tr>
<tr>
<td>1</td>
<td>36</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Burris et al, Cancer 2013, 119(10):1908-15
mTOR inhibitors: Drug-Drug Interactions

• Avoid use of strong CYP3A4 inhibitors (eg, ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole)

• Cautious use moderate CYP3A4 and/or P-glycoprotein inhibitors (eg, amprenavir, fosamprenavir, aprepitant, erythromycin, fluconazole, verapamil, diltiazem) (reduce dose)

• Avoid use of strong CYP3A4 inducers (eg, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital)
Are side effects dose-dependent?

steady state, predose pharmacokinetic samples were taken from patients with solid tumors administered everolimus 10mg/day

- Efficacy and safety were evaluable for 945 and 938 patients, respectively
- Co-administering EVE with strong CYP3A4 and PgP inhibitors increased EVE $C_{\text{min}}$ by 10% and 20%, respectively; coadministration with CYP3A4 inducers reduced $C_{\text{min}}$ by 7%
- A 2-fold increase in EVE $C_{\text{min}}$ increased the risk of grade 3 pulmonary (RR 1.93, 95% CI 1.12–3.34), stomatitis (RR 1.49, 95% CI 1.05–2.10) and metabolic (RR 1.30, 95% CI 1.02–1.65) events.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soria et al. [8]</td>
<td>Advanced NSCLC</td>
</tr>
<tr>
<td>RADIANT-1 [18]</td>
<td>Advanced pNET</td>
</tr>
<tr>
<td>RECORD-1 [2]</td>
<td>mRCC</td>
</tr>
<tr>
<td>RADIANT-3 [3]</td>
<td>Advanced pNET</td>
</tr>
</tbody>
</table>
## Hyperlipidemia: Management

<table>
<thead>
<tr>
<th>Grade</th>
<th>Laboratory values</th>
<th>Treatment</th>
<th>Dose modification</th>
</tr>
</thead>
</table>
| 1     | • Colesterol: >ULN-300 mg/dL  
   • Triglicerids: >ULN-2.5 × ULN | • None | • No dose modification |
| 2     | • Colesterol: >300-400 mg/dL  
   • Triglicerids: >2.5-5.0 × ULN | • Treat hyperlipidemia following standard guidelines  
   • Triglicerid levels ≥500 mg/dL increase the risk of pancreatitis; it is recommended the use of fibrates | • Maintain dose level if good tolerance  
   • If the patient has problems tolerating the dose, dose interruption until recovery of grade ≤1; then restart at the same dose |
| 3     | • Colesterol: >400-500 mg/dL  
   • Triglicerids: >5.0-10 × ULN | | • Dose interruption until recovery to grade ≤1; then restart the treatment with dose reduction o permanently stop the therapy according to medical criteria |
| 4     | • Colesterol: >500 mg/dL  
   • Triglicerids: >10 × ULN | | • Definitively stop mTOR inhibitor |

Case Report

• Patient that developed grade 2 hypertriglyceridemia (480 mg/dL), and was started on fenofibrate 160 mg/day

• Everolimus trough plasma concentration was 10.1 ng/mL (within the range described in the phase I trial at this dosage) before introduction of fenofibrate. Two weeks later, stomatitis had regressed, but everolimus trough concentration had dropped to 4.2 ng/mL.

• Fenofibrate is known to induce the activity of CYP3A4, with previously documented impact on the pharmacokinetics and activity of erlotinib, another substrate of CYP3A4.

• Fenofibrate was withdrawn. Two weeks later, everolimus trough concentration raised up to 11.5 ng/mL, and grade 1 stomatitis had recurred.
Are there differences between ethnicities?

Higher incidence of NIP (22% vs 14%) and grade 3-4 thrombocytopenia (31% vs 23%)

Less hypercholesterolemia (13 vs 77%), hyperglycemia (17 vs 57%), hypertriglyceridemia (13 vs 73%)
And age?

Safety and Efficacy of Everolimus With Exemestane vs. Exemestane Alone in Elderly Patients With HER2-Negative, Hormone Receptor—Positive Breast Cancer in BOLERO-2

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Age &lt; 70 years</th>
<th>Age ≥ 70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EVE + EXE</td>
<td>PBO + EXE</td>
</tr>
<tr>
<td>Grade</td>
<td>Any</td>
<td>3/4</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>62</td>
<td>8</td>
</tr>
<tr>
<td>Rash</td>
<td>42</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>37</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>34</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>30</td>
<td>0.3</td>
</tr>
<tr>
<td>Appetite decrease</td>
<td>29</td>
<td>1</td>
</tr>
<tr>
<td>Weight decrease</td>
<td>27</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>26</td>
<td>0.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients, %</th>
<th>Age &lt; 70 years</th>
<th>Age ≥ 70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EVE + EXE (n = 364)</td>
<td>PBO + EXE (n = 196)</td>
</tr>
<tr>
<td>Discontinued</td>
<td>81.6</td>
<td>95.9</td>
</tr>
<tr>
<td>Reason for discontinuation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease progression</td>
<td>67.0</td>
<td>88.8</td>
</tr>
<tr>
<td>Patient withdrew consent</td>
<td>6.3</td>
<td>2.0</td>
</tr>
<tr>
<td>Adverse events</td>
<td>6.3</td>
<td>4.1</td>
</tr>
<tr>
<td>Death</td>
<td>0.8</td>
<td>0.5</td>
</tr>
<tr>
<td>Protocol deviation</td>
<td>0.3</td>
<td>1.7</td>
</tr>
<tr>
<td>New cancer therapy</td>
<td>0.5</td>
<td>0</td>
</tr>
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</table>

Summary

• mTOR inhibition may be associated with class effects such as stomatitis, NIP, infections, metabolibic side effects, and skin rash
• These drugs have a predictable and well-characterized safety profile that is consistent across tumor types
• Adverse events are manageable
• Strategies for effectively managing adverse events include
  – Patient education
  – Practical management recommendations
  – Dose modifications
Final thought

“...What I learned from this is not to get overly excited about big announcements of wonder treatments anymore. Each one has to be carefully considered for the individual.

I should have paid more attention to my mother’s best advice..."never be the first one to buy anything".