

Advances in Oral Oncolytic Agents for Breast Cancer and Recommendations for Promoting Adherence

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Abstract

Hormone receptor positivity and early stage diagnosis are generally considered signs of good prognosis in breast cancer. However, breast cancer all too frequently can become resistant to hormone-based therapies, and women can experience recurrence of their breast cancer decades after the diagnosis of early stage disease. To address the therapeutic needs for advanced and metastatic hormone receptor-positive (HR+) and human epidermal growth factor receptor 2-negative (HER2-) breast cancer, a number of new drugs have been tested and approved for this indication, including the class of drugs that works as cyclin-dependent kinase (CDK) 4/6 inhibitors. These drugs, often combined with other hormone-based therapy, have demonstrated considerable success in clinical trials and are now being used widely in oncology practices. Because all of the currently approved CDK4/6 inhibitor agents (palbociclib, ribociclib, and abemaciclib) are given orally, issues of patient comprehension of and adherence to prescribed regimens should be at the forefront of practitioners' concerns about these drugs. In addition, ways to support and facilitate decision-making by patients related to this class of agents and other therapies recently approved for the same indication require focused attention by health-care providers. Oncology has continued to move toward a more patient-specific, precision medicine approach. Likewise, advanced practitioners have the opportunity to identify patient characteristics, preferences, and needs that are unique to individual patients to enhance precision treatment.

Breast cancer represents the most common cancer among women in the United States and worldwide. The aging of the “baby boom” generation has contributed to an increase in breast cancer cases, since increasing age is a primary risk factor for breast cancer diagnosis (National Comprehensive Cancer Network [NCCN] Guidelines, 2019). Likewise, as women age and undergo menopause, if breast cancer develops, they are more likely to be diagnosed with

hormone receptor positive (HR+) breast cancer, including estrogen receptor positive (ER+), progesterone receptor positive (PR+), or both receptors (Kolečková et al., 2017; Pourzand et al., 2011; Rochman et al., 1985). Other factors that may contribute to HR+ breast cancer include the use of hormone replacement therapy for at least 5 years, age \geq 30 years at age of first child's birth, and significant weight gain (\geq 30 kg [66 lb]) during adulthood (Rost & Roter, 1987).

According to the latest US Surveillance, Epidemiology, and End Result (SEER) data, the incidence of breast cancer is approximately 127.5 per 100,000 women per year, with a mortality rate of 20.6 per 100,000 women per year (National Cancer Institute, 2019). Overall, close to 90% of all women diagnosed with breast cancer will survive 5 years. Approximately 67% to 80% of all breast cancers are estimated to be HR+. SEER data indicate that approximately 72% of US cases are HR+/human epidermal growth factor receptor 2 (HER2) negative (National Cancer Institute, 2019). Although men can develop breast cancer, the incidence among men is substantially lower than that among women, with approximately 2,670 new breast cancers diagnosed among men per year, and 500 deaths per year (American Cancer Society, 2019).

Only 6% of cases are metastatic breast cancer (mBC) at the time of diagnosis (de novo; O'Shaughnessy, 2005; SEER, 2004). Methods used to calculate rates of recurrence among those originally found to have early stage disease are more challenging because population-based registries generally do not collect data on disease progression (Mariotto, Etzioni, Hurlbert, Penberthy, & Mayer, 2017). It is estimated that 20% to 30% of women diagnosed with early stage breast cancer will experience cancer recurrence or progression and metastatic disease (Mayer, 2014). Recurrence or metastases may occur long after the original diagnosis, perhaps up to 15 to 20 years later. In a single-institution retrospective study of 1,727 women who were diagnosed with invasive breast cancer and followed for a 30-year period, metastasis-free probability was calculated as 53.1% at 25 years, with patients developing metastases at a rate of 1.5% even at 15 years after diagnosis (Houzé de l'Aulnoit et al., 2017). Five-year survival for women diagnosed with metastatic breast cancer is only

about 22% (Metastatic Breast Cancer Alliance, 2014). Clearly, a significant need exists to understand the underlying etiology of mBC to prevent and treat it more effectively.

TREATMENT OPTIONS FOR HR+/HER2- POSTMENOPAUSAL METASTATIC BREAST CANCER

This paper will focus on HR+, HER2-, postmenopausal mBC. Although endocrine therapy serves as the keystone for treatment of HR+ breast cancer, not all breast cancers will respond to first-line hormone-based therapy. In addition, some cancers that may start responding to endocrine therapy may become resistant to endocrine therapy and ultimately relapse or metastasize (El-Sayed et al., 2019).

For women with HR+/HER2- breast cancer that metastasizes, use of endocrine therapy may be advised for those with a low burden of metastatic disease. In addition, those women who experienced a significant disease-free interval ($>$ 2 years) might indicate disease that is more likely to respond to endocrine approaches (Cardoso et al., 2017).

The NCCN Clinical Practice Guidelines for ER+, PR+, recurrent, or stage IV disease for HER2-, postmenopausal women (or premenopausal receiving ovarian ablation or suppression) list multiple treatment options, including Category 1 evidence to support the following regimens (NCCN Guidelines, 2019):

- Aromatase inhibitor (AI) with cyclin-dependent kinase (CDK) 4/6 inhibitor (abemaciclib, palbociclib, ribociclib)
- Fulvestrant with CDK4/6 inhibitor (abemaciclib, palbociclib, ribociclib)
- Fulvestrant with alpelisib for *PIK3CA* mutation-positive tumors
- Selective ER downregulator (fulvestrant)
- Ribociclib with tamoxifen is not promoted as first-line therapy due to QTc prolongation risk; however, ribociclib with tamoxifen, anastrozole, or letrozole, along with goserelin, may be indicated as first-line therapy for HR+, HER2- mBC in the case of premenopausal patients with ovarian suppression or ablation (U.S. Food & Drug Administration [FDA], 2018).

Nonhormonal-based therapies that rely on chemotherapeutic agents may also be indicated in certain circumstances for recurrent or stage IV mBC, including poly (ADP-ribose) polymerase (PARP) inhibitors (Layman, 2019).

CDK4/6 INHIBITORS AND THEIR INDICATIONS

Models of endocrine resistance have demonstrated that growth of hormone-driven breast cancer depends on cyclin D1, which represents a direct transcriptional target of the estrogen receptor (Matutino, Joy, Brezden-Masley, Chia, & Verma, 2018). Cyclin D1 activates CDK4 and 6, which allows for G1 to S phase transition in the cell cycle (Spring et al., 2016). Transition from the G1 phase to the S phase is controlled by the retinoblastoma tumor suppressor gene (*RB*; Thangavel et al., 2011). The product of the retinoblastoma gene, Rb, prevents premature cell division in the cell cycle through the addition of phosphate groups to Rb. CDK4/6 and cyclin D1 act as targets for the class of drugs known as CDK4/6 inhibitors, which are highly selective oral agents that stop the proliferation of tumor cells that are Rb-positive (Spring, Bardia, & Modi, 2016; Thangavel et al., 2011). These agents act by arresting the cell cycle at G1.

Currently, three CDK4/6 inhibitors have received FDA approval in advanced or metastatic HR+/HER2- breast cancer (Table 1; Ramos-Esquivel, Hernández-Steller, Savard, & Landaverde, 2018; FDA, 2017a, 2017b, 2018a, 2018b).

All 3 drugs are given orally. Palbociclib and ribociclib are given as pills daily for 21 days on and 7 days off, for a 28-day cycle. Both drugs were tested in randomized phase III clinical trials and demonstrated significantly improved median disease-free survival when combined with either letrozole or fulvestrant, compared to placebo with letrozole or fulvestrant (Murphy, 2019; Sammons, Topping, & Blackwell, 2017). Abemaciclib is taken once daily, also with fulvestrant or an AI, but has also been approved as monotherapy (taken twice per day) based on objective response rate as well as progression-free survival (PFS; Tables 2 and 3; Eggersmann, Degenhardt, Gluz, Wuerstlein, & Harbeck, 2019).

Overall Survival

Among the three CDK4/6 inhibitors, ribociclib and abemaciclib have demonstrated superior overall survival (OS) in advanced/metastatic breast cancer to date. In the MONALEESA-7 trial, the median OS was not reached for ribociclib + tamoxifen/nonsteroidal AI compared to 40.9 months for endocrine therapy alone in pre-/perimenopausal women as initial treatment (hazard ratio (HR), 0.712; Hurvitz et al., 2019), with an estimated OS at 42 months of 70.2% in the ribociclib group and 46.0% in the placebo group (HR, 0.71; Im et al., 2019). Statistically significant improvements in OS were also demonstrated in the MONALEESA-3 trial of ribociclib plus fulvestrant in postmenopausal women in the first- and second-line setting (Slamon et al., 2019) and in the MON-

Table 1. FDA Approvals for CDK4/6 Inhibitors

CDK4/6 inhibitor	Initial endocrine-based therapy	After disease progression following endocrine therapy
Palbociclib	With letrozole first line in postmenopausal women With an AI in postmenopausal women With an AI in postmenopausal women or in men	With fulvestrant
Ribociclib	With an AI in postmenopausal women With an AI in pre-/perimenopausal women With fulvestrant in postmenopausal women	With fulvestrant in postmenopausal women
Abemaciclib	With an AI in postmenopausal women	With fulvestrant As monotherapy in adult patients with prior chemotherapy in metastatic setting

Note. AI = aromatase inhibitor.

Table 2. CDK4/6 Inhibitors in the First-Line Setting

Study/arms	Phase	N	Median PFS (mo)		HR (95% CI)	p value
			Placebo	CDK4/6 Inhibitor		
PALOMA-1 Letrozole ± palbociclib	II	165	10.2	20.2	0.488 (0.319–0.748)	.0004
PALOMA-2 Letrozole ± palbociclib	III	666	14.5	24.8	0.58 (0.46–0.72)	.000001
MONALEESA-2 Letrozole ± ribociclib	III	668	16.0	25.3	0.568 (0.457–0.704)	9.63 × 10 ⁻⁸
MONALEESA-7 Tamoxifen/NSAI + goserelin ± ribociclib	III	672	13.0	23.8	0.553 (0.441–0.694)	.0000000983
MONARCH 3 NSAIs ± abemaciclib	III	493	14.76	28.18	0.540 (0.418–0.698)	.000002

Note. PFS = progression-free survival; HR = hazard ratio; CI = confidence interval; NSAI = nonsteroidal aromatase inhibitor.

ARCH 2 trial of abemaciclib plus fulvestrant in patients previously treated with endocrine therapy (Sledge et al., 2019). In the MONALEESA-3 trial, the median OS in patients treated with ribociclib plus fulvestrant was not reached vs. 40.0 months for treatment with placebo plus fulvestrant, a 28% risk reduction (HR, 0.724; $p = .0045$). The median OS in the MONARCH 2 trial was 46.7 months for abemaciclib plus fulvestrant compared with 37.3 months for placebo plus fulvestrant, a 24% reduction in risk (HR, 0.757; $p = .0137$).

CDK4/6 INHIBITORS AND THEIR ADVERSE EVENTS

Many of the notable toxicities associated with CDK4/6 inhibitors include neutropenia and gas-

trointestinal toxicities (Thill & Schmidt, 2018). Table 4 highlights the differences in neutropenia and diarrhea rates from clinical trials of these agents. Most adverse events associated with these therapies can generally be readily managed by dose adjustments (Cazzaniga et al., 2019). Cazzaniga and colleagues have summarized recommendations for the management of toxicities associated with targeted therapies for HR+ metastatic breast cancer (Cazzaniga et al., 2019), including:

- Dose reductions for grade 2 to 3 adverse events are feasible in many instances and have no detrimental effect on efficacy. Grade 1 toxicities usually do not require dose modifications, while grade 4 toxicities

Table 3. CDK4/6 Inhibitors: After Disease Progression Following Endocrine Therapy

Study/arms	Phase	N	Median PFS (mo)		HR (95% CI)	p value
			Placebo	CDK4/6 Inhibitor		
PALOMA-3 Fulvestrant ± palbociclib	III	521	4.6	9.5	0.46 (0.36–0.59)	.0001
MONALEESA-3 Fulvestrant ± ribociclib	III	726	12.8	20.5	0.593 (0.480–0.732)	.00000041
MONARCH 2 Fulvestrant ± abemaciclib	III	669	9.3	16.4	0.553 (0.45–0.68)	.000001
Study/arms	Phase	N	Investigator-assessed ORR			
MONARCH 1 Single-agent abemaciclib	II	132	19.7%			

Note. ORR = overall response rate.

Table 4. Neutropenia and Diarrhea Rates in CDK4/6 Inhibitor Trials

CDK4/6 Inhibitor	Trial	Neutropenia			Diarrhea		
		All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Palbociclib + letrozole	PALOMA-2	80%	56%	10%	26%	1%	0%
Palbociclib + fulvestrant	PALOMA-3	83%	55%	11%	24%	0%	0%
Ribociclib + letrozole	MONALEESA-2	75%	50%	10%	35%	1%	0%
Ribociclib + fulvestrant	MONALEESA-3	69%	46%	7%	29%	< 1%	0%
Ribociclib + NSAI + goserelin	MONALEESA-7	78%	55%	10%	NR	NR	NR
Abemaciclib monotherapy	MONARCH 1	37%	19%	5%	90%	20%	0%
Abemaciclib + fulvestrant	MONARCH 2	46%	24%	3%	86%	13%	0%
Abemaciclib + anastrozole or letrozole	MONARCH 3	41%	20%	2%	81%	9%	0%

Note. CDK = cyclin-dependent kinase; NR = not reported; NSAI = nonsteroidal aromatase inhibitor. Information from Eli Lilly and Company (2019); Novartis Pharmaceuticals Corp. (2018); Pfizer Oncology (2019).

should prompt permanent discontinuation of the treatment.

- Neutropenia induced by CDK4/6 inhibitors is reversible and can be readily managed by dose interruption or modification without compromising treatment efficacy, as described in the drug labels.
- Antidiarrheal agents, such as loperamide, should be started at the first sign of loose stools with abemaciclib; otherwise, diarrhea induced by CDK4/6 inhibitors should initially be treated with nonpharmacologic interventions; antiemetics can be used for nausea and vomiting after evaluation of possible drug interactions.
- Liver function tests should be performed before initiating treatment with abemaciclib and ribociclib, and liver function should be monitored throughout treatment.
- Patients should be seen by a cardiologist when QT prolongation is > 500 ms; prolonged QT during treatment and presence of symptoms of heart disease; history of arrhythmias; history of presyncope or syncope with a likely cardiac origin; or prolonged QT and bradycardia < 60 bpm.

PI3K α -SPECIFIC INHIBITOR, ALPELISIB, AND ITS INDICATION

In May 2019, the FDA approved alpelisib for the treatment of postmenopausal women and men with HR+, HER2-, *PIK3CA* mutation-positive, advanced or metastatic breast cancer following progression on or after an endocrine-based regimen (FDA, 2019). In the SOLAR-1 trial for patients with *PIK3CA* mutations, subjects who received alpelisib with fulvestrant demonstrated significantly lower risk for progression or death compared to those who received placebo with fulvestrant (HR, 0.65 in favor of alpelisib; 95% confidence interval [CI] = 0.50–0.85; $p = .00065$). For those patients with tumors that did not contain a *PIK3CA* mutation, alpelisib treatment did not result in improvement in median PFS.

Alpelisib, like the CDK4/6 inhibitors, is given orally (300 mg once daily, with food) along with fulvestrant. The main side effect reported in clinical trials was hyperglycemia. Thus, before starting alpelisib, providers should check fasting glucose and HbA1c levels and address glycemic control throughout therapy (Novartis Pharmaceuticals Corp., 2019). Other side effects include elevated creatinine and liver enzyme levels, and skin rash.

Due to the possible severity of the skin rash, providers are warned not to prescribe alpelisib in patients with a preexisting history of other severe skin conditions, such as Stevens-Johnson syndrome, erythema multiforme, or toxic epidermal necrolysis. Patients may also experience a hypersensitivity reaction; therefore, health-care providers need to be alert to any signs of symptoms of this reaction (André et al., 2018).

Despite their similarities, the CDK4/6 inhibitors, as well as alpelisib, have some important differences among them (Fedele and Cinieri, 2019). All three CDK4/6 inhibitor drugs are approved as initial endocrine-based therapy in postmenopausal women, as well as for disease progression after endocrine therapy. However, ribociclib has an additional approval for initial endocrine-based therapy in pre- or perimenopausal women. Abemaciclib has unique approval as monotherapy for disease progression following endocrine therapy (Asghar, Witkiewicz, Turner, & Knudsen, 2015). Alpelisib is approved for treatment following progression on prior endocrine therapy and only when *PIK3CA* mutations are present. Other factors to compare these agents are shown in Table 5.

IMPLICATIONS FOR THE ADVANCED PRACTITIONER: DECISION-MAKING IN ADVANCED AND METASTATIC HR+/HER2- BREAST CANCER

News of a diagnosis of recurrent or metastatic disease is always shocking to the patient and family, particularly if the breast cancer was diagnosed at a very early stage and there has been no evidence of disease for many years. A key role for the advanced practitioner and oncology nurse is to help facilitate informed decision-making for treatment options as the next step in addressing the disease. The timing for discussion of treatment decisions may be important because it may take a while for the patient to accept that the cancer has recurred/spread and the oncologist may be pressing to initiate treatment quickly.

A number of factors come into play when making a decision about the choice of therapies to be used when HR+/HER2- breast cancer first becomes metastatic (Bellet et al., 2019). Unless visceral disease is of grave concern, the initial treatment is likely to be an endocrine agent. Decisions

about specific endocrine agents need to take into account the patient's menopausal status, previous adjuvant therapy, concomitant comorbidities, individual preference, and associated toxicities (Matutino et al., 2018). For example, a woman in whom severe osteoporosis developed in the interval since her initial breast cancer diagnosis may not be a good candidate for an AI, which can exacerbate osteoporosis (Mazziotti, Canalis, & Giustina, 2010). Likewise, tamoxifen may not be the ideal endocrine therapy choice in the context of women who smoke or may have risk factors for thromboembolism (Decensi et al., 2005).

Although all of the CDK4/6 inhibitors demonstrate similar mechanisms of action, there are differences in terms of the side effect profile of each drug. Because there have not been any published head-to-head trials to allow direct comparison of each CDK4/6 inhibitor, it is not possible to draw any conclusions in terms of one drug being superior to another in terms of efficacy (Mistry et al., 2018). However, two of the CDK4/6 inhibitors, ribociclib and abemaciclib, do have data to support them having significantly improved OS compared to placebo (Hurvitz et al., 2019).

In the absence of comparative data, the patient may rely on factors such as personal preference (i.e., OS, disease-free survival, out-of-pocket costs, etc.), easiest regimen in terms of adherence, or certain toxicities. The advanced practitioner and oncology nurse is in the ideal position to evaluate these factors along with the patient and others as part of the health-care team to make decisions that meet patient criteria for satisfaction and are based on evidence and/or personal preference. Following the baseline assessments, including history and physical examination, key data about the patient would be available to integrate into the decision-making process. Some of those data points and ensuing questions are outlined in Table 6.

The baseline assessment and evaluation of history and behaviors enable the provider and patient to critically appraise factors that might contribute to specific risks associated with various therapies, and then reduce that risk if possible. For example, a patient with a history of significant cardiac disease might consider other options besides ribociclib due to an associated risk for prolonged QT interval. Likewise, a patient with a history of skin

Table 5. Comparison of CDK4/6 Inhibitors and PI3K α -Specific Inhibitor

HR+/HER2- advanced or metastatic breast cancer	Palbociclib	Ribociclib	Abemaciclib	Alpelisib
Initial endocrine-based therapy in postmenopausal women	With AI	With fulvestrant or AI	With AI	-
Initial endocrine-based therapy in pre-/perimenopausal women	-	With AI	-	-
Indication for disease progression following endocrine therapy	With fulvestrant	With fulvestrant	With fulvestrant or as monotherapy	With fulvestrant
Significant improvement in DFS and/or response rates compared to placebo + endocrine therapy demonstrated	Yes	Yes	Yes	Yes
Significant improvement in OS demonstrated	No	Yes	Yes	No
Dose/schedule	21 days on, 7 days off (28-day cycle)	21 days on, 7 days off (28-day cycle)	Continuously until disease progression or unacceptable toxicity	Continuously
Dose and frequency	125 mg once daily	600 mg (three 200 mg pills) once daily	150 mg twice daily with fulvestrant or AI; or 200 mg twice daily as monotherapy	300 mg once daily
With/without food	With	With or without	With or without	With
Presence of <i>PIK3CA</i> mutation	No	No	No	Yes
Primary potential side effect(s) of concern	Neutropenia	Neutropenia Prolonged QT interval Hepatotoxicity	Diarrhea Hepatotoxicity Venous thromboembolism	Hyperglycemia ^a Rash Hypersensitivity
Recommended patient monitoring	CBC count baseline; D1 & D15 (C1-C2) then D1 each cycle	CBC count baseline; then every 2 wk (C1-C2) then D1 each cycle (C3-C6) LFTs baseline; then every 2 wk (C1-C2) then D1 each cycle (C3-C6) ECG baseline and D14 (C1) and D1 (C2) Electrolytes baseline then D1 (C1-C6)	CBC count baseline; then every 2 wk for first 2 mo, then monthly for next 2 mo LFT baseline; then every 2 wk for first 2 mo, then monthly for next 2 mo At first sign of loose stools, initiate antidiarrheal therapy, increase oral fluids Monitor for signs and symptoms of thrombosis and pulmonary embolism; treat as medically appropriate	Fasting glucose and HbA1c baseline; then every 2 wk for first 2 mo Assess prior serious skin conditions Assess prior history of hypersensitivity reaction at baseline

Note. AI = aromatase inhibitor; DFS = disease-free survival; OS = overall survival; CBC = complete blood count; C = cycle; D = day; LFT = liver function tests.

^aInsufficient evidence currently exists to determine whether alpelisib is contraindicated in type 1 or 2 diabetes.

conditions, such as erythema multiforme, might be deemed a poor candidate for alpelisib. Such facts brought out during a thorough history and physical

examination will greatly facilitate sifting through various data points to determine which optimal choices might be available (Cazzaniga et al., 2019).

Table 6. Key Data Points and Questions Related to Patient Decision-Making for Treatment of HR+/HER2- Advanced or Metastatic Breast Cancer

Data point from baseline assessment, H&P, or personal preference	Questions related to patient data
<i>Baseline assessments: Laboratory tests</i>	
CBC, creatinine, LFTs, electrolytes, glucose, HbA1c	<ul style="list-style-type: none"> Does the patient have baseline problems with anemia, liver abnormalities, fasting blood sugar, or HbA1c?
<i>Other baseline tests</i>	
ECG	<ul style="list-style-type: none"> Does the patient have baseline heart issues demonstrated on the ECG? Long QT syndrome is a well-known condition that may cause tachycardia and possibly lead to TdP, which can be life-threatening. Risk factors for TdP include structural heart damage (e.g., myocardial infarction or cardiomyopathy) and prolonged baseline QTc (> 470 ms in females and > 450 ms in males)
<i>History & physical</i>	
Diabetes (type 1 or 2)	<ul style="list-style-type: none"> Does the patient have a diagnosis of type 1 or 2 diabetes or prediabetes? If so, is it well-controlled? By what means?
History of chronic or severe diarrhea	<ul style="list-style-type: none"> Does the patient have a tendency to develop chronic or serious diarrhea due to drugs or other exposures? What works to prevent this? What works to relieve diarrhea?
History of DVT, PE, or other thromboembolic event	<ul style="list-style-type: none"> Has the patient had a previous DVT, PE, or any other type of VTE? What were the factors that contributed to these events? What works to prevent VTE? What was used to treat the VTE? Does the patient have a good awareness of signs and symptoms of VTE and need to report ASAP?
History of serious skin diseases, e.g. Stevens-Johnson syndrome, erythema multiforme, or toxic epidermal necrolysis	<ul style="list-style-type: none"> Does the patient have or previously had a serious skin disease? What works to prevent these skin problems? What was effective in treating them when they occurred?
History of severe hypersensitivity reactions to drugs, food, or other types of exposures	<ul style="list-style-type: none"> Does the patient have a history of significant hypersensitivity to any exposures? What were the factors that led this reaction? What works to prevent hypersensitivity? What has been used effectively to treat hypersensitivity reaction?
History of osteoporosis, bone fractures	<ul style="list-style-type: none"> Does the patient currently have or had a prior history of osteoporosis? What is being done to prevent or treat this condition? What is most effective for this patient?
History of smoking	<ul style="list-style-type: none"> Does the patient currently smoke? Smoked in the past? How much and for how long?
<i>Adherence</i>	
Previous oral therapy or treatment regimen requiring long-term adherence	<ul style="list-style-type: none"> What previous regimens does the patient have experience with that required a high level of adherence on the part of the patient? Is s/he currently taking drugs daily or regularly that require constant adherence? How well does the patient adhere to these types of regimens? What does the patient use, or used successfully in the past, to promote adherence (e.g., reminders, written diary)?
<p><i>Note.</i> CBC = complete blood count; LFT = liver function tests; ECG = electrocardiogram; TdP = torsades de pointes; DVT = deep venous thrombosis; PE = pulmonary embolism. Information from Thill & Schmidt (2018).</p>	

Integrated into this process is patient preference. This preference might mirror those conclusions related to facts and evidence but could also be quite different. A patient, as an example, may display some baseline anemia, but like the idea of taking a drug once per day, so opt to pursue palbociclib as treatment. Another patient might have

a history of a cardiac condition but wants to take the agent that has demonstrated improvement in OS, rather than disease-free survival, so has expressed a preference for ribociclib or abemaciclib. Another patient may be highly motivated by any differences in costs, including out-of-pocket costs, or availability of the drugs.

ADHERENCE: TIPS AND TOOLS

Regardless of the drug that is chosen, among these agents used in mBC, all of them are taken orally, either continuously or for 3-week cycles, for the remainder of the person's life or until progression or lack of tolerance. So adherence to the prescribed regimen is tremendously important. Again, it is the primary role of the advanced practitioner or oncology nurse to work with the patient and family to identify strategies to promote adherence.

Although oral anticancer therapy has been in existence for more than 40 years (tamoxifen, one of the first oral oncolytic drugs, was approved in 1977 for mBC), the number and availability of oral oncolytic agents have increased considerably (Osterberg & Blaschke, 2005). The advent of targeted agents, such as tyrosine kinase inhibitors, introduced a throng of oral oncolytic agents into clinical practice. At this time, almost 50% of the molecules approved for targeted treatment of cancer since 2000 are only available as oral agents, with the majority of new drugs under development focused on creating oral formulations (Colomer et al., 2010). Thus, issues in adherence to these oral oncolytic agents have similarly grown exponentially, and the need for better adherence will continue in the future.

The reasons for increasing numbers of oral agents in cancer are varied, including the desire for fewer clinic visits translating to reduced time and costs devoted to travel by the patient to the clinic, escape from traditional IV drug infusions, higher quality of life, and moving control from the provider team to the patient/family (Ruddy, Mayer, & Partridge, 2009). While these are all recognized positive aspects of oral oncolytic agents, some negative attributes also accompany the push toward oral drugs. Negative features of oral anticancer drugs include a lack of adherence. Only 50% of medications for chronic diseases, such as cancer or cardiovascular disease, are taken as intended; approximately 20% to 30% of prescriptions are not even filled (World Health Organization, 2003). Reasons for poor adherence range from more complex medication schedules or polypharmacy to the need to report and address symptoms from a distance, costs, and greater investment and time from nursing and pharmacy resources (Viswanathan et al., 2012).

Although lack of adherence can affect an individual patient's life and outcomes, poor adherence overall affects the health-care system in broad ways, resulting in a less effective system. A systematic review estimated that lack of adherence costs \$100 to \$289 billion dollars in the United States, reflecting the need to treat diseases and conditions that might have been prevented, controlled, or eradicated through adherence to prescribed treatment (Viswanathan et al., 2012). Approximately 10% of hospitalizations in the United States are due to lack of adherence (Sokol, McGuigan, Verbrugge, & Epstein, 2005). Nonadherence can also prove fatal; studies estimate that 125,000 deaths per year in the United States result from poor adherence to prescribed oral medication (Benjamin, 2012).

The International Society for Pharmacoeconomics and Outcome Research has differentiated between adherence (following the prescribed dose, timing, and frequency) and persistence (amount of time from starting to stopping the medication; Fallowfield et al., 2006). A review by Ruddy and colleagues (2009) examined methods used to measure adherence, which include self-reporting, medication diary, pill counts, microelectronic monitoring system on a "smart" pill bottle cap, or more objective measures such as serum or urine levels of medication exposure or metabolism.

Although numerous studies have tried to identify underlying reasons for and barriers to nonadherence, evidence is limited and results can be contradictory. For example, advancing age has been cited in some studies as a barrier to adherence, but those findings have not been reported consistently (Rost & Roter, 1987; Smith, Mucklow, & Wandless, 1979). More important than age may be the complexity of the regimen, frequency of dosing, and the duration that the patient is required to take the medication (Claxton, Cramer, & Pierce, 2001). Considering that patients with mBC will take medication for the remainder of their lives or until intolerance develops, and are often older and thus more likely to have polypharmacy as an additional factor, the risk is high among this population for nonadherence. Sociodemographic variables such as socioeconomic status, insurance coverage, educational level, and health literacy may also predict lack of adherence or persistence (Osterberg and Blaschke,

2005). However, other studies have found a minor or no clear relationship between demographic factors and adherence (Atreja et al., 2005).

Interventions to improve patient adherence have been studied primarily in nononcology settings; however, in view of the increasing number of oral oncolytic medications, investigations of the efficacy of strategies to enhance adherence are greatly needed. Standard approaches to increasing adherence include organizing medication dosing for each day, making the medication schedule as simple as possible, reminder systems (phone calls, texts, alarms, calendars), tracking the dosing for each day (medication diaries or records), and educating the patient and family so they comprehend the benefits of adherence and risks associated with nonadherence (Ruddy et al., 2009). One well-established strategy is “SIMPLE,” which breaks down approaches to improving medication adherence as shown in Table 7 (Atreja et al., 2005).

For drugs such as palbociclib and ribociclib, which are given for 21 days with a 7-day “break,” a need exists to ensure that the drug dosing resumes on schedule each cycle. In addition to using pill-

boxes that accommodate weekly or even monthly medication scheduling, having the drugs packaged in blister packs for the entire 28-day cycle, with “placebos” for the 7-day break period, as is done for oral contraceptives, is another option. Abemaciclib and alpelisib are taken continuously, every day, but abemaciclib must be taken twice a day (Fogli et al., 2019). Setting a watch or smart speaker to remind the patient when medications are due are technologically savvy ways to enhance adherence.

For patients dealing with polypharmacy, particularly if there are issues with comprehension of a complex dosing schedule for many different drugs, a viable option may be multi-dose packs prepared by a commercial pharmacy. Certain pharmacies will prepare a 30-day supply of all the patient’s medications in individual packaging with labels designating dose, date, time of day, and icons representing morning, midday, evening, and bedtime to assist with adherence (CVS Pharmacy, 2019).

While considerable effort has gone into developing methods to package medications more effectively, limited research has evaluated the impact of these methods on adherence. A review by Hers-

Table 7. “SIMPLE” Strategies to Improve Medication Adherence

Simplifying regimen characteristics	Adjusting timing, frequency, amount, and dosage Matching to patients’ activities of daily living Using adherence aids, such as medication boxes and alarms
Imparting knowledge	Discussion with physician, advanced practitioner, pharmacist Distribution of written information, pamphlets Accessing health education information from the internet
Modifying patient beliefs	Assessing perceived susceptibility, severity, benefit, and barriers Rewarding, tailoring, and contingency contracting
Patient and family communication	Active listening and providing clear, direct messages Including patients in decisions Sending reminders via mail, e-mail, or phone Convenience of care, scheduled appointment Home visits, family support, counseling
Leaving the bias	Tailoring the education to patients’ level of understanding. Demographic factors play a minor role in adherence behavior, if at all, and there is no clear relationship between adherence and race, sex, educational experience, intelligence, marital status, occupational status, income, and ethnic or cultural background.
Evaluating adherence	Self-reports Pill counting, measuring serum or urine levels, MEMS

Note. MEMS = medication event monitoring system. Adapted from Atreja et al. (2005).

berger, Boeni, and Arnet (2013) examined a wide range of interventions related to dose-dispensing services, but noted that dose-dispensing technology often was combined with other methods to increase adherence, so it was difficult to judge the role of dose administration aids alone. George, Elliott, and Stewart (2008) conducted a systematic review of dose-dispensing aids but were unable to determine that a specific aid was better than any other was. Another review focused on strategies to enhance adherence to cardiovascular medication did show that certain interventions resulted in adherence or persistence as well as improved clinical outcomes (van Dalem et al., 2012).

However, a Swedish study also reported that simply relying on dose-dispensing technology is insufficient to ensure high quality of the drug treatment itself (Sjöberg et al., 2011). Mistakes in packaging happen and it is imperative that the advanced practitioner, including the pharmacist, the oncology nurse, and others on the health-care team provide a detailed medication review at the start of any packaging services, and throughout the course of the patient's treatment, with particular attention to any changes in dosing or medication (Mathews, 2015). For example, dose reduction of oral oncolytic agents will not be reflected in packaging completed earlier in the monthly cycle, so careful patient education along with analysis of the prepackaged drugs are critical to ensure the patient is not inappropriately medicated. Additional research, especially prospective randomized controlled trials, are needed to evaluate whether dose-dispensing aids and services provide a significant improvement in adherence and other important outcomes, compared to other interventions (Viswanathan et al., 2012).

CONCLUSIONS

Recurrent and metastatic breast cancer is a serious and increasing clinical scenario as the US population continues to age. A new class of agents, CDK4/6 inhibitors, has been approved for HR+, HER2- breast cancer, and demonstrated significant improvements in disease-free survival (palbociclib, abemaciclib, ribociclib) or OS (ribociclib, abemaciclib), when given with other endocrine therapy, or as monotherapy (abemaciclib; Kolberg et al., 2019; Tien et al., 2019). All current CDK4/6 inhibitors are oral agents. This route of administration raises

concerns about patients reporting side effects as well as need for adherence to the drug regimens. Lack of adherence affects toxicities, costs, quality of life, and key outcomes, including survival. Multiple approaches to enhance adherence to oral oncolytic agents have been implemented, including "SIMPLE" strategies, application of smart technology, and drug dispensing aids and services. Limited data and lack of high levels of evidence point to a need for additional research in methods to increase drug adherence, particularly in view of the growing number of oral anticancer targeted agents.

ORAL THERAPY COMPLIANCE AND TREATMENT RESOURCE KIT

Readers can access the associated Oral Therapy Compliance and Treatment Resource Kit at http://bit.ly/OralTherapyComplianceKit_1635, a resource for advanced practitioners and patients/caregivers, including:

- Pocket Reference Guide
 - » For oncology advanced practitioners to use not only as a clinical reinforcement for best practices, but also as a point-of-practice patient education tool
 - » Includes strategies to improve adherence, dosage and modifications, common adverse events, and indications for CDK4/6 inhibitors
- Tip Sheet
 - » For patients and caregivers
 - » Advanced practitioners can distribute during patient consultations to facilitate oral therapy compliance and early side effect reporting
 - » Includes a "what to do and what to look for" list for monitoring side effects, common adverse events, strategies for remembering to take medications, list of health-care team, and additional resources. ●

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