Promoting Oral Therapy Adherence

Consensus statements from the faculty of the Melanoma Nursing Initiative on oral melanoma therapies

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BACKGROUND: Inhibitors of BRAF and the downstream signaling protein MEK have improved outcomes for patients with BRAF-mutant advanced malignant melanoma. Despite their ease of administration, these oral therapies pose adherence challenges.

OBJECTIVES: This article aims to increase awareness of causes of nonadherence to oral targeted therapies in advanced malignant melanoma and to provide oncology nurses with strategies to address these nonadherence issues.

METHODS: Members of the Melanoma Nursing Initiative explored issues related to adherence to targeted therapies in advanced malignant melanoma. The current literature and clinical experience were reviewed.

FINDINGS: The authors present a care step pathway focused on increased patient engagement and rapid identification and optimal management of toxicities to avoid toxicity-related nonadherence. Other causes for nonadherence and employment of individualized strategies to support patient adherence are addressed.

KEYWORDS
medication adherence; BRAF; MEK; targeted therapy; oral administration

DIGITAL OBJECT IDENTIFIER
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THERAPIES TARGETED TO THE MITOGEN-ACTIVATED PROTEIN KINASE (MAPK) pathway have improved the treatment options for patients with v-Raf murine sarcoma viral oncogene homolog B (BRAF)–mutant metastatic or unresectable advanced melanoma, increasing response rates and rates of overall and progression-free survival (Chapman et al., 2011; Flaherty et al., 2012; Larkin et al., 2014; McArthur et al., 2014; Robert et al., 2015; Welsh & Corrie, 2015). The targeted therapies approved by the U.S. Food and Drug Administration for use in melanoma are cobimetinib (Cotellic®), dabrafenib (Tafinlar®), trametinib (Mekinist®), and vemurafenib (Zelboraf®). Although generally well tolerated, these oral medications are associated with toxicity profiles unlike those of traditional cytotoxic chemotherapy. Clinical trials are examining their application in the adjuvant or neoadjuvant setting, and newer BRAF/mitogen-activated protein kinase kinase (MEK) agents are in development (Bendell et al., 2017; van Zeijl, van den Eertwegh, Haanen, & Wouters, 2017). Therefore, the important role of BRAF/MEK inhibitors in melanoma is likely to expand.

Researchers have categorized factors affecting adherence to long-term medications (Sabaté, 2003) and interventions to support adherence to oral anticancer medications in particular (Timmers et al., 2017). Oral delivery presents challenges for patient engagement and adherence that differ from those associated with IV administration (Weingart et al., 2008). Patients with cancer are viewed as particularly motivated to adhere to anticancer regimens (Weingart et al., 2008). In the authors' clinical experience, although patients with advanced malignant melanoma are usually highly invested in their therapy, they still face obstacles to adherence (Schneider, Adams, & Gosselin, 2014), such as delays in accessing drugs from specialty pharmacies, high co-pays and coinsurance, difficulty following complex dosing regimens, reluctance to report adverse events, and challenges to management of adverse events.

As trusted members of the oncology care team, nurses are well equipped to deliver interventions promoting patient adherence to oral medication regimens (Schneider et al., 2014; Schneider, Hess, & Gosselin, 2011). For the purposes of development of this article, members of the Melanoma Nursing Initiative (MNI) focused specifically on identifying and addressing factors that affect adherence to oral targeted therapies introduced for metastatic/unresectable melanoma.

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The authors convened to discuss the current literature and their clinical experience regarding adherence to oral advanced malignant melanoma therapies and interventions to increase adherence, then drafted the care step pathway, which illustrates strategies to engage patients with BRAF-mutant advanced malignant melanoma and foster adherence to targeted oral therapy (see Figure 1). This article outlines interventions nurses can incorporate to improve adherence at each of the care steps in the patient treatment journey.

Findings and Recommendations to Improve Adherence

Pretreatment

Pretreatment assessment should include identification of patient- and disease-related factors that may affect the patient's ability to adhere to the prescribed medication regimen. Cognitive ability, learning style, and family/social support should be evaluated (Schneider et al., 2011; Shinnick & Woo, 2015). Cognitive limitations owing to organic causes, such as brain metastases or dementia, or other learning barriers may hinder the patient's ability to follow dosing instructions and/or to observe and report adverse events. Asking patients to verbally demonstrate their understanding by using the teach-back method can serve as a check on the patient's comprehension (Agency for Healthcare Research and Quality, 2015).

Inadequate social support has been associated with nonadherence to oral medication (Partridge, Avorn, Wang, & Winer, 2002; Weingart et al., 2008). Family or friends can report adverse events, provide reminders to take medication, encourage patients to attend regular follow-up visits, and transport patients to those visits if necessary. Patient education is best delivered with a family member or caregiver present (Clay & Parsh, 2016). If the patient is not accompanied to a clinic visit by an involved caregiver, the nurse should ask the patient for a contact who can help with these issues. This question may prompt the patient to identify a supportive family member or friend. However, some patients are reluctant to ask family or friends for assistance. Others may not have individuals in their lives who can provide support and may be reluctant to share that information with the nurse or other members of the clinical team. A social worker, if one is available to the practice, should be engaged to connect such patients to local resources for services, such as transportation to medical appointments and assistance with medication cost.

Education

Patients' knowledge, attitudes, beliefs, perceptions, and expectations about the course of the disease and their ability to manage their illness and treatment regimen affect adherence (Sabaté, 2003; Timmers et al., 2017). Patients may perceive oral medication as less important or effective or as safer and more forgiving of dosage and administration errors as compared to IV therapy (Weingart et al., 2008). Communicating key results from clinical trials, including risks, benefits, and expected treatment outcomes, may motivate patients to integrate the dosing schedule, follow-up appointments, and management of adverse events into their lives.

> **"Prompt identification and management of adverse events are crucial for ensuring that patients are able to continue treatment."**

Adverse events affect adherence. In one study, one-third of those who discontinued oral anticancer medications reported side effects as a reason (Timmers et al., 2014). Prompt identification and management of adverse events are crucial for ensuring that patients are able to continue treatment (Welsh & Corrie, 2015). This point needs to be emphasized to patients before treatment initiation and throughout the course of therapy. Patients may not report side effects out of fear that therapy could be discontinued (Weingart et al., 2008). Some may choose to skip doses because of the discomfort or pain of particular symptoms (Schneider et al., 2014). Patients should be reminded about when to call the clinic or healthcare provider regarding adverse events.

Explaining that the clinical team shares the goals of continuing therapy and optimizing outcomes as long as the treatment is working and the patient is tolerating it is important. Those goals can be achieved safely. Prompt reporting of adverse events can allow for immediate intervention and possible dose modifications, as appropriate, in lieu of discontinuation of therapy. However, waiting until an adverse event has become severe may necessitate treatment cessation. Self-medicating to alleviate adverse events may lead to other problems, such as drug–drug interactions or worsening or development of additional adverse events. Of note, family members often provide valuable insight into the clinical situation and may report symptoms that patients minimize or fail to mention.

Patients receiving oral therapy instead of IV therapy may not adhere to the recommended schedule for follow-up appointments. Asking open-ended, nonjudgmental questions about the reasons for not keeping follow-up appointments and acknowledging the legitimacy of the issues the patient identifies are helpful communication techniques. Such dialogue may open a way to address those obstacles and serve as a teachable moment about the importance of periodic assessments (see Table 1). Stressing to patients that periodic assessments are crucial to evaluate toxicity and efficacy and maintain treatment safety is important.

FIGURE 1.
CARE STEP PATHWAY TO OPTIMIZE ADHERENCE TO ORAL MEDICATIONS IN MELANOMA

STEP 1: INITIAL ASSESSMENT AND EVALUATION

General

- Assess patient's ability to understand directions and follow treatment schedule, including asking about learning barriers or organic causes of cognitive deficits.
- Assess patient's available family and social supports.

Education

- Go over risks and benefits.
- Instruct patients on how to store and take medications.
- Emphasize the importance of follow-up visits.
- Remind patients to take medications at about the same time each day (go over dosing calendar).
- Provide instructions about what to do about missed doses.
- Discuss safe sex and birth control.
- Discuss common side effects.
- Discuss when to call the clinic.

Pharmacy and insurance

- Assess whether patient has prescription benefits and what those benefits are (e.g., co-pay).
- Find out whether prior authorization is required.
- Determine whether medication has to be filled at a specialty pharmacy and whether that pharmacy is mail-order or local.
- Obtain medication reconciliation or at least the medication list.

Relevant medical history

- Assess ability to tolerate oral medications (solids and liquids). Ask if patient can swallow pills.
- Ask about nausea/vomiting and absorption issues.
- Determine previous gastrointestinal toxicity from immunotherapy, bowel obstruction from tumor, etc.
- Ask about other comorbidities (e.g., diabetes, heart disease).

STEP 2: SCREENING PRIOR TO INITIATION OF BRAF/MEK THERAPY

General examination

- Check vitals and perform comprehensive history and physical examination to assess for preexisting thromboembolic, cardiac, ocular, and other conditions per the manufacturer's instructions.
- Assess for previous toxicity (e.g., pulmonary, liver, ocular).

Laboratory testing

- Obtain CBC with differential and complete metabolic panel (with glucose for dabrafenib), as well as levels of alkaline phosphatase, ALT, AST, total and direct bilirubin, creatine kinase (for cobimetinib), and gamma-glutamyltransferase (for cobimetinib and vemurafenib).

Cardiac

- Perform echocardiogram for left ventricular ejection fraction for any MEK-containing regimen and ECG for vemurafenib.

Dermatologic

- Perform thorough skin assessment. Refer to dermatology provider if patient has not had a comprehensive dermatologic examination for 1 year or has a strong history of other nonmelanoma skin cancer.

STEP 3: CONTINUED ASSESSMENT AND EVALUATION

Ongoing counseling

- Query patients about how they are taking medications (e.g., storage, fasting, medication list changes).
- Probe for side effects (checklist preferred).
- Query about any hospitalizations or care by another provider.
- Review when to call the clinic or provider, emphasizing need for oncology team to be first contact for medical issues.

Laboratory testing

- Repeat baseline laboratories at 1 month.

Cardiac

- Repeat echocardiography at 1 month and every 2–3 months while on treatment.
- If ECG is performed on vemurafenib, repeat at 14 days, monthly for 3 months, and then every 2–3 months while on treatment.
- Perform ECG more frequently if on medications affecting QTc or as needed if patient starts new agents that may have QTc prolongation.

Dermatologic

- Perform in-office skin examinations by clinical provider every 2 months.

RED FLAGS

- High co-pay
- Crushing or breaking pills; altering the schedule to save money (once daily versus twice daily)

ALT—alanine aminotransferase; AST—aspartate transaminase; CBC—complete blood count; ECG—electrocardiogram
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TABLE 1.
EXAMPLES OF OPEN-ENDED MOTIVATIONAL INTERVIEWING QUESTIONS TO PROMOTE ADHERENCE TO ORAL TARGETED THERAPY FOR ADVANCED MELANOMA

GENERAL QUESTION	MOTIVATIONAL INTERVIEWING QUESTION
Are you taking the medicine as directed?	Describe how you typically take your medicine. Do you have any trouble swallowing the medication? Potential follow-up questions: ■ When do you usually take the medication? ■ What helps you remember when to take it? ■ What do you do if you forget a dose? ■ Is it harder to remember a particular dose (e.g., evening dose on a day you meet friends for dinner)? ■ Tell me about ways that have helped you keep track of other things in your life, such as cell-phone reminders, calendars, or sticky notes.
Have you experienced any adverse events?	Ask specifically about every side effect of interest, using a checklist for adverse events associated with the patient's regimen and yes-or-no questions. Follow up any "yes" responses with open-ended questions (e.g., what seems to trigger that symptom?).
Did you refill the prescription?	Has the pharmacy provided the medication? If no, use these follow-up questions: ■ Did you forget to call the pharmacy for refill? ■ Did the pharmacy indicate that there has been a delay because of insurance issues? Many patients have trouble remembering to call for refills. What would help you remember?
You need to keep follow-up appointments or we will not renew the medication.	I'm sorry that you have not made it in for the follow-up appointments. We all understand that you are committed to the treatment. Let's talk about what issues are making it difficult to come to the office and how we can address them?

Establishing "no refills" on initial prescriptions can encourage patients to return to the office.

Following Complex Regimens

Greater regimen complexity has been associated with lower levels of adherence (Schneider et al., 2011; Spoelstra et al., 2013). In one analysis, noncontinuous oral regimens have been associated with lower adherence rates than continuous oral treatment schedules (88% for a continuous schedule versus 35% and 33% for two intermittent schedules) (Spoelstra et al., 2013). The combination of cobimetinib and vemurafenib is an example of two different dosing schedules within the same regimen. Vemurafenib is given continuously, and cobimetinib is only taken for three weeks out of a four-week cycle. In addition, vemurafenib is taken twice daily (roughly 12 hours apart), whereas cobimetinib is a once-daily medication (see Figure 2). In the dabrafenib/trametinib combination, dabrafenib is taken twice a day, whereas trametinib is taken once daily (see Figure 3). Given these complex dosing schedules, patient education by the nurse is paramount.

Anticipatory guidance to help patients identify strategies to manage these complex regimens is an important component of nursing care. Available downloadable resources to support adherence are listed in Figure 4. Dosing calendars; pillboxes; smartphone alarms; and reminders on mirrors, doors, or laptop computers may help, depending on the patient's lifestyle and preference (Schneider et al., 2011). However, a study by Choudry et al. (2017) found that three types of pillboxes with different reminder devices did not increase the odds of optimal adherence as compared to a standard pillbox. These findings suggest that behavioral interventions are needed in addition to technological reminders. The nurse should assess which techniques are likely to work for the individual patient, possibly by querying him or her about strategies that currently work as reminder systems for the patient in other aspects of life.

Patients with preexisting nausea and vomiting may find it challenging to swallow medications first thing in the morning after an overnight fast. In these situations, the nurse can advise patients to eat breakfast and then wait two hours to take dabrafenib or trametinib, providing an adequate fast period that is more tolerable than an overnight fast. Patients should also be instructed about what to do if they miss a scheduled dose. Dosing calendars can address this question for each regimen.

Medication Storage and Disposal

Trametinib must be kept refrigerated and stored in the original bottle with the lid closed tightly to protect the pills from heat, light, and moisture (Novartis, 2016). The nurse should instruct patients to keep all medications with them when traveling and not to place them in a stored baggage area, where temperatures are not controlled. In addition, trametinib bottles can be kept in refrigerated lunch packs. If the patient inadvertently leaves an opened bottle of trametinib out of the refrigerator, temperature excursion data have shown that the medication is not damaged by storage outside the refrigerator for as many as 30 days if it is maintained at a temperature below 86°F (30°C) (Novartis, 2017). Therefore, the nurse can typically advise the patient who has inadvertently left the medication out to simply keep the medication cool and get it back in the refrigerator as soon as possible.

Contraception and Family Planning

Before initiating any of the targeted therapies, patients must be counseled about pregnancy, fertility, and contraception. All four oral targeted agents approved for metastatic/unresectable melanoma can cause fetal harm. Some patients view themselves as sterile because of prior anticancer therapies or assume that they will be rendered sterile by targeted therapy. It is important to emphasize the need for effective birth control even in the face of these beliefs. Women of childbearing age must be advised to use effective birth control during treatment and for at least two weeks (for cobimetinib, dabrafenib, and vemurafenib) to four months (for trametinib) after treatment ends (Genentech,

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FIGURE 2.
DOSING CALENDAR FOR ZELBORAF® (VEMURAFENIB) AND COTELLIC® (COBIMETINIB)

START DATE: _____

WEEK 1	DATE:	DATE:	DATE:	DATE:	DATE:	DATE:	DATE:
	☼ Zelboraf ☐ ☾ Zelboraf ☐	☼ Zelboraf ☐ ☾ Zelboraf ☐	☼ Zelboraf ☐ ☾ Zelboraf ☐	☼ Zelboraf ☐ ☾ Zelboraf ☐	☼ Zelboraf ☐ ☾ Zelboraf ☐	☼ Zelboraf ☐ ☾ Zelboraf ☐	☼ Zelboraf ☐ ☾ Zelboraf ☐
	Cotellic ☐	Cotellic ☐	Cotellic ☐	Cotellic ☐	Cotellic ☐	Cotellic ☐	Cotellic ☐
WEEK 2	**DATE:**	**DATE:**	**DATE:**	**DATE:**	**DATE:**	**DATE:**	**DATE:**
	☼ Zelboraf ☐ ☾ Zelboraf ☐	☼ Zelboraf ☐ ☾ Zelboraf ☐	☼ Zelboraf ☐ ☾ Zelboraf ☐	☼ Zelboraf ☐ ☾ Zelboraf ☐	☼ Zelboraf ☐ ☾ Zelboraf ☐	☼ Zelboraf ☐ ☾ Zelboraf ☐	☼ Zelboraf ☐ ☾ Zelboraf ☐
	Cotellic ☐	Cotellic ☐	Cotellic ☐	Cotellic ☐	Cotellic ☐	Cotellic ☐	Cotellic ☐
WEEK 3	**DATE:**	**DATE:**	**DATE:**	**DATE:**	**DATE:**	**DATE:**	**DATE:**
	☼ Zelboraf ☐ ☾ Zelboraf ☐	☼ Zelboraf ☐ ☾ Zelboraf ☐	☼ Zelboraf ☐ ☾ Zelboraf ☐	☼ Zelboraf ☐ ☾ Zelboraf ☐	☼ Zelboraf ☐ ☾ Zelboraf ☐	☼ Zelboraf ☐ ☾ Zelboraf ☐	☼ Zelboraf ☐ ☾ Zelboraf ☐
	Cotellic ☐	Cotellic ☐	Cotellic ☐	Cotellic ☐	Cotellic ☐	Cotellic ☐	Cotellic ☐
WEEK 4	**DATE:**	**DATE:**	**DATE:**	**DATE:**	**DATE:**	**DATE:**	**DATE:**
	☼ Zelboraf ☐ ☾ Zelboraf ☐	☼ Zelboraf ☐ ☾ Zelboraf ☐	☼ Zelboraf ☐ ☾ Zelboraf ☐	☼ Zelboraf ☐ ☾ Zelboraf ☐	☼ Zelboraf ☐ ☾ Zelboraf ☐	☼ Zelboraf ☐ ☾ Zelboraf ☐	☼ Zelboraf ☐ ☾ Zelboraf ☐
	No Cotellic this week						

What if you forget a dose of Zelboraf or Cotellic?

- For Cotellic, if 4 hours or less from scheduled dosing time, take the dose; if more than 4 hours, hold that dose and take the next scheduled dose at the normal time.
- For Zelboraf, a missed dose can be taken up to 4 hours prior to the next dose.
- Do NOT take a double dose to make up for a missed dose.

Note. Based on information from Genentech, 2016a, 2016b.
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2016a, 2016b; Novartis, 2015, 2016). Dabrafenib can interact with hormonal contraceptives (oral pills, injections, or patches), rendering them ineffective; therefore, women must be counseled to use nonhormonal contraception during and immediately after treatment with this drug (Novartis, 2016). Many practices advise patients to use two nonhormonal (barrier) methods of contraception to increase effectiveness.

Impact on fertility in humans is not known, but cobimetinib, dabrafenib, and trametinib have been shown to impair fertility in male and female animal models (Genentech, 2016a, 2016b; Novartis, 2015, 2016). Dabrafenib may irreversibly limit fertility in males (Novartis, 2016). Men should be counseled regarding decreased chances of impregnating a female partner while receiving treatment with any of the four targeted agents (OncoLink, 2015a, 2015b, 2016a, 2016b).

Beyond immediate fertility and pregnancy effects, patients may have questions surrounding future family planning. Nurses should be prepared to discuss options for sperm banking and egg freezing and offer supportive counseling regarding the prospect of family planning in the setting of advanced melanoma. Prognosis and life expectancy should be considered. Such discussions may become more commonplace if targeted therapies become available for use in the adjuvant setting.

Pharmacy and Insurance Issues

Cost and Access

Because most oral medications are covered under prescription insurance plans versus major medical plans (as with IV infusions), cost can be a significant barrier to medication initiation and refill

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FIGURE 3.
DOSING CALENDAR FOR TAFINLAR® (DABRAFENIB) AND MEKINIST® (TRAMETINIB)

START DATE: _____

WEEK 1	**DATE:**	**DATE:**	**DATE:**	**DATE:**	**DATE:**	**DATE:**	**DATE:**
	☼ Tafinlar ☐ ☾ Tafinlar ☐	☼ Tafinlar ☐ ☾ Tafinlar ☐	☼ Tafinlar ☐ ☾ Tafinlar ☐	☼ Tafinlar ☐ ☾ Tafinlar ☐	☼ Tafinlar ☐ ☾ Tafinlar ☐	☼ Tafinlar ☐ ☾ Tafinlar ☐	☼ Tafinlar ☐ ☾ Tafinlar ☐
	Mekinist ☐	Mekinist ☐	Mekinist ☐	Mekinist ☐	Mekinist ☐	Mekinist ☐	Mekinist ☐
WEEK 2	**DATE:**	**DATE:**	**DATE:**	**DATE:**	**DATE:**	**DATE:**	**DATE:**
	☼ Tafinlar ☐ ☾ Tafinlar ☐	☼ Tafinlar ☐ ☾ Tafinlar ☐	☼ Tafinlar ☐ ☾ Tafinlar ☐	☼ Tafinlar ☐ ☾ Tafinlar ☐	☼ Tafinlar ☐ ☾ Tafinlar ☐	☼ Tafinlar ☐ ☾ Tafinlar ☐	☼ Tafinlar ☐ ☾ Tafinlar ☐
	Mekinist ☐	Mekinist ☐	Mekinist ☐	Mekinist ☐	Mekinist ☐	Mekinist ☐	Mekinist ☐
WEEK 3	**DATE:**	**DATE:**	**DATE:**	**DATE:**	**DATE:**	**DATE:**	**DATE:**
	☼ Tafinlar ☐ ☾ Tafinlar ☐	☼ Tafinlar ☐ ☾ Tafinlar ☐	☼ Tafinlar ☐ ☾ Tafinlar ☐	☼ Tafinlar ☐ ☾ Tafinlar ☐	☼ Tafinlar ☐ ☾ Tafinlar ☐	☼ Tafinlar ☐ ☾ Tafinlar ☐	☼ Tafinlar ☐ ☾ Tafinlar ☐
	Mekinist ☐	Mekinist ☐	Mekinist ☐	Mekinist ☐	Mekinist ☐	Mekinist ☐	Mekinist ☐
WEEK 4	**DATE:**	**DATE:**	**DATE:**	**DATE:**	**DATE:**	**DATE:**	**DATE:**
	☼ Tafinlar ☐ ☾ Tafinlar ☐	☼ Tafinlar ☐ ☾ Tafinlar ☐	☼ Tafinlar ☐ ☾ Tafinlar ☐	☼ Tafinlar ☐ ☾ Tafinlar ☐	☼ Tafinlar ☐ ☾ Tafinlar ☐	☼ Tafinlar ☐ ☾ Tafinlar ☐	☼ Tafinlar ☐ ☾ Tafinlar ☐
	Mekinist ☐	Mekinist ☐	Mekinist ☐	Mekinist ☐	Mekinist ☐	Mekinist ☐	Mekinist ☐

What if you forget a dose of Tafinlar or Mekinist? Take the missed dose as soon as you remember unless:

- You missed Tafinlar and it is less than 6 hours until your next dose. If so, SKIP missed dose and continue your next dose at the regular time. Do NOT take a double dose to make up for a missed one.
- You missed Mekinist and it is less than 12 hours until your next dose. If so, SKIP missed dose and continue your next dose at the regular time. Do NOT take a double dose to make up for a missed one.

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(Schneider et al., 2014). To save money, patients with high out-of-pocket costs (i.e., co-pays or coinsurance) might delay treatment initiation or refills or dose less frequently than prescribed (Winn, Keating, & Dusetzina, 2016; Zafar et al., 2013). Patients covered by commercial, which must include prescription drug coverage, rather than government (e.g., Medicare, Medicaid) insurance have access to manufacturer co-pay cards that reduce patient financial responsibility. In addition, manufacturers of the targeted therapies for melanoma offer resources to reduce co-pays and connect patients on government insurance to foundations or other organizations that may offer assistance with the patient's share of medication cost (see Figure 4).

Health system barriers to obtaining and refilling medication in a timely manner may affect a substantial number of patients (Schneider et al., 2014). Obstacles can include (a) a requirement to use a specialty or mail-order pharmacy, (b) delays while processing a prior authorization, and (c) a requirement for a signature if delivered to home. Of particular concern is expediting access to the initial prescription.

Patients and pharmacies may not understand the urgency of promptly initiating treatment in the setting of a life-threatening disease. Nurses should impress on patients and their family members that immediately returning pharmacy calls is crucial to starting and maintaining medication supply. Manufacturers of targeted therapies offer support to facilitate prior authorizations and otherwise speed access to therapy. The nurse or other healthcare team members should provide assistance with clearing the barriers to drug access as much as possible.

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Current Medications

Patients receiving medications to manage comorbid conditions, control cancer symptoms, or manage toxicities of previous anticancer therapies may be at high risk for drug–drug interactions. As with any drug therapy, a pharmacist should ideally review the patient's medications, identify absolute and relative contraindications, and suggest possible dose adjustments or alternate medications to prevent or reduce the risk of drug–drug interactions. The specialty pharmacy contracted with the patient's insurer may be able to offer this reconciliation service (Weingart et al., 2008). Pharmacy departments at academic medical centers and comprehensive cancer centers may provide a pharmacy consultation for patients even if the insurer will not cover prescriptions filled at those centers. In the absence of these pharmacy resources, the nurse should obtain a list of current medications, which includes any over-the-counter medications, herbals, supplements, and vitamins. It is important to explain to patients that some of these substances can lead to drug–drug interactions, which can increase the risk for toxicities or render the targeted melanoma therapy less efficacious (Carrington, 2015; Genentech, 2016a; Welsh & Corrie, 2015).

Relevant Medical History

Toxicities associated with targeted therapies can affect organ systems that already may be compromised by comorbid conditions and/or previous melanoma therapies. The average age at melanoma diagnosis is 63 years (American Cancer Society, 2017). Cardiovascular disease, diabetes, and certain visual impairments become more common in older adults, and adverse events can exacerbate these conditions. Patients with these conditions

FIGURE 4.
RESOURCES TO SUPPORT ADHERENCE TO ORAL TARGETED THERAPIES FOR ADVANCED MELANOMA

FOR PATIENTS

DRUG ACCESS AND FINANCIAL RESOURCES

Novartis (dabrafenib and trametinib): Co-pay assistance, insurance verification, covered pharmacy, free 30-day trial

- www.us.tafinlarmekinist.com/advanced-melanoma/patient-support/cost-support

Genentech (vemurafenib and cobimetinib): Co-pay assistance foundations, financial assistance, coverage checks, and specialty pharmacy lists

- www.genentech-access.com/patient/brands/cotellic/how-we-help-you.html

Genentech (vemurafenib and cobimetinib): Patient assistance tools for co-pays and assistance foundations

- www.genentech-access.com/hcp/brands/cotellic/find-patient-assistance.html

ADHERENCE AIDS

Novartis (dabrafenib and trametinib): Patient support for dabrafenib and trametinib with brochures, treatment diary, and dosing calendars

- www.us.tafinlarmekinist.com/advanced-melanoma/patient-support/patient-resources

Genentech (vemurafenib and cobimetinib): Resources for vemurafenib and cobimetinib with patient guides, dosing calendars, and a nurse hotline

- 1-855-MY-COTELLIC
- www.cotellic.com

PATIENT ADVOCACY AND NURSE SUPPORT

Speak with an oncology nurse at no charge.

- 1-877-246-2635
- www.aimatmelanoma.org/living-with-melanoma/nurse-on-call

Patient and caregiver resources from AIM at Melanoma Foundation

- www.aimatmelanoma.org/living-with-melanoma/patient-caregiver-resources

Patient symposiums

www.aimatmelanoma.org/living-with-melanoma/patient-caregiver-symposiums

FOR NURSES

DRUG ACCESS AND FINANCIAL RESOURCES

Novartis (dabrafenib and trametinib): Co-pay assistance, insurance verification, alternative funding sources, free 30-day trial

- www.hcp.novartis.com/products/tafinlar-mekinist/advanced-metastatic-melanoma/access

Genentech (vemurafenib and cobimetinib): My Patient Solutions™

- www.genentech-access.com/hcp/brands/cotellic/learn-about-our-services/my-patient-solutions.html

Genentech (vemurafenib and cobimetinib): Patient assistance tools for co-pays and assistance foundations

- www.genentech-access.com/hcp/brands/cotellic/find-patient-assistance.html

ADHERENCE AIDS

Novartis (dabrafenib and trametinib): Patient support with brochures, treatment diary, and dosing calendars

- www.us.tafinlarmekinist.com/advanced-melanoma/patient-support/patient-resources

Genentech (vemurafenib and cobimetinib): Resources library with patient guides and dosing calendars

- www.cotellic.com/hcp/support-resources/cotellic-patient-resources.html

PATIENT ADVOCACY AND NURSE SUPPORT

Toolkits for promoting adherence and managing adverse events, downloadable patient materials, and community nurse portal

- www.themelanomanurse.org

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FIGURE 5.
COMMON ADVERSE EVENT CHECKLIST FOR ORAL TARGETED THERAPIES FOR MELANOMA

FOLLOW-UP CLINIC VISIT TEMPLATE FOR PATIENTS RECEIVING BRAF/MEK INHIBITORS

Stage: _____

GENERAL ASSESSMENT

Pain

- Location: _____
- Intensity: _____
- Interventions: _____

Fatigue	☐
Appetite	☐
Nausea	☐
Headaches or visual changes	☐
Lightheadedness or dizziness	☐
Lymphedema	☐
Cough or shortness of breath	☐
Fever	☐
Skin changes, rash, or pruritis	☐

ADDITIONAL CLASS-SPECIFIC SIDE EFFECTS

Eye pain or dryness	☐
Hand-foot syndrome	☐
Bone or joint pain	☐
Number of stools per day: _____	

ACTION PLAN

Assessment	☐
Medical recommendations	☐
Prescription refills	☐
Documentation in note	☐
Other	☐

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may take other medications, potentially raising the risk of drug–drug interactions (Spoelstra et al., 2013). In addition, patients with more comorbidities may report higher severity of adverse events to oral anticancer medications, as observed in a study by Spoelstra et al. (2015). Patients who have received prior anticancer regimens may have residual toxicities before starting targeted therapy. A baseline assessment is important to identify patients whose health is already compromised and to distinguish emerging adverse events from preexisting conditions.

Screening

Pretreatment screening should include assessment of vital signs, laboratory values, blood pressure, oxygen saturation, and cardiac function testing. Combination targeted therapies can cause fever, cardiomyopathy, arrhythmias, endocrinopathies, and hepatotoxicity (Genentech, 2016a; 2016b; Novartis, 2015, 2016; Welsh & Corrie, 2015). Creatine kinase is measured before and during cobimetinib administration because of risk of rhabdomyolysis (Genentech, 2016a). Gamma-glutamyltransferase is assessed for patients prescribed cobimetinib or vemurafenib because these drugs can cause elevation of this specific liver enzyme (Genentech, 2016a, 2016b). Liver function and kidney function should be checked on a periodic basis.

BRAF inhibitors are associated with the development of nonmelanoma skin cancers (keratinocyte carcinomas, such as basal cell and squamous cell carcinomas) and new primary melanoma malignancies. Patients should undergo a skin examination before treatment initiation and every two months during treatment and for as many as six months after treatment cessation (Genentech, 2016a, 2016b; Novartis, 2015, 2016). The MNI advises that individuals who have not had a comprehensive dermatologic examination within the past year or who have a history of basal cell or squamous cell carcinoma should receive a skin examination from a dermatologist with expertise in cutaneous malignancies prior to starting targeted therapy. Although the clinical trials using BRAF combination therapies require baseline ocular examinations by ophthalmology, oncology practices typically reserve these examinations for patients who develop symptoms of ocular toxicities. In addition, at baseline, evaluation of ejection fraction is needed when using an oral MEK inhibitor, and an electrocardiogram is recommended with use of vemurafenib (Genentech, 2016a, 2016b; Novartis, 2015, 2016).

Anticipatory Guidance During Treatment

Ongoing Patient Counseling

Toxicity education and monitoring are key roles of the oncology nurse. Monitoring between subsequent cycles promotes early detection of adverse events or other obstacles to adherence so that these issues can be addressed promptly. For example, pyrexia occurring with dabrafenib-containing regimens often requires active pharmacologic management and potential dose reduction. In addition, visits or telephone calls represent a chance to evaluate patient psychosocial status and offer emotional support (Schneider et al., 2011). In a study by Schneider et al. (2014), a nurse-coaching intervention delivered through telephone calls was associated with higher pharmacy refill rates compared with standard pretreatment education alone. During the calls, nurses discussed factors that could affect adherence, identified any issues interfering with the patient taking medication as prescribed, and brainstormed with the patient on strategies to address those issues. Such an approach is likely to be helpful to patients receiving targeted therapy. Every visit should include asking the patient about the routine employed for taking medication, any new symptoms or signs of adverse events, new disease symptoms, changes in other medications, and visits to other clinicians.

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Clinical Examination and Testing During Follow-Up

Anticipatory guidance should include explaining to patients that vital signs must be measured at every follow-up visit. Regular monitoring promotes early detection of any adverse events and facilitates early management. Laboratory measures should be evaluated at follow-up visits and more frequently if clinically indicated (Genentech, 2016a, 2016b; Novartis, 2015, 2016). Echocardiography should be followed as recommended.

Because cutaneous toxicity is common with BRAF/MEK inhibitors, frequent skin examinations during treatment are important to screen for new melanomas and keratinocyte carcinomas, as well as to detect rashes, papillomas, and calluses. Dabrafenib and trametinib each carry a warning about palmar-plantar erythrodysesthesia, also called hyperkeratosis or hand-foot syndrome. This toxicity is also reported with vemurafenib (Anforth et al., 2012; Genentech, 2016a, 2016b; Novartis, 2015, 2016; Vanneste, Wolter, Van den Oord, Stas, & Garmyn, 2015). Patients may not recognize the redness, swelling, and pain on the palms of the hands and/or the soles of the feet as a treatment side effect. Hyperkeratotic lesions also can develop in other areas of the body (Livingstone, Zimmer, Vaubel, & Schadendorf, 2014). Palmar-plantar hyperkeratosis can be managed by counseling patients to minimize pressure and friction on the areas; wear soft, broad shoes; and use topical keratolytic medications containing urea, salicylic acid, or, rarely, steroids. Frequent paring by a podiatrist can relieve pressure and pain (Livingstone et al., 2014).

Eliciting Adverse Events and Nonadherence

When probing for adverse events of therapy, specific rather than general queries are more likely to elicit informative responses. Patients may respond "no" when asked if they have experienced any adverse events, but asking about every possible side effect may uncover new symptoms. Open-ended questions (e.g., what bothersome symptoms have you experienced since your last visit?) also may elicit information. Patients may not detect some changes or may view them as insignificant and, therefore, not mention them to the nurse or others on the clinical team. The authors recommend use of a structured checklist to probe for adverse events (see Figure 5).

If nonadherence is suspected, the nurse should continue to connect with the patient while showing acceptance, empathy, and support, which can facilitate trust and foster communication (Komatsu & Yagasaki, 2014). Motivational interviewing is one strategy for building a connection. A technique developed by Miller and Rollnick (2013) in addiction treatment, motivational interviewing has been defined as "a collaborative conversation style for strengthening a person's own motivation and commitment to change" (p. 10). It builds on the person's motivation for change rather than leaving the individual feeling defensive or shamed for not engaging in a certain behavior (Miller & Rollnick, 2013). Techniques drawing on the principles of motivational interviewing have improved patient self-management in multiple disease states. A study applying these techniques to promote adherence to oral anticancer therapies is in progress (Spoelstra, Burhenn, DeKoekkoek, & Schueller, 2016).

IMPLICATIONS FOR PRACTICE

- Encourage patients to promptly report toxicity, emphasizing the rationale for early intervention.
- Employ case management and other resources to navigate insurance and pharmacy barriers that interfere with patients' ability to obtain prescribed medication.
- Use tools, such as adverse event checklists, open-ended questions, and motivational interviewing techniques, to elicit and overcome barriers to adherence, and incorporate compassionate encouragement and psychosocial counsel.

Conclusion

Medication adherence issues associated with oral therapy for advanced melanoma differ from those observed with other treatment delivery routes. Responsibility for administration and self-management of potentially life-prolonging therapy shifts from the clinical team to the patient. The life-threatening nature of the disease, characteristics of the patient population, medication adverse events, insurance coverage, and access issues with oral medication create adherence obstacles in this setting. The assertive approach outlined in this article to elicit adverse events and address barriers to adherence should increase the likelihood of patients staying on these therapies and lead to improved outcomes.

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REFERENCES

Agency for Healthcare Research and Quality. (2015). Use the teach-back method: Tool #5. Rockville, MD: Author. Retrieved from http://bit.ly/2uNDbo2

American Cancer Society. (2017). Key statistics for melanoma skin cancer. Retrieved from https://www.cancer.org/cancer/melanoma-skin-cancer/about/key-statistics.html

Anforth, R.M., Blumetti, T.C., Kefford, R.F., Sharma, R., Scolyer, R.A., Kossard, S., . . . Fernandez-Peñas, P. (2012). Cutaneous manifestations of dabrafenib (GSK2118436): A selective inhibitor of mutant BRAF in patients with metastatic melanoma. *British Journal of Dermatology, 167*, 1153–1160. doi:10.1111/j.1365-2133.2012.11155.x

Bendell, J.C., Javle, M., Bekaii-Saab, T.S., Finn, R.S., Wainberg, Z.A., Laheru, D.A., . . . Patnaik, A. (2017). A phase 1 dose-escalation and expansion study of binimetinib (MEK162), a potent and selective oral MEK1/2 inhibitor. *British Journal of Cancer, 116*, 575–583. doi:10.1038/bjc.2017.10

Carrington, C. (2015). Oral targeted therapy for cancer. *Australian Prescriber, 38*(5), 171–176. doi:10.18773/austprescr.2015.060

Chapman, P.B., Hauschild, A., Robert, C., Haanen, J.B., Ascierto, P., Larkin, J., . . . McArthur, G.A. (2011). Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *New England Journal of Medicine, 364*, 2507–2516. doi:10.1056/NEJMoa1103782

Choudhry, N.K., Krumme, A.A., Ercole, P.M., Girdish, C., Tong, A.Y., Khan, N.F., . . . Franklin, J.M. (2017). Effect of reminder devices on medication adherence: The REMIND randomized clinical trial. *JAMA Internal Medicine, 177*, 624–631. doi:10.1001/jamainternmed.2016.9627

Clay, A.M., & Parsh, B. (2016). Patient- and family-centered care: It's not just for pediatrics anymore. *AMA Journal of Ethics, 18*, 40–44. doi:10.1001/journalofethics.2016.18.1.medu3-1601

Flaherty, K.T., Robert, C., Hersey, P., Nathan, P., Garbe, C., Milhem, M., . . . Schadendorf, D. (2012). Improved survival with MEK inhibition in BRAF-mutated melanoma. *New England Journal of Medicine, 367*, 107–114. doi:10.1056/NEJMoa1203421

Genentech. (2016a). *Cotellic® (cobimetinib)* [Package insert]. Retrieved from http://bit.ly/2sM02ij

Genentech. (2016b). *Zelboraf® (vemurafenib)* [Package insert]. Retrieved from http://bit.ly/2t0C2fh

Komatsu, H., & Yagasaki, K. (2014). The power of nursing: Guiding patients through a journey of uncertainty. *European Journal of Oncology Nursing, 18*, 419–424. doi:10.1016/j.ejon.2014.03.006

Larkin, J., Ascierto, P.A., Dréno, B., Atkinson, V., Liszkay, G., Maio, M., . . . Ribas, A. (2014). Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. *New England Journal of Medicine, 371*, 1867–1876. doi:10.1056/NEJMoa1408868

Livingstone, E., Zimmer, L., Vaubel, J., & Schadendorf, D. (2014). BRAF, MEK and KIT inhibitors for melanoma: Adverse events and their management. *Chinese Clinical Oncology, 3*(3), 29. doi:10.3978/j.issn.2304-3865.2014.03.03

McArthur, G.A., Chapman, P.B., Robert, C., Larkin, J., Haanen, J.B., Dummer, R., . . . Hauschild, A. (2014). Safety and efficacy of vemurafenib in BRAF(V600E) and BRAF(V600K) mutation-positive melanoma (BRIM-3): Extended follow-up of a phase 3, randomised, open-label study. *Lancet Oncology, 15*, 323–332. doi:10.1016/s1470-2045(14)70012-9

Miller, W.R, & Rollnick, S. (Eds.). (2013). Conversations about change. In *Motivational interviewing: Helping people change* (3rd ed., pp. 3–13). New York, NY: Guilford Publications.

Novartis. (2015). *Mekinist® (trametinib)* [Package insert]. Retrieved from https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/mekinist.pdf

Novartis. (2016). *Tafinlar® (dabrafenib)* [Package insert]. Retrieved from https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/tafinlar.pdf

Novartis. (2017, March 16). Storage, stability, and handling of Mekinist tablets. [Standard response letter to Valerie Guild, AIM at Melanoma Foundation].

OncoLink. (2015a). Dabrafenib (Tafinlar®). Retrieved from http://bit.ly/2ueD4Vo

OncoLink. (2015b). Vemurafenib (Zelboraf®). Retrieved from http://bit.ly/2t0PvUr

OncoLink. (2016a). Cobimetinib (Cotellic®). Retrieved from http://bit.ly/2tJERi9

OncoLink. (2016b). Trametinib (Mekinist®). Retrieved from http://bit.ly/2tEQ4SD

Partridge, A.H., Avorn, J., Wang, P.S., & Winer, E.P. (2002). Adherence to therapy with oral antineoplastic agents. *Journal of the National Cancer Institute, 94*, 652–661.

Robert, C., Karaszewska, B., Schachter, J., Rutkowski, P., Mackiewicz, A., Stroiakovski, D., . . . Schadendorf, D. (2015). Improved overall survival in melanoma with combined dabrafenib and trametinib. *New England Journal of Medicine, 372*, 30–39. doi:10.1056/NEJMoa1412690

Sabaté, E. (2003). *Adherence to long-term therapies: Evidence for action*. Geneva, Switzerland: World Health Organization. Retrieved from http://bit.ly/1dHSkqy

Schneider, S.M., Adams, D.B., & Gosselin, T. (2014). A tailored nurse coaching intervention for oral chemotherapy adherence. *Journal of the Advanced Practitioner in Oncology, 5*(3), 163–172.

Schneider, S.M., Hess, K., & Gosselin, T. (2011). Interventions to promote adherence with oral agents. *Seminars in Oncology Nursing, 27*, 133–141. doi:10.1016/j.soncn.2011.02.005

Shinnick, M.A., & Woo, M.A. (2015). Learning style impact on knowledge gains in human patient simulation. *Nurse Education Today, 35*, 63–67. doi:10.1016/j.nedt.2014.05.013

Spoelstra, S.L., Burhenn, P.S., DeKoekkoek, T., & Schueller, M. (2016). A trial examining an advanced practice nurse intervention to promote medication adherence and symptom management in adult cancer patients prescribed oral anti-cancer agents: Study protocol. *Journal of Advanced Nursing, 72*, 409–420. doi:10.1111/jan.12828

Spoelstra, S.L., Given, B.A., Given, C.W., Grant, M., Sikorskii, A., You, M., & Decker, V. (2013). An intervention to improve adherence and management of symptoms for patients prescribed oral chemotherapy agents: An exploratory study. *Cancer Nursing, 36*, 18–28. doi:10.1097/NCC.0b013e3182551587

Spoelstra, S.L., Given, C.W., Sikorskii, A., Majumder, A., Schueller, M., & Given, B.A. (2015). Treatment with oral anticancer agents: Symptom severity and attribution, and interference with comorbidity management. *Oncology Nursing Forum, 42*, 80–88. doi:10.1188/15.ONF.42-01p

Timmers, L., Boons, C.C., Kropff, F., van de Ven, P.M., Swart, E.L., Smit, E.F., . . . Hugtenburg, J.G. (2014). Adherence and patients' experiences with the use of oral anticancer agents. *Acta Oncologica, 53*, 259–267. doi:10.3109/0284186x.2013.844353

Timmers, L., Boons, C.C., Verbrugghe, M., van den Bemt, B.J., Van Hecke, A., & Hugtenburg, J.G. (2017). Supporting adherence to oral anticancer agents: Clinical practice and clues to improve care provided by physicians, nurse practitioners, nurses and pharmacists. *BMC Cancer, 17*, 122. doi:10.1186/s12885-017-3110-2

van Zeijl, M.C., van den Eertwegh, A.J., Haanen, J.B., & Wouters, M.W. (2017). (Neo)adjuvant systemic therapy for melanoma. *European Journal of Surgical Oncology, 43*, 534–543. doi:10.1016/j.ejso.2016.07.001

Vanneste, L., Wolter, P., Van den Oord, J.J., Stas, M., & Garmyn, M. (2015). Cutaneous adverse effects of BRAF inhibitors in metastatic malignant melanoma, a prospective study in 20 patients. *Journal of the European Academy of Dermatology and Venereology, 29*, 61–68. doi:10.1111/jdv.12449

Weingart, S.N., Brown, E., Bach, P.B., Eng, K., Johnson, S.A., Kuzel, T.M., . . . Walters, R.S. (2008). NCCN Task Force Report: Oral chemotherapy. *Journal of the National Comprehensive Cancer Network, 6*(Suppl. 3), S1–S14.

Welsh, S.J., & Corrie, P.G. (2015). Management of BRAF and MEK inhibitor toxicities in patients with metastatic melanoma. *Therapeutic Advances in Medical Oncology, 7*, 122–136. doi:10.1177/1758834014566428

Winn, A.N., Keating, N.L., & Dusetzina, S.B. (2016). Factors associated with tyrosine kinase inhibitor initiation and adherence among medicare beneficiaries with chronic myeloid leukemia. *Journal of Clinical Oncology, 34*, 4323–4328. doi:10.1200/jco.2016.67.4184

Zafar, S.Y., Peppercorn, J.M., Schrag, D., Taylor, D.H., Goetzinger, A.M., Zhong, X., & Abernethy, A.P. (2013). The financial toxicity of cancer treatment: A pilot study assessing out-of-pocket expenses and the insured cancer patient's experience. *Oncologist, 18,* 381–390. doi:10.1634/theoncologist.2012-0279