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REVIEW ARTICLE

Novel agents and associated toxicities of inhibitors of the PI3K/Akt/mTOR pathway for the treatment of breast cancer

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ABSTRACT

The PI3K/Akt/mTOR (phosphatidylinositol 3 kinase/Akt/mammalian target of rapamycin) signalling pathway is an established driver of oncogenic activity in human malignancies. Therapeutic targeting of this pathway holds significant promise as a treatment strategy. Everolimus, an mTOR inhibitor, is the first of this class of agents approved for the treatment of hormone receptor–positive, human epidermal growth factor receptor 2–negative advanced breast cancer. Everolimus has been associated with significant improvements in progression-free survival; however, it is also associated with increased toxicity related to its specific mechanism of action.

Methods

A comprehensive review of the literature conducted using a focused MEDLINE search was combined with a search of current trials at http://ClinicalTrials.gov/. Summary tables of the toxicities of the various classes of PI3K/Akt/mTOR inhibitors were created. A broad group of Canadian health care professionals was assembled to review the data and to produce expert opinion and summary recommendations for possible best practices in managing the adverse events associated with these pathway inhibitors.

Results

Differing toxicities are associated with the various classes of PI3K/Akt/mTOR pathway inhibitors. The most common unique adverse events observed in everolimus clinical trials in breast cancer include stomatitis (all grades: approximately 60%), noninfectious pneumonitis (15%), rash (40%), hyperglycemia (15%), and immunosuppression (40%). To minimize grades 3 and 4 toxicities and to attempt to attain optimal outcomes, effective management of those adverse events is critical. Management should be interdisciplinary and should use approaches that include education, early recognition, active intervention, and potentially prophylactic strategies.

Discussion

Everolimus likely represents the first of many complex oral targeted therapies for the treatment of breast cancer. Using this agent as a template, it is essential to establish best practices involving and integrating multiple disciplines for the management of future PI3K/Akt/mTOR signalling pathway inhibitors.

KEY WORDS

Breast cancer, PI3K/Akt/mTOR, everolimus, adverse events

1. INTRODUCTION

The PI3K/Akt/mTOR (phosphatidylinositol 3 kinase/Akt/mammalian target of rapamycin) signalling cascade is well characterized and plays crucial roles in a variety of physiologic processes (Figure 1): cell cycle progression, differentiation, transcription, translation, apoptosis, motility, autophagy, anabolic processes (including protein and lipid synthesis), and metabolic processes (including normal glucose homeostasis)[1]. Activation of the PI3K/Akt/mTOR signalling pathway is implicated in tumourigenesis, and PI3K/Akt/mTOR is the most frequently mutated pathway in breast cancer (Tables I and II)[2–8]. The Cancer Genome Atlas Network recently profiled (by next-generation sequencing) tumours from 825 breast cancer patients and demonstrated that the most frequently observed somatic mutation occurs in the *PIK3CA* gene, in luminal breast cancers in particular[2,3]. Overall, activation of the PI3K/Akt/mTOR signalling pathway in breast cancer could be as frequent as 70%, and some studies suggest that its activation is associated with aggressive features such as high histologic grade, the basal-like and HER2 phenotypes, and poor clinical outcome[7].

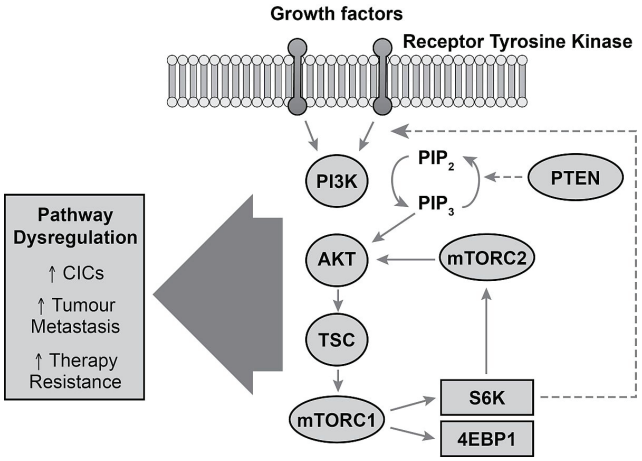

FIGURE 1 The PI3K/Akt/MTOR signalling pathway in cancer. The dashed line indicates negative feedback. PI3K = phosphatidylinositol 3 kinase; PIP = phosphatidylinositol-4 phosphate; PTEN = phosphatase and tensin homolog; CIC = cancer-initiating cell; Akt = v-akt murine thymoma viral oncogene; MTOR = mammalian target of rapamycin; TSC = tuberous sclerosis; S6K = S6 kinase; 4EBP1 = 4E-binding protein.

Furthermore, activation of the PI3K pathway has been implicated in resistance to hormonal therapy, and inhibition of MTOR has been associated with restoration of hormone sensitivity, particularly when inhibitors are given in combination with hormonal agents[9].

A number of novel anticancer agents targeting the PI3K/Akt/MTOR signalling pathway have been developed for the treatment of various malignancies, including breast cancer (Figure 2). As those agents enter clinical trials and show encouraging clinical activity, relevant drug-related adverse events (AEs) must be considered.

Everolimus, an inhibitor of MTOR, has been approved (in combination with exemestane) for patients with hormone receptor (HR)–positive, HER2 (human epidermal growth factor receptor 2)–negative advanced breast cancer after progression on non-steroidal aromatase inhibitors (AIs). The AE profile of everolimus does not overlap with the profiles of existing hormonal systemic therapies, but understanding of the benefits, tolerability, and risks of everolimus–exemestane therapy is growing[10]. The need to develop strategies to proactively manage clinically relevant AEs related to MTOR inhibition—as for other tyrosine kinase inhibitors—is becoming increasingly clear.

Across Canada, oncology physicians, pharmacists, and nurses are using interdisciplinary approaches for the practical management of AEs associated with everolimus. Protocols include education of patients about the potential types of toxicities; early recognition and frequent monitoring for toxicity; and active intervention and prophylactic strategies. Once established, models of care that comprehensively address toxicities relevant to everolimus administration should inform future prevention, monitoring, and proactive treatment strategies for AEs associated with the new anticancer agents targeting the PI3K/Akt/MTOR signalling pathway.

TABLE I Genetic aberrations of the PI3K/Akt/MTOR signalling pathway in cancer[a]

Gene	*Alteration*	*Tumour types*
PIK3CA	Gain-of-function mutation	Breast, colorectal, glioblastoma, endometrial, cervical, esophageal, gastric, head-and-neck, liver, lung, lymphoma, ovarian, pancreatic, prostate, thyroid
	Amplification	Breast, cervical, gastric, lung, ovarian, prostate
PIK3R1	Gain-of-function mutation	Brain, colon, ovarian
PTEN	Loss-of-function mutation	Bladder, brain, breast, cervical, colorectal, endometrial, gastric, head-and-neck, renal
	Deletion	Leukemia, liver, lung, lymphoma, melanoma, ovarian, prostate, thyroid
	Epigenetic silencing	Breast, colon, melanoma
AKT1	Gain-of-function mutation	Breast, colon, endometrial, melanoma, ovarian
AKT2	Gain-of-function mutation	Colorectal
	Amplification	Breast, colon, lymphoma, pancreatic
AKT3	Gain-of-function mutation	Melanoma
PDK1	Gain-of-function mutation	Colorectal
MTOR	Gain-of-function mutation	Renal, brain, colorectal, breast, endometrial, bladder, gastric, ovarian, lung (non-small cell)

[a] Adapted from Courtney *et al.,* 2010,[5] and Grabiner *et al.,* 2014[6]. PI3K = phosphatidylinositol 3 kinase; Akt = v-akt murine thymoma viral oncogene; MTOR = mammalian target of rapamycin.

2. METHODS

The MEDLINE database (2009–2014) and http://ClinicalTrials.gov/ were searched for relevant evidence. The search used combinations of these key words: "PI3K," "MTOR," "MTORC1," "MTORC2,"

"pathway," "breast cancer," "METABRIC," "TCGA," "aberrations," "inhibition," "mechanism," "toxicity," "adverse events," "everolimus," "intervention," "management," "education," "patient," and "stomatitis." In addition, the proceedings of the 2013–2014 American Society of Clinical Oncology and the 2013–2014 European Society for Medical Oncology annual meetings were searched for abstract reports of relevant studies. The searches identified 383 reports, of which 37 are discussed in this review.

3. RESULTS AND DISCUSSION

3.1 PI3K/Akt/mTOR Signalling Pathway Inhibitors in Clinical Development

Five main classes of PI3K/Akt/mTOR signalling pathway inhibitors are currently being investigated in advanced (primarily estrogen receptor–positive) breast cancer[8] (Figure 2, Table III):

- Pan-PI3K inhibitors block all class IA PI3Ks. They are represented by several small-molecule drugs

TABLE II The PI3K/Akt/mTOR signalling pathway alterations in human breast cancers by molecular subtype[a]

Gene	*Protein*	*Alteration*	*Effect on signalling*	*Frequency (%)*		
				Luminal[b]	*HER2-positive*	*Basal*[c]
ERBB2	HER2	Gene amplification or overexpression	Hyperactivation of ErbB2 signalling (PI3K, MEK)	10	~100	0
PTEN	PTEN	Loss-of-function mutation or reduced expression	Hyperactivation of PI3K signalling	29–44	22	67
PIK3CA	p110α/PI3K	Activating mutation	Hyperactivation of PI3K signalling	48–47	23–33	8–25
PIK3CB	p110β/PI3K	Amplification	Unknown		5 (of all cases)	
IGF1R and *INSR*	IGF1R, InsR	Receptor activation, *IGF1R* amplification	Activates IGF-IR/InsR signalling (PI3K, MEK)	41–48	18–64	42
FGFR1		Amplification, activating mutation	Hyperactivation of FGFR signalling (PI3K, MEK)	8.6–11.6	5.4	5.6
RPS6K1	p70S6K	Amplification	Unknown		3.8–12.5 (of all cases)	
INPP4B		Reduced expression or genomic loss	Hyperactivation of PI3K signalling	10–33	54	53
PIK3R1	p85α/PI3K	Inactivating mutation	Depression of catalytic activity of p110α		2 (of all cases)	
AKT1		Activating mutation	Hyperactivation of Akt	2.6–3.8	0	0
AKT2		Amplification	Hyperactivation of Akt		2.8	
EGFR	EGFR	Amplification	Hyperactivation of EGFR signalling (PI3K, MEK)		0.8 (of all cases)	
PDK1		Amplification or overexpression	Hyperactivation of PDK1 (Akt, TORC1)	22	22	38
KRAS	K-ras	Activating mutation	Hyperactivation of PI3K and MEK		4–6 (of all cases)	

[a] Adapted from Miller *et al.,* 2011[8].
[b] Estrogen receptor–positive.
[c] Triple-negative.

PI3K = phosphatidylinositol 3 kinase; Akt = v-akt murine thymoma viral oncogene; mTOR = mammalian target of rapamycin; HER2 = human epidermal growth factor receptor 2; ErbB2 = v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2; MEK = mitogen-activated protein kinase kinase; PTEN = phosphatase and tensin homolog; IGF-1R = insulin like growth factor 1 receptor; InsR = insulin receptor; FGFR = fibroblast growth factor receptor; EGFR = epidermal growth factor receptor; PDK1 = phosphoinositide-dependent kinase 1; TORC1 = transducer of regulated CREB activity 1; K-ras = Kirsten rat sarcoma viral oncogene homolog.

including buparlisib (BKM120), pilaralisib (XL147), and pictilisib (GDC-0941)[12].
- The PI3K isoform-specific inhibitors, including alpelisib (BYL719) and taselisib (GDC-0032), selectively inhibit the PI3K p110α, β, γ, or δ isoforms[12].
- Pan-Akt inhibitors target the three isoforms of Akt (Akt1, 2, and 3). Because of the structural similarities between the three isoforms, isoform-specific inhibitors are proving challenging to develop.
- The mTORC1 (mammalian target of rapamycin complex 1) inhibitors, including sirolimus and its analogs (temsirolimus, everolimus, and deforolimus), are allosteric irreversible inhibitors of mTORC1 kinase[13]; the mTORC1 or 2 inhibitors block both mTORC1-dependent phosphorylation of S6K1 and mTORC2-dependent phosphorylation of Akt[13].
- Dual PI3K and mTOR inhibitors target the p110 subunit of PI3K and mTOR. This dual targeting might increase clinical efficacy because of more complete inhibition of the PI3K/Akt/mTOR signalling pathway and blockade of pathway activation through loss of negative feedback loops. However, it might also result in unforeseen clinically relevant side effects[13].

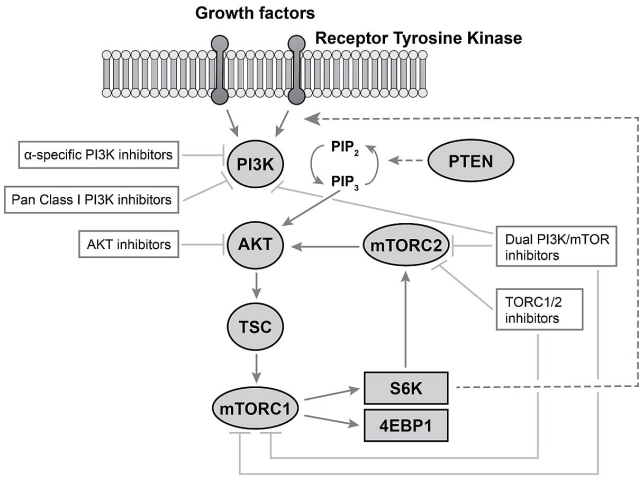

FIGURE 2 Classes of PI3K/Akt/mTOR signalling pathway inhibitors in breast cancer phase I, II, and III clinical trials. The dashed line indicates negative feedback. PI3K = phosphatidylinositol 3 kinase; PIP = phosphatidylinositol-4 phosphate; PTEN = phosphatase and tensin homolog; Akt = v-akt murine thymoma viral oncogene; mTOR = mammalian target of rapamycin; TSC = tuberous sclerosis; S6K = S6 kinase; 4EBP1 = 4E-binding protein.

The foregoing therapeutics are associated with a number of potential toxicities, some of which are shared by the various classes of agents. The AEs common to several PI3K/Akt/mTOR signalling pathway inhibitors include hyperglycemia and rash. Hyperglycemia has been observed in clinical trials of all five classes of PI3K/Akt/mTOR signalling pathway inhibitors[14–17], a finding that is not unexpected considering the role of the PI3K/Akt/mTOR signalling pathway in regulating glucose metabolism. Rash has been reported in patients treated with pan-PI3K inhibitors, pan-Akt inhibitors, and mTOR inhibitors; those events have been attributed to cytokine and chemokine deregulation resulting from pathway inhibition[17,18].

Other AEs associated with administration of specific PI3K/Akt/mTOR signalling pathway inhibitors include neutropenia, gastrointestinal toxicity, and mood disorders, which have so far been observed only in clinical trials of pan-PI3K inhibitors[19–21]. Stomatitis and noninfectious pneumonitis have so far been reported only in patients treated with mTOR inhibitors[14]. Recognition of the varying toxicities associated with agents used to inhibit the PI3K/Akt/mTOR signalling

TABLE III Classes of PI3K/Akt/mTOR signalling pathway inhibitors in breast cancer from phase I, II, and III clinical trials[a]

Inhibitor type	*Action*	*Agents in clinical trials*
Pan-PI3K	Inhibit the 4 class I PI3K p110 isoforms: p110α, p110β, p110γ, p110δ	Buparlisib (BKM120), pilaralisib (XL147), pictilisib (GDC-0941)
Isoform-specific PI3K	Selectively inhibit specific p110 catalytic forms of class I PI3K	Alpelisib (BYL719; p110α), taselisib (GDC-0032; p110α)
Pan-Akt	Inhibit all Akt isoforms (Akt1, 2, 3)	MK-2206, uprosertib (GSK2141795), ipatasertib (GDC-0068), AZD5363
mTORC1	Bind allosterically to and inhibit mTORC1	Everolimus,[b] ridaforolimus, temsirolimus, sirolimus
mTORC1 and 2	Bind to ATP binding site of mTOR kinase and inhibit mTORC1 and mTORC2	AZD2014, AZD8055, INK128 (MLN0128), CC-223
Dual PI3K and mTORC1 or 2	Inhibit PI3K, mTORC1, and mTORC2	Voxtalisib (XL765), apitolisib (GDC-0980), gedatolisib (PF-05212384), PI-103

[a] Adapted from Burris *et al.,* 2013[11].

[b] Approved in Canada in January 2013 for the treatment of postmenopausal women with hormone receptor–positive, HER2-negative advanced breast cancer in combination with exemestane when recurrence or progression follows treatment with letrozole or anastrozole.

PI3K = phosphatidylinositol 3 kinase; Akt = v-akt murine thymoma viral oncogene; mTOR = mammalian target of rapamycin; mTORC = mammalian target of rapamycin complex; ATP = adenosine triphosphate.

pathway is essential to inform best practices for patient management and education, and to optimize safety and clinical benefit.

3.2 Everolimus in Advanced Breast Cancer

Everolimus is the only PI3K/Akt/mTOR signalling pathway inhibitor and the first mTOR inhibitor approved in Europe and North America (in combination with exemestane) for the treatment of HR-positive, HER2-negative advanced breast cancer for patients with progressive disease on a nonsteroidal AI. The approval was based on BOLERO-2[22], a randomized placebo-controlled phase III trial that accrued 724 postmenopausal patients with HR-positive, HER2-negative advanced breast cancer who had experienced disease progression on a nonsteroidal AI, and that compared exemestane 25 mg daily plus everolimus 10 mg daily with exemestane plus placebo. In the trial, everolimus–exemestane was associated with improved median progression-free survival (local investigator assessment: 7.8 months vs. 3.2 months with exemestane alone; hazard ratio: 0.45; 95% confidence interval: 0.38 to 0.54; log-rank $p < 0.0001$; independent central radiology review: 11.0 months vs. 4.1 months; hazard ratio: 0.38; 95% confidence interval: 0.31 to 0.48; log-rank $p < 0.0001$) in the overall population and in all prespecified clinical subgroups. That magnitude of improvement in progression-free survival was both statistically and clinically significant. Furthermore, everolimus–exemestane was associated with an overall survival duration that was numerically increased to 31 months from 26.6 months with exemestane–placebo, a difference of 4.4 months (hazard ratio: 0.89; 95% confidence interval: 0.73 to 1.10; $p = 0.1426$)[23]. That endpoint did not reach statistical significance, but it is the longest duration reported to date in a phase III trial involving HR-positive, HER2-negative advanced breast cancer after prior treatment with a nonsteroidal AI.

The open-label randomized phase II TAMRAD trial involved 111 postmenopausal patients with HR-positive, HER2-negative breast cancer who had previously been treated with an AI. It compared tamoxifen 20 mg plus everolimus 10 mg with tamoxifen alone. The clinical benefit rate (objective response or stable disease for at least 6 months according to the *Response Evaluation Criteria in Solid Tumors,* version 1.0) was higher in the everolimus–tamoxifen treatment arm than in the tamoxifen-alone arm (61% vs. 42%). Median time to progression (8.6 months vs. 4.5 months, exploratory $p = 0.002$) and overall survival were also longer in the combined treatment arm[24].

3.3 Everolimus-Related Toxicities

The unique AE profile of everolimus includes epithelial and cutaneous events (stomatitis, rash), pulmonary dysfunction (noninfectious pneumonitis), hyperglycemia, and immunosuppression (Table IV)[26].

3.4 Recommended Management Strategies for Everolimus-Related Toxicities

To establish evidence-based management strategies that provide comprehensive supportive care for patients while on treatment, an understanding of the toxicities associated with everolimus is essential. Because the class-effect AE profile observed with everolimus plus endocrine therapy is distinct from that of endocrine therapy alone, education of health care providers and patients is critical to minimize toxicities, improve safety, and optimize adherence and clinical outcomes. Real-world experiences of health care professionals suggest that an interdisciplinary approach to the proactive management of patients receiving everolimus should include

- comprehensive education of patients about the range of toxicities,
- early toxicity recognition and frequent monitoring,
- active intervention, and
- prophylactic strategies.

Recommended management strategies for everolimus-related toxicities are summarized in Table V and Figure 3.

3.4.1 Stomatitis

Stomatitis associated with mTOR inhibitors is characterized by discrete, superficial, aphthous-like ulcers with a grayish-white pseudomembrane; it is clinically distinct from conventional chemotherapy-induced mucositis (Table V)[25,27]. Stomatitis events typically occur within 2–8 weeks of the initiation of mTOR inhibitor treatment; the incidence drops considerably after the first 6–8 weeks. Stomatitis was the most commonly reported all-grade AE in TAMRAD (56%) and BOLERO-2 (59%), and it was among the most commonly reported grades 3 and 4 AEs. Importantly, most patients (>97%) can experience complete resolution of stomatitis (approximately 16–22 days from onset) with symptomatic interventions and dose modification.

Early Recognition and Frequent Monitoring: Everolimus-treated patients must be educated and prepared for the possibility of developing stomatitis. Early clinical contact by a member of the oncology health care team—for example, at weeks 2, 4, and 8 of treatment—is recommended[25]. Patients should be advised to contact their health care provider at the first sign of mouth discomfort or lesions that interfere with eating and drinking.

Active Intervention: Clinical management depends on symptom severity. Patients should be instructed to avoid agents (for instance, mouthwashes) containing alcohol and hydrogen peroxide derivatives. Because of the possibility of immunosuppression related to everolimus, patients should be evaluated for herpetic

TABLE IV Incidence of common everolimus-related adverse events in patients enrolled in TAMRAD and BOLERO-2[a]

Variable	*Study*			
	TAMRAD		*BOLERO-2*	
	Tamoxifen plus everolimus (10 mg daily)	*Tamoxifen plus placebo*	*Exemestane plus everolimus (10 mg daily)*	*Exemestane plus placebo*
Patients (*n*)	54	57	485	239
Stomatitis (%)				
All grades	56	7	59	12
Grades 3–4	11	0	8	<1
Noninfectious pneumonitis (%)				
All grades	17	4	16	0
Grades 3–4	2	4	3	0
Rash (%)				
All grades	44	7	39	7
Grades 3–4	4	0	1	0
Hyperglycemia (%)				
All grades	Not reported	Not reported	14	2
Grades 3–4	Not reported	Not reported	<6	<1
Immunosuppression [infections (%)]				
All grades	35	19	44	21
Grades 3–4	7	5	6	2

[a] Adapted from Yardley *et al.,* 2013[22]; Bachelot *et al.,* 2012[24]; Peterson, 2013[25].

and fungal infections and treated appropriately. Early use of topical steroid mouth rinses should be considered, even for grade 1 stomatitis. Everolimus dose modifications (50% of the dose previously administered) can be implemented, particularly for grade 3 stomatitis and relapsing or recurrent grade 2 stomatitis (Table V)[27].

Prophylactic Strategies: Patients should be educated about good oral hygiene and encouraged to attend regular dental examinations and to maintain good toothbrushing habits using a soft toothbrush. Patients should be advised to use bland mouth rinses such as sterile water, normal saline, sodium bicarbonate, or tea, and to modify oral intake to minimize spicy and acidic foods. Newer recommendations for the prevention of stomatitis include using 15 mL of a baking soda or salt mouth rinse, followed 10–15 minutes later by 10 mL of a prescribed "miracle mouthwash" [320 mL Benadryl (diphenhydramine solution: Johnson & Johnson, New Brunswick, NJ, U.S.A.), 2 g tetracycline powder, 80 mg hydrocortisone, 40 mL nystatin suspension, and enough added water to reach a total of 473 mL] 4 times daily[29]. A phase II trial of the prophylactic use of a steroid-based mouth rinse to reduce the incidence and severity of stomatitis is ongoing (search for NCT02069093 at http://ClinicalTrials.gov/).

A recent meta-analysis observed that patients who experience stomatitis derive a clinical benefit from everolimus that is similar to the benefit derived by the overall trial population, suggesting that, with proactive management and dose adjustment according to the approved prescribing information, everolimus can be continued in most patients who experience stomatitis[30]. Interim analyses from a large German non-interventional study (BRAWO) of 3000 patients with advanced or metastatic HR-positive, HER2-negative breast cancer treated with everolimus and exemestane suggest that physician experience, prophylactic measures, and close monitoring of patients can reduce the incidence of stomatitis. Those observations emphasize that proactive communication and management strategies are essential[31,32].

3.4.2 Noninfectious Pneumonitis

Noninfectious pneumonitis is a non-malignant inflammatory pulmonary infiltrate that, when it occurs, generally arises over time. Radiologic findings include "ground glass" opacities and focal consolidation. All-grade noninfectious pneumonitis was relatively common in TAMRAD (17%) and BOLERO-2 (16%), and was the most common AE leading to treatment discontinuation in BOLERO-2 (5.6%). However, the incidence of grade 3 or 4 noninfectious pneumonitis was low (2%–4%) across the randomized trials[22,24].

TABLE V Clinical presentation and management strategy for three side effects in patients receiving everolimus[a]

Side effect and grade	*Description*		*Management*	*Everolimus dose modification*[b]
	Clinical exam	*Symptoms*		
Stomatitis				
Low/1	Discrete, superficial, well-demarcated, aphthous-like ulcers with a grayish-white pseudomembrane	Minimal symptoms; normal diet	• Alcohol-free mouthwash or 0.9% saline several times daily • Cooling with ice, frozen pineapple chunks, or balls of frozen pineapple juice • Avoid alcohol, hydrogen peroxide, iodine, or thyme-containing mouthwashes	• None recommended
2		Symptomatic; able to eat and swallow a modified diet	• Topical oral treatments: · Strepsils[c] lozenges · Lidocaine-containing denture adhesive for denture wearers · Mouthwash with local anesthetic (for example, benzocaine 15 mL every 3 hours), with or without steroids · Rinse with supersaturated calcium phosphate solution (moistens mouth and makes it slippery) · Gelclair[d] oral gel (3 times daily, or as needed ≥1 hour before next oral intake), undiluted or diluted (15 mL in 40 mL water); rinse mouth thoroughly for ≥1 minute · Rinse with "magic mouthwash" containing analgesic or anesthetic · Ketamine oral rinse (ketamine 20 mg in 5 mL saliva replacement fluid or isotonic saline) every 4 hours for stomatitis pain	• Temporary interruption until recovery to grade ≤1; restart at same dose • Recurrence at grade 2: temporary interruption as already described, but restart at reduced dose
3		Symptomatic; unable to adequately eat and drink orally		• Temporary interruption until recovery to grade ≤1; restart at reduced dose • Discontinue if no recovery to grade ≤1 within 4 weeks
4		Symptoms associated with life-threatening consequences	• Topical corticosteroids • Antiviral therapy for confirmed herpes simplex virus infection • Topical antifungal therapy as appropriate • Systemic antifungal therapy for refractory or severe fungal infection • Avoid alcohol-, hydrogen peroxide–, iodine-, or thyme-containing mouthwashes	• Discontinue treatment and treat with appropriate medical therapy
Noninfectious pneumonitis				
Low/1		Asymptomatic; radiographic findings only	• Observation: Clinical every 2 weeks Imaging every 4 weeks	• None recommended

TABLE V Continued

Side effect and grade	*Description*		*Management*	*Everolimus dose modification*[b]
	Clinical exam	*Symptoms*		
Noninfectious pneumonitis				
2		Symptomatic; no impairment of activities of daily living	Depending on symptom severity • Observation: Clinical every 1–2 weeks Imaging every 2–4 weeks • Consult pulmonologist • Consider diagnostics to rule out infection (fiberoptic bronchoscopy and bronchoalveolar lavage) • Consider corticosteroids until symptoms improve to grade ≤1	• Temporary interruption until recovery to grade ≤1; restart at reduced dose • Discontinue if no recovery to grade ≤1 within 4 weeks
3		Symptomatic; impairment of activities of daily living; supplemental oxygen required	• Consult pulmonologist • Diagnostics to rule out infection (fiberoptic bronchoscopy and bronchoalveolar lavage) • Corticosteroids if infectious cause excluded • For impending respiratory distress, concomitant antibiotics and corticosteroids	• Temporary interruption until recovery to grade ≤1; restart at reduced dose • Recurrence at grade 3: consider treatment discontinuation with appropriate medical therapy
4		Strong impairment of activities of daily living; mechanical ventilation required; life-threatening consequences		• Discontinue treatment and treat with appropriate medical therapy
Immuno-suppression				
1		None	• Institute antibiotics, as appropriate	• None recommended
2		Localized infection	• Perform culture and be aware of atypical infections • Administer prophylaxis with entecavir or tenofovir in patients who test positive for hepatitis	• Temporary interruption until recovery to grade ≤1; restart at same dose • Recurrence at grade 2: consider treatment interruption until recovery to grade ≤1; restart at lower dose

TABLE V Continued

Side effect and grade	*Description*		*Management*	*Everolimus dose modification*[b]
	Clinical exam	*Symptoms*		
Immuno-suppression				
3		Intravenous antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or surgery indicated	• Provide intravenous antibiotic, antifungal, or antiviral therapy; institute additional interventions as for grade 2 • Avoid co-administration of everolimus with strong CYP3A4 inhibitors[e]	• Temporary interruption until recovery to grade ≤1; restart at reduced dose • Recurrence at grade 3: consider treatment discontinuation with appropriate medical therapy • Dose reduction when everolimus is co-administered with moderate CYP3A4 or PgP inhibitors (or both)[f] • Dose increase when everolimus is co-administered with strong CYP3A4 inducers[g]
4		Life-threatening consequences such as septic shock, hypotension, acidosis, or necrosis	• Provide appropriate standard therapy	• Discontinue treatment

[a] Adapted from Aapro *et al.,* 2014[27]; Albiges *et al.,* 2012[28]; Peterson *et al.,* 2013[25].
[b] Cases of severe or intolerable adverse reactions could require temporary dose reduction or interruption of everolimus therapy. If dose reduction is required, the suggested dose is approximately 50% of the dose previously administered.
[c] RB plc, Slough, Berkshire, U.K.
[d] Helsinn Healthcare, Biasca, Switzerland.
[e] Strong CYP3A4 inhibitors such as ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, atazanavir, saquinavir, ritonavir, indinavir, nelfinavir, and nefazodone increase the concentration of everolimus and should not be used.
[f] Moderate CYP3A4 or PgP inhibitors such as fluconazole, erythromycin, amprenavir, fosamprenavir, verapamil, aprepitant, and diltiazem also increase the concentration of everolimus and require an everolimus dose reduction.
[g] Strong CYP3A4 inducers such as rifampin, rifabutin, rifapentine, phenytoin, phenobarbital, and carbamazepine lower the concentration of everolimus and require an everolimus dose increase.
CYP = cytochrome P.

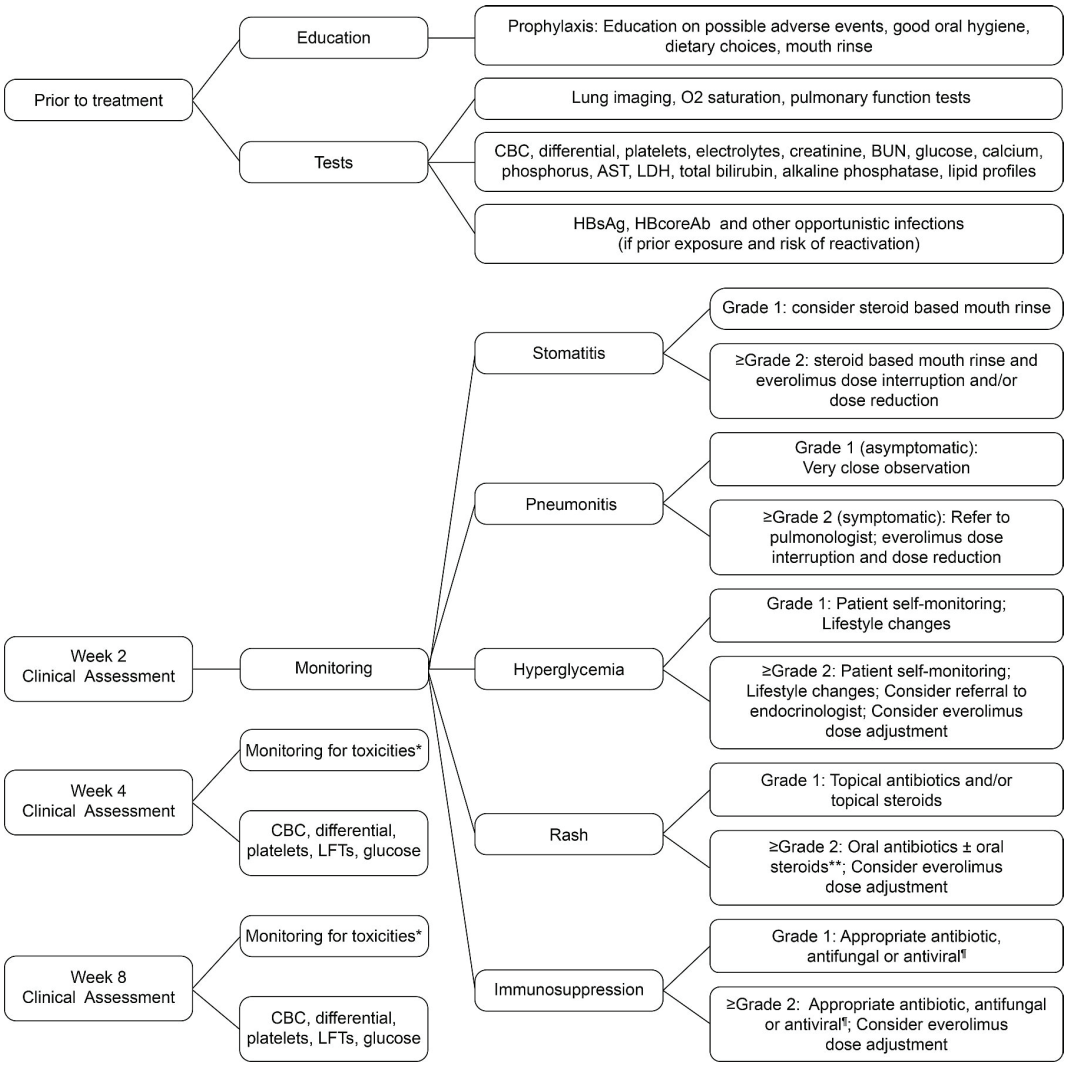

FIGURE 3 Management flow chart for patients treated with everolimus [a] Identified toxicities—and new toxicities—are treated as in week 2. [b] Caution is required when using oral steroids to treat symptomatic rash in patients prone to infection or hyperglycemia. [c] Drug interactions are possible.

Early Recognition and Frequent Monitoring: To avoid delays in diagnosis or intervention, primary health care providers should be educated about noninfectious pneumonitis. To facilitate diagnosis, especially for patients with baseline respiratory symptoms or with documented lung metastases, pre-treatment chest radiography or, preferably, computed tomography should be performed to help distinguish treatment-associated noninfectious pneumonitis on subsequent examinations. Pulmonary function tests can also be considered in selected patients before initiation of everolimus[25]. Patients should be educated about noninfectious pneumonitis and advised to contact their health care provider with any new respiratory symptoms.

Active Intervention: Grade 1 noninfectious pneumonitis is asymptomatic and diagnosed incidentally by radiologic findings. If asymptomatic, no acute intervention is necessary, but close observation, with repeat clinical evaluation (every 1–2 weeks) and imaging (every 2–4 weeks), is essential until resolution is confirmed. Grade 2 and higher noninfectious pneumonitis is symptomatic, and everolimus should be interrupted in all cases. Appropriate imaging should be obtained to rule out alternative diagnoses (for example, progressive disease, pleural effusion, pulmonary embolism, infectious pneumonitis). Corticosteroids—and urgent consultation with a respirologist—should be considered, with co-administration of broad-spectrum antibiotics because of the nonspecific nature of the imaging findings and the potential for everolimus-induced immunosuppression. Hospitalization and, potentially, bronchoalveolar lavage should be considered for progressive or non-resolving grade 2 symptoms and

for any grade 3 or 4 events[25,27]. Everolimus dose modifications (50% of the dose previously administered) should be implemented, particularly in grades 2 and 3 pneumonitis (Table V)[27,28].

3.4.3 Rash

Everolimus-associated rash presents as an acneiform dermatitis that starts as an inflammatory lesion (papule or pustule), with the subsequent appearance of comedones (blackheads). The rash is widely distributed and is often found on the upper extremities and neck. All-grade rash was reported in 44% of patients treated with everolimus in TAMRAD and in 39% of patients in BOLERO-2. The incidence of grades 3 and 4 rash was 4% in TAMRAD, but only 1% in BOLERO-2[22,24].

Early Recognition and Frequent Monitoring: Patients should be informed of the possibility of developing rash and educated about the signs and symptoms. They should also be advised to contact their health care provider at the first sign of rash.

Active Intervention: Grade 1 rashes typically resolve without therapeutic intervention, but for symptomatic events, topical low- to moderate-strength corticosteroid, with or without topical antibiotics, is recommended. For symptomatic grades 2 and 3 rash, a 2- to 4-week course of oral antibiotics should be administered, and treatment interruption and dose reduction (50% of the dose previously administered) should be considered[25]. If oral steroids are being considered, caution is required because of everolimus-associated immunosuppression, infection, and hyperglycemia[27].

Prophylactic Strategies: Patients receiving everolimus should be educated about moisturizing frequently with a thick, alcohol-free emollient cream [examples include Eucerin (Beiersdorf AG, Hamburg, Germany), Aquaphor (Beiersdorf AG), or Cetaphil (Galderma Laboratories, Lausanne, Switzerland)]; using mild fragrance-free soap; taking short, lukewarm showers or baths with the addition of 1–2 cups of baking soda or Aveeno (Johnson & Johnson); and using sunscreen of SPF 15 or higher containing zinc oxide or titanium oxide[25].

3.4.4 Hyperglycemia

Hyperglycemia is defined as a fasting glucose level exceeding 7.0 mmol/L or a postprandial level exceeding 11.1 mmol/L[33]. Symptoms of hyperglycemia include frequent urination, increased thirst, fatigue, blurred vision, weight loss, headaches, and difficulty concentrating[25]. In patients treated with everolimus, the incidence of all-grade hyperglycemia was 14% in BOLERO-2. Grade 3 or 4 hyperglycemia was reported in fewer than 6% of patients in BOLERO-2[22].

Early Recognition and Frequent Monitoring: Health care providers should ensure that, before initiating everolimus therapy, patients have optimum glycemic control. Patients should be educated about the possible symptoms of hyperglycemia and advised to contact their health care provider at the first sign of hyperglycemia. In patients with glycemic dysfunction that is under control, frequent glucose monitoring (for example, daily self-monitoring) is recommended during the first month of everolimus therapy; thereafter, the frequency of monitoring can be decreased if adequate glycemic control is established. Patients with prediabetes should also be monitored to reduce the risk of hyperglycemia and to facilitate early intervention. Patients with uncontrolled diabetes (fasting serum glucose more than 1.5 times the upper limit of normal) should not receive everolimus therapy[25].

Active Intervention: All patients who develop hyperglycemia should be advised to drink plenty of water, exercise regularly, reduce dietary carbohydrates and sugar, and use frequent glucose self-monitoring (frequency is individualized, but can be 2 or more times daily)[34]. Clinical management depends on the severity of hyperglycemia. Patients who develop grade 1 hyperglycemia (8.9 mmol/L glucose) do not require treatment modification. Patients with grade 2 (8.9–13.9 mmol/L glucose), 3 (>13.9 mmol/L to 27.7 mmol/L glucose), or 4 hyperglycemia (>27.7 mmol/L glucose) should be treated according to the 2013 Canadian Diabetes Association algorithm[35], with referral to subspecialty diabetes management as required.

3.4.5 Immunosuppression

Patients receiving everolimus can be predisposed to bacterial, fungal, viral, or protozoal infections, including pneumonia, sepsis, mycobacterial infections, aspergillosis, candidiasis, and reactivation of hepatitis B virus. In patients treated with everolimus, infections occurred in 44% of patients overall in BOLERO-2, but the incidence of grade 3 or 4 infections was low (grade 3, 4%; grade 4, 2%)[25].

Early Recognition and Frequent Monitoring: A full medical history of prior infections should be obtained from the patient, and for those at baseline risk, laboratory tests for hepatitis (B and C), HIV, and other opportunistic infections (tuberculosis, for instance) should be conducted before everolimus therapy commences. The oncology health care team should be vigilant in watching for infections, and patients should be advised to contact their health care provider immediately on observation of infection-related signs or symptoms (fever, cough, and so on)[27].

Active Intervention: Recommended management strategies for patients presenting with an infection involve diagnosis and treatment with the appropriate antibiotic, antifungal, or antiviral agents[27]. Caution is required when treating infections, because drug

interactions with everolimus must be taken into account. Everolimus dose modifications (50% of the dose previously administered) can be implemented (Table V)[25,27].

Prophylactic Strategies: For patients with hepatitis B virus infection, liver enzymes and hepatitis B viral DNA should be monitored, and prophylactic antiviral treatment should be given[25].

3.5 Interdisciplinary Strategies for Management of Everolimus-Related Toxicities in Canada

Recognition of the complex AE profiles associated with oral anticancer agents has raised awareness of the need for effective management strategies for patients on such therapies. In response, oncology health care providers across Canada continue to develop strategies for the management of those therapies. The goal is for each Canadian health care region to adopt an interdisciplinary approach that incorporates the various members of the health care team involved in patient care. Although the ideal model has yet to be realized, oncology physicians, pharmacists, and nurses in several Canadian health care settings are providing coordinated and complementary supportive patient care using detailed protocols that allow care team members to individualize treatment plans and to optimize treatment outcomes. The strategies aim to embrace principles for the management of oral cancer medications in general, with specific targeted interventions for the unique aspects of everolimus.

3.5.1 Oncology Physicians

Oncology physicians assume primary responsibility for the care of patients throughout the course of their disease. The physician's role includes explaining the cancer diagnosis and disease stage; discussing all treatment options and recommending the best course or courses of therapy; delivering high-quality, compassionate care; and helping to maintain the patient's quality of life by managing cancer-related pain and other symptoms or treatment-related side effects.

When considering everolimus, these key principles apply:

- Prescribing safely, ideally through the use of computerized physician order entry (where available) or preprinted orders (This principle aligns with best practices in oral medication prescription and is vital for cancer drugs in particular. In addition, to ensure that toxicities are managed appropriately, patients should ideally be evaluated by the physician or health care team every cycle before the prescription is renewed.)
- Modifying treatment, including interrupting or ceasing therapy, and modifying the dose based on efficacy and toxicity
- Initiating education about management and possible AEs
- Planning for monitoring everolimus toxicities
- Outlining the benefit–risk scenario
- Making necessary referrals, overseeing the treatment team, and coordinating with the pharmacist and nurse

Canadian health care providers are increasingly recognizing that all members of the patient care team should have an informed working knowledge of the toxicities that patients exposed to everolimus could potentially develop and of the appropriate management strategies. Once the oncologist has prescribed everolimus, members of the patient care team should be providing a standardized approach to surveillance and management of the patient. In particular, pharmacists and nurses are playing active and essential roles in patient education and monitoring.

3.5.2 Oncology Pharmacists

In Canada, the involvement of oncology pharmacists in the management of patients receiving oral cancer medications—before therapy, at therapy initiation, and after therapy start—is becoming more widespread. Consultation with various Canadian pharmacists has identified several Canadian programs that are suggested as models of care:

- ***Patient Management Before Everolimus Therapy*** In a pharmacist-led program at the Grand River Regional Cancer Centre (Kitchener, ON), pharmacist involvement begins before patients initiate therapy. The pharmacist reviews the patient's prescribed and nonprescribed therapies to consider potential interactions and toxicities. Alternatives for therapeutics that could be problematic while the patient is receiving everolimus are suggested. The pharmacist emphasizes to the patient that *any* new medication taken while using everolimus has to be reviewed for possible interactions (for example, antibiotics prescribed by a general practitioner). If patients acquire their medication from a community pharmacy, a link with a regular physician in the community is required, and a prescription information sheet is provided to community pharmacists to ensure that they have sufficient information to safely and competently dispense oral targeted therapies with knowledge of the range of associated toxicities (The Ottawa Hospital, Ottawa, ON). The community pharmacist should maintain constant communication with the oncology team.
- ***Patient Follow-Up After the Start of Everolimus Therapy*** One pharmacist-led follow-up program at the Dr. H. Bliss Murphy Cancer Clinic (St. John's, NL) allows pharmacists to assess adherence, drug interactions, toxicities, and laboratory values after the first 2 cycles of treatment in patients receiving

oral anticancer medicines. During those initial cycles, physician involvement is limited to consultation if needed. The patient meets with the medical oncologist before the 3rd cycle of treatment to review the overall treatment plan and to discuss whether to proceed with another cycle. This is an example of one such model that is perhaps suited for situations in which access to a medical oncologist is limited.

- ***Patient Callback Program*** Pharmacist-led callback programs are facilitating identification and resolution of drug-related problems experienced by oncology patients (Dr. H. Bliss Murphy Cancer Centre)[36]. To ensure that pathways capture relevant, often time-sensitive, AEs, those pathways are specific to each anticancer drug. One example (The Ottawa Hospital, Ottawa, ON) involves a program for patients whose oral mTOR-targeted agents are dispensed at a cancer centre: pharmacists call the patient on days 7, 14, 28, and 49 (and at other times based on patient status) to help proactively manage emerging toxicities. A pilot quality improvement study being organized at Sunnybrook Odette Cancer Centre (Toronto, ON) will investigate the value of developing program-specific patient navigation binders with self-management tools and important disease- and treatment-related information. These types of initiatives improve the chances that patient toxicities will be managed in a timely fashion, thus reducing the occurrence of progressive AEs and, potentially, acute-care visits.

3.5.3 Oncology Nurses

Across Canada, nurses are playing an integral role in the identification and management of everolimus-related toxicities. The Canadian Association of Nurses in Oncology released a position paper promoting evidence-based and timely support for patients on oral therapy—and their families. The paper identifies a shift in responsibility for administering medications from knowledgeable oncology nurses to family members, patients, home care agencies, and non-oncology-focused inpatient facilities[37].

One nurse-led, patient-focused oral therapy navigator program in Canada (Simcoe Muskoka Regional Cancer Centre, Barrie, ON) helps patients and their families demonstrate self-efficacy with behaviors surrounding oral treatments[38]. Patients receive education, coaching, support, advocacy, and assistance in overcoming barriers to adherence to treatment. Through the program,

- patients receive an initial 60-minute individual education session delivered by an oral therapy nurse navigator.
- patients who have obtained their medication and are ready to start therapy receive a telephone call initiated on day 1 by the oral therapy nurse.

During that call,

- medication, dose, administration, safety, and adherence are reviewed; and
- patients are reminded of the contact information they should use for any symptom concerns.
- patients receive another planned telephone call on day 10 of treatment. At that point, the nurse makes an assessment for early everolimus side effects such as stomatitis and rash.

Education is consistently reinforced. Patients are requested to come to the clinic for an in-person assessment if they develop symptoms, and they visit the oral therapy nurse navigator monthly during ongoing treatment.

3.5.4 Challenges

Establishing new approaches to health care delivery is often associated with challenges, and developing models of care that comprehensively address toxicities relevant to oral anticancer drugs is no exception. In particular,

- few evidence-based guidelines are available about the optimal management of patients on oral targeted cancer therapies (compared with classical intravenous chemotherapy).
- patients receiving oral targeted cancer therapies can experience unique toxicities that are different from those associated with conventional cytotoxic and hormonal agents.
- patients are often charged with managing oral targeted drugs and their adverse effects at home, and the potential for suboptimal adherence must be considered.
- the combination of toxicities and adherence issues for agents given together (such as everolimus and exemestane) can further complicate management. (Each individual agent can have non-overlapping, but also varied, toxicities.)
- nursing and pharmacy experience in counselling patients about these novel oral agents can be variable.
- patients who fill prescriptions for oral targeted therapy at local community pharmacies might not receive optimal medication counselling and follow-up, because those establishments are often not familiar with these unique agents.
- the development of interdisciplinary management programs involves time and costs that are not currently acknowledged in most cancer care programs.

4. CONCLUSIONS

A comprehensive understanding of everolimus-associated toxicities and the development of management strategies are essential to optimize the appropriate clinical use of everolimus and other

targeted oral anticancer agents currently in clinical development (PIK3 and Akt inhibitors, for instance). New models of care that include multiple health disciplines should be explored to optimize the safety and efficacy of those drugs. For everolimus in HR-positive, HER2-negative metastatic breast cancer in particular, organized and systematic management beyond that required for endocrine therapy alone has to be implemented. That management includes comprehensive education, counselling, and intervention individualized to patient needs. Interdisciplinary toxicity management for oral anticancer therapies represents a new but essential component in the optimal delivery of oncology health care services. All members of a health care team, including oncologists (medical, surgical, radiation), nurses, and pharmacists should have a good working knowledge of the toxicities that patients exposed to oral anticancer therapies can potentially develop. Equally important is the need for appropriate AE management strategies. Everolimus, being the first of many complex oral targeted therapies that will be available to women with advanced breast cancer, serves as a template for the future. As the number of approved oral anticancer agents expands, best practices for management strategies have to be established to optimize safety, adherence, quality of life, and ultimately treatment outcomes for patients.

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