CDK4/6 Inhibitors: Game Changers in HR+ Breast Cancer?

Mirat Shah, Maria Raquel Nunes, Vered Stearns

Checkpoint Inhibitor Combos in Melanoma: The Issues

Allison Betof Warner, Michael A. Postow

POINT/COUNTERPOINT
Chemotherapy vs Abiraterone for New Metastatic Prostate Cancer

Pedro Isaacsson Velho & Mario Eisenberger vs Robert J. Jones

Published in affiliation with
Integrative Oncology
**Indication**

Metastatic Breast Cancer

HALAVEN (eribulin mesylate) Injection is indicated for the treatment of patients with metastatic breast cancer (mBC) who have previously received at least 2 chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting.

**Selected Safety Information**

**Neutropenia:** Severe neutropenia (ANC <500/mm³) lasting >1 week occurred in 12% of patients with mBC. Febrile neutropenia occurred in 5% of patients with mBC and 2 patients (0.4%) died from complications. Patients with mBC with elevated liver enzymes >3 × ULN and bilirubin >1.5 × ULN experienced a higher incidence of Grade 4 neutropenia and febrile neutropenia than patients with normal levels. Monitor complete blood cell counts prior to each dose, and increase the frequency of monitoring in patients who develop Grade 3 or 4 cytopenias. Delay administration and reduce subsequent doses in patients who experience febrile neutropenia or Grade 4 neutropenia lasting >7 days.

**Peripheral Neuropathy:** Grade 3 peripheral neuropathy occurred in 8% of patients with mBC (Grade 4=0.4%) and 22% developed a new or worsening neuropathy that had not recovered within a median follow-up duration of 269 days (range 25-662 days). Neuropathy lasting >1 year occurred in 5% of patients with mBC. Patients should be monitored for signs of peripheral motor and sensory neuropathy. Withhold HALAVEN in patients who experience Grade 3 or 4 peripheral neuropathy until resolution to Grade 2 or less.

**Embryo-Fetal Toxicity:** HALAVEN can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with HALAVEN and for at least 2 weeks following the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with HALAVEN and for 3.5 months following the final dose.

**QT Prolongation:** Monitor for prolonged QT intervals in patients with congestive heart failure, bradyarrhythmias, drugs known to prolong the QT interval, and electrolyte abnormalities. Correct hypokalemia or hypomagnesemia prior to initiating HALAVEN and monitor these electrolytes periodically during therapy. Avoid in patients with congenital long QT syndrome.

From the Phase III, randomized, open-label, multicenter, multinational Eisai Metastatic Breast Cancer Study Assessing Physician’s Choice versus E7389 (Eribulin) (EMBRACE) trial of HALAVEN versus TPC in patients with mBC (N=762). Primary endpoint was OS.\(^1\)\(^4\)

**Results of the updated analysis, conducted when 77% of events (deaths) had been observed, were consistent with the primary analysis,** which was conducted when ~50% of events (deaths) had been observed. HALAVEN demonstrated a median OS of 13.1 months (95% CI: 11.8, 14.3, 274 deaths) vs 10.6 months with the TPC arm (95% CI: 9.3, 12.5, 148 deaths), hazard ratio (HR)=0.81 (95% CI: 0.66, 0.99) (P=0.041).\(^1\)\(^4\)

**OS=overall survival; CI=confidence interval.**

Please see Selected Safety Information continued on the following page and adjacent brief summary of HALAVEN full Prescribing Information.
HALAVEN® offers a meaningful survival benefit and an established safety profile4

HALAVEN is for patients with mBC
HALAVEN may be appropriate for your patients who are ready for chemotherapy in third-line mBC and who have received 2 prior chemotherapies for mBC. Their previous treatment should have included an anthracycline and a taxane in the adjuvant or metastatic setting.4

Patients in the HALAVEN arm of the EMBRACE trial:

A growing body of real-world experience

Number of patients at risk at measured timepoints were as follows3:

- HALAVEN arm: n=508 (month 0), 406 (month 6), 274 (month 12), 142 (month 18), 54 (month 24), 11 (month 30), and 0 (month 36)
- TPC arm: n=254 (month 0), 178 (month 6), 106 (month 12), 61 (month 18), 26 (month 24), 5 (month 30), and 0 (month 36)

NCCN®=National Comprehensive Cancer Network®.

Vist us at booth 7025

ERIBULIN (HALAVEN) IS LISTED AS A PREFERRED SINGLE AGENT FOR mBC IN THE NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY (NCCN GUIDELINES)®

Selected Safety Information

Adverse Reactions
In patients with mBC receiving HALAVEN, the most common adverse reactions (≥25%) were neutropenia (82%), anemia (58%), asthenia/fatigue (54%), alopecia (45%), peripheral neuropathy (35%), nausea (35%), and constipation (25%). Febrile neutropenia (4%) and neutropenia (2%) were the most common serious adverse reactions. The most common adverse reaction resulting in discontinuation was peripheral neuropathy (5%).

Use in Specific Populations

Lactation: Because of the potential for serious adverse reactions in breastfed infants from eribulin mesylate, advise women not to breastfeed during treatment with HALAVEN and for 2 weeks after the final dose.

Hepatic and Renal Impairment: A reduction in starting dose is recommended for patients with mild or moderate hepatic impairment and/or moderate or severe renal impairment.

References:
HALAVEN® (eribulin mesylate) Injection, for intravenous use

BRIEF SUMMARY – See package insert for full prescribing information.

DOSAGE AND ADMINISTRATION

Recommended Dose: The recommended dose of HALAVEN is 1.4 mg/m² administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle.

In patients with mild hepatic impairment (Child-Pugh A) it is 1.1 mg/m² administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle.

The recommended dose of HALAVEN in patients with moderate hepatic impairment (Child-Pugh B) is 0.7 mg/m² administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle.

The recommended dose of HALAVEN in patients with moderate or severe renal impairment (creatinine clearance (ClCr) 15-49 mL/min) is 1.1 mg/m² administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle.

Dose Modification: Access for peripheral neuropathy and obtain complete blood cell counts prior to each dose.

Recommended dose reductions

- Do not administer HALAVEN on Day 1 or Day 8 for any of the following: • ANC < 1000/mm³ • Platelets < 75,000/mm³
- Grade 3 or 4 non-hematological toxicities.
- The Day 8 dose may be delayed for a maximum of 1 week.
- If toxicities do not resolve or improve to ≤ Grade 2 severity by Day 15, omit the dose.
- If toxicities resolve or improve to ≤ Grade 2 severity by Day 15, administer HALAVEN at a reduced dose and initiate the next cycle no sooner than 2 weeks later.

Recommended dose reductions

- If a dose has been delayed for toxicity and toxicities have recovered to Grade 2 severity or less, resume HALAVEN at the reduced dose as set out in Table 1.
- Do not re-scale HALAVEN dose after it has been reduced.

Table 1: Recommended Dose Reductions

<table>
<thead>
<tr>
<th>Event Description</th>
<th>Recommended HALAVEN Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permanently reduce the 1.4 mg/m² HALAVEN dose for any of the following:</td>
<td></td>
</tr>
<tr>
<td>• ANC &lt; 1000/mm³ for ≥ 7 days</td>
<td>Discontinue HALAVEN</td>
</tr>
<tr>
<td>• ANC &lt; 1000/mm³ with fever or infection</td>
<td>Discontinue HALAVEN</td>
</tr>
<tr>
<td>• Platelets &lt; 25,000/mm³</td>
<td>Discontinue HALAVEN</td>
</tr>
<tr>
<td>• Pain ≥ 7 (upper limit of normal)</td>
<td>Discontinue HALAVEN</td>
</tr>
<tr>
<td>• Non-hematological Grade 4 toxicities</td>
<td>Discontinue HALAVEN</td>
</tr>
<tr>
<td>• Omission or delay of Day 8 HALAVEN dose in previous cycle for toxicity</td>
<td>Discontinue HALAVEN</td>
</tr>
<tr>
<td>Occurrence of any event requiring permanent dose reduction</td>
<td>Discontinue HALAVEN</td>
</tr>
<tr>
<td>Occurrence of any event requiring permanent dose reduction while receiving 0.7 mg/m²</td>
<td>Discontinue HALAVEN</td>
</tr>
</tbody>
</table>

Teratogenicity: In animal reproduction studies, HALAVEN has been administered to 1963 pregnant women including 467 patients exposed to HALAVEN for 8 months or longer. The majority of the 1963 patients were women (92%) with a median age of 55 years (range: 17 to 85 years). The racial and ethnic distribution was White (72%), Black (4%), Asian (9%), and other (3%).

Metastatic Breast Cancer: The most common adverse reactions (>25%) reported in patients receiving HALAVEN were neutropenia, anemia, asthenia/fatigue, alopecia, peripheral neuropathy, nausea, and constipation. The most common adverse reactions reported in patients receiving HALAVEN were febrile neutropenia (4%) and neutropenia (2%). The most common adverse reactions occurring in >10% of patients receiving HALAVEN was peripheral neuropathy (5%).

The most common adverse reactions reported in Table 2 were identified in 756 patients treated in Study 1. In Study 1, patients were randomized (2:1) to receive either HALAVEN (1.4 mg/m² on Days 1 and 8 of a 21-day cycle) or single agent treatment chosen by their physician (control group). A total of 563 patients received HALAVEN and 247 patients in the control group received therapy consisting of chemotherapy [total 97% (anthracyclines 16%, capecitabine 16%, gemcitabine 19%, taxanes 15%, vinorelbine 25%, other chemotherapies 16%) or hormonal therapy (3%). The median duration of exposure was 118 days for patients receiving HALAVEN and 63 days for patients receiving control therapy. Table 2 reports the most common adverse reactions occurring in at least 10% of patients in either group.

Table 2: Adverse Reactions* with a Per-Patient Incidence of at Least 10% in Study 1

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Control Group</th>
<th>HALAVEN</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>82%</td>
<td>57%</td>
<td>53%</td>
</tr>
<tr>
<td>Anemia</td>
<td>38%</td>
<td>2%</td>
<td>5%</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy head</td>
<td>35%</td>
<td>6%</td>
<td>16%</td>
</tr>
<tr>
<td>Headache</td>
<td>19%</td>
<td>&lt;1%</td>
<td>12%</td>
</tr>
<tr>
<td>General disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>14%</td>
<td>10%</td>
<td>11%</td>
</tr>
<tr>
<td>Pain</td>
<td>21%</td>
<td>2%</td>
<td>23%</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>9%</td>
<td>1%</td>
<td>10%</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>4%</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>45%</td>
<td>NA</td>
<td>10%</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>10%</td>
<td>1%</td>
<td>5%</td>
</tr>
</tbody>
</table>

* adverse reactions were graded per National Cancer Institute Criteria for Adverse Events version 4.0. * based upon laboratory data. * includes peripheral neuropathy, peripheral sensorimotor neuropathy, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, and paresthesia. * not applicable; (grading system does not specify > Grade 2 for alopecia).

No adverse reactions were considered to be causally related to the death of 2 patients receiving placebo. Infections were the most common serious adverse reaction reported in HALAVEN-treated patients, occurring in 5% (10%) of patients treated with HALAVEN and 247 patients in the control group receiving control therapy.

ADVERSE REACTIONS

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in clinical practice. The following adverse reactions are discussed in detail in other sections of the labeling:

- Neutropenia
- Peripheral neuropathy
- Anemia
- Arthralgia
- Headache
- Nausea
- Vomiting
- Peripheral sensory neuropathy
- Alopecia
- Asthenia
- Anorexia
- Dyspnea
- Urinary tract infection
- Skin and subcutaneous tissue disorders
- Infections

Less Common Adverse Reactions: The following additional adverse reactions were reported in <1% to <10% of the HALAVEN-treated group:

- Eye Disorders: increased intraocular pressure
- Gastrointestinal Disorders: dyspepsia, abdominal pain, constipation, diarrhea, dyspepsia, abdominal pain, nausea, vomiting, diarrhea
- General Disorders and Administration Site Conditions: peripheral edema, subcutaneous edema, injection site reaction, injection site induration, injection site inflammation
- Metabolic and Nutrition Disorders: hypokalemia
- Musculoskeletal and Connective Tissue Disorders: muscle spasms
- Nervous System Disorders: dizziness, dysesthesia
- Psychiatric Disorders: insomnia, depression
- Skin and Subcutaneous Tissue Disorders: rash

In an uncontrolled open-label ECG study in 26 patients, QT prolongation was observed on Day 8, independent of eribulin concentration, with no QT prolongation observed on Days 1 and 8. ECG monitoring is recommended if therapy is initiated in patients with congestive heart failure, bradyarrhythmias, drugs known to prolong the QT interval, including Class la and III antiarrhythmics, and electrolyte abnormalities. Correct hypokalemia or hypomagnesemia prior to initiating HALAVEN and administer these electrolytes periodically during therapy. Avoid HALAVEN in patients with congenital long QT syndrome.
Liposarcoma: The safety of HALAVEN was evaluated in Study 2, an open-label, randomized, multicenter, adaptive-controlled trial, in which patients were randomized (1:1) to receive either HALAVEN 1.4 mg/m² on Days 1 and 8 of a 21-day cycle or dacarbazine at doses of 650 mg/m² (20%), 1000 mg/m² (40%), or 1200 mg/m² (40%) every 3 weeks. A total of 222 patients received HALAVEN and 221 patients received dacarbazine. Patients were required to have received at least two prior systemic chemotherapeutic regimens. The trial excluded patients with pre-existing ≥ Grade 3 peripheral neuropathy, known central nervous system metastases, evidence of skin ulceration or significant chronic liver disease, history of myocardial infarction within 6 months, history of New York Heart Association Class III or IV heart failure, or cardiac arrhythmia requiring treatment. The median age of the safety population in Study 2 was 56 years (range 24 to 83 years; 67% female; 73% White; 3% Black or African American, 8% Asian/Pacific Islander, and 15% unknown; 99% received prior anthracycline-containing regimen; and 39% received ≥ 2 prior regimens. The median duration of exposure was 2.3 months (range 21 days to 26 months) for patients receiving HALAVEN.

The most common adverse reactions (≥25%) reported in patients receiving HALAVEN were fatigue, nausea, alopecia, constipation, peripheral neuropathy, and pyrexia. The most common (≥5%) Grade 3-4 laboratory abnormalities reported in patients receiving HALAVEN were neutropenia, hypokalemia, and hyponatremia. The most common serious adverse reactions reported in patients receiving HALAVEN were neutropenia (4.9%) and pyrexia (4.5%). Permanent discontinuation of HALAVEN due to adverse reactions occurred in 9% of patients. The most common adverse reactions resulting in discontinuation of HALAVEN were fatigue and thrombocytopenia (0.9%). Twenty-six percent of patients required at least one dose reduction. The most frequent adverse reactions that led to dose reduction were neutropenia (18%) and peripheral neuropathy (6%).

Table 3 summarizes the incidence of adverse reactions occurring in at least 10% of patients in the HALAVEN-treated arm in Study 2.

### Table 3: Adverse Reactions Occurring in ≥10% (All Grades) of Patients Treated on the HALAVEN arm and at a Higher Incidence than in the Dacarbazine Arm (Between Arm Difference of ≥5% for All Grades or ≥2% for Grades 3 and 4) (Study 2)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>HALAVEN</th>
<th>Dacarbazine</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall nausea and vomiting</td>
<td>11%</td>
<td>3%</td>
<td>0.001</td>
</tr>
<tr>
<td>Headache</td>
<td>18%</td>
<td>10%</td>
<td>0.012</td>
</tr>
<tr>
<td>General disorders</td>
<td>13%</td>
<td>14%</td>
<td>0.647</td>
</tr>
<tr>
<td>Nausea</td>
<td>22%</td>
<td>9%</td>
<td>0.0001</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15%</td>
<td>14%</td>
<td>0.453</td>
</tr>
<tr>
<td>Alopecia</td>
<td>5%</td>
<td>2%</td>
<td>0.014</td>
</tr>
<tr>
<td>Infections</td>
<td>11%</td>
<td>5%</td>
<td>0.043</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>11%</td>
<td>2%</td>
<td>0.014</td>
</tr>
</tbody>
</table>

Other clinically important adverse reactions occurring in ≥10% of the HALAVEN-treated patients were:

- **Gastrointestinal Disorders:** Nausea (41%) vomiting (19%), diarrhea (17%)
- **General Disorders:** asthenia (fatigue) (62%) peripheral edema (12%)
- **Metabolism and Nutrition Disorders:** decreased appetite (19%)
- **Musculoskeletal and Connective Tissue Disorders:** arthralgia/myalgia (16%), back pain (16%)
- **Respiratory Disorders:** cough (18%)

Less Common Adverse Reactions: The following additional clinically important adverse reactions were reported in ≥5% to <10% of the HALAVEN-treated group:

- **Blood and Lymphatic System Disorders:** thrombocytopenia
- **Eye Disorders:** cataracts
- **Gastrointestinal Disorders:** dyspepsia
- **Metabolism and Nutrition Disorders:** hyperglycemia
- **Musculoskeletal and Connective Tissue Disorders:** muscle spasms, musculoskeletal pain
- **Nervous System Disorders:** dizziness, dysgeusia
- **Psychiatric Disorders:** insomnia, anxiety
- **Respiratory, Thoracic, and Mediastinal Disorders:** oropharyngeal pain
- **Vascular Disorders:** hypertension

### Table 4: Laboratory Abnormalities Occurring in ≥10% (All Grades) of Patients Treated on the HALAVEN arm and at a Higher Incidence than in the Dacarbazine Arm (Between Arm Difference of ≥5% for All Grades or ≥2% for Grades 3 and 4) (Study 2)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>HALAVEN</th>
<th>Dacarbazine</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>75%</td>
<td>45%</td>
<td>0.012</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>63%</td>
<td>52%</td>
<td>0.004</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>43%</td>
<td>23%</td>
<td>0.003</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase (AST)</td>
<td>43%</td>
<td>18%</td>
<td>0.003</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>35%</td>
<td>14%</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>28%</td>
<td>13%</td>
<td>0.453</td>
</tr>
</tbody>
</table>

*Each test incidence is based on the number of patients who had both baseline and at least one on-study measurement and at least 1 grade increase from baseline.HALAVEN group (range 221-222) and dacarbazine group (range 214-215). Laboratory results were graded per NCIC CTCAE v4.03.

Postmarketing Experience: The following adverse drug reactions have been identified during post-approval of HALAVEN. Because these reactions are reported voluntarily from a population of unknowable size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- **Hematologic and Lymphatic System Disorders:** lymphopenia
- **Gastrointestinal Disorders:** pancreatitis
- **Hepatobiliary Disorders:** hepatotoxicity
- **Immune System Disorders:** drug hypersensitivity
- **Infections and Infections: Staphylococcal infection**
- **Metabolism and Nutrition Disorders:** hypoglycemia, dehydration
- **Respiratory, Thoracic and Mediastinal Disorders:** interstitial lung disease

**Skin and Subcutaneous Tissue Disorders:** pruritus, Stevens-Johnson syndrome, toxic epidermal necrolysis

### USE IN SPECIFIC POPULATIONS

**Pregnancy**

Risk Summary: Based on findings from an animal reproduction study and its mechanism of action, HALAVEN can cause fetal harm when administered to a pregnant woman. There are no available data on the use of HALAVEN during human pregnancy. In an animal reproduction study, eribulin mesylate caused embryo-fetal toxicity when administered to pregnant rats during organogenesis at doses below the recommended human dose. Advise pregnant women of the potential risk to a fetus. The estimated background risks of major birth defects and miscarriage for the indicated populations are unknown. In clinical trials, the estimated background risk of major birth defects and miscarriage in clinically-recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

**Data**

In an embryo-fetal developmental toxicity study, pregnant rats received intravenous infusion of eribulin mesylate during organogenesis (Gestation Days 8, 10, and 12) at doses approximately 0.4, 0.13, 0.43 and 0.64 times the recommended human dose, based on body surface area. Increased embryo-fetal death/resorption, reduced fetal weights, and minor skeletal anomalies consistent with developmental delay were also reported at doses of 0.64 times the recommended human dose.

**Females and Males of Reproductive Potential**

**Contraception**

Females: Based on findings from an animal reproduction study and its mechanism of action, HALAVEN can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with HALAVEN and for at least 2 weeks following the final dose.

Males: Based on its mechanism of action, advise males with female partners of reproductive potential to use effective contraception during treatment with HALAVEN and for 3.5 months following the final dose.

**Infertility**

Males: Based on animal data, HALAVEN may result in damage to male reproductive tissues leading to impaired fertility of unknown duration.

**Pediatric Use:** The safety and effectiveness of HALAVEN in pediatric patients below the age of 18 years have not been established.

**Hepatic Impairment:** Administration of HALAVEN at a dose of 1.1 mg/m² to patients with mild hepatic impairment and 0.7 mg/m² to patients with moderate hepatic impairment resulted in similar exposure to eribulin as a dose of 1.4 mg/m² to patients with normal hepatic function. Therefore, a lower starting dose of 1.1 mg/m² is recommended for patients with mild hepatic impairment (Child-Pugh A) and of 0.7 mg/m² for patients with moderate hepatic impairment (Child-Pugh B). HALAVEN was not studied in patients with severe hepatic impairment (Child-Pugh C).

**Renal Impairment:** For patients with moderate or severe renal impairment (Ccr <15 mL/min), reduce the starting dose to 1.1 mg/m².

**OVERDOSAGE**

Overdosage of HALAVEN has been reported at approximately 4 times the recommended dose, which resulted in Grade 3 neutropenia lasting seven days and a Grade 3 hypersensitivity reaction lasting one day.

There is no known antidote for HALAVEN overdose.

**NONCLINICAL TOXICOLOGY**

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Carcinogenicity studies have not been conducted with eribulin mesylate. Eribulin mesylate was not mutagenic in in vitro bacterial reverse mutation assays (Ames test). Eribulin mesylate was positive in mouse lymphoma mutagenesis assays, and was clastogenic in an in vivo bone marrow micronucleus assay.

Fertility studies have not been conducted with eribulin mesylate in humans or animals; however, nonclinical findings in repeat-dose dog and rat toxicology studies suggest that male fertility may be compromised by treatment with eribulin mesylate. Rate exhibited teratogenicity (hypoplasia of seminiferous epithelium with hypospermiain/aspermia) following dosing with eribulin mesylate at or above 0.43 times the recommended human dose (based on body surface area) given once weekly for 3 weeks, or at or above 0.21 times the recommended human dose (based on body surface area) given once weekly for 3 out of 5 weeks, repeated for 6 cycles. Teratogenicity was also observed in dogs given 0.64 times the recommended human dose (based on body surface area) weekly for 3 out of 5 weeks, repeated for 6 cycles.

**Pregnancy Risk Summary:** Based on findings from an animal reproduction study and its mechanism of action, HALAVEN can cause fetal harm when administered to a pregnant woman. Advise pregnant women of reproductive potential to use effective contraception during treatment with HALAVEN and for at least 2 weeks after the final dose.

**Advises Women not to breastfeed during treatment with HALAVEN and for 2 weeks after the final dose.

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AVP, Merck Oncology Clinical Research

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INDICATION
ERLEADA™ (apalutamide) is an androgen receptor inhibitor indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer.

IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS
Pregnancy—ERLEADA™ can cause fetal harm and potential loss of pregnancy.

WARNINGS AND PRECAUTIONS
Falls and Fractures—In a randomized study (SPARTAN), falls and fractures occurred in 16% and 12% of patients treated with ERLEADA™ compared to 9% and 7% treated with placebo, respectively. Falls were not associated with loss of consciousness or seizure. Evaluate patients for fracture and fall risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone targeted agents.

Seizure—In a randomized study (SPARTAN), 2 patients (0.2%) treated with ERLEADA™ experienced a seizure. Permanently discontinue ERLEADA™ in patients who develop a seizure during treatment. It is unknown whether anti-epileptic medications will prevent seizures with ERLEADA™. Advise patients of the risk of developing a seizure while receiving ERLEADA™ and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others.

ADVERSE REACTIONS
Adverse Reactions—The most common adverse reactions (≥10%) were fatigue, hypertension, rash, diarrhea, nausea, weight decreased, arthralgia, fall, hot flush, decreased appetite, fracture, and peripheral edema.

Laboratory Abnormalities—All Grades (Grade 3-4)
• Hematology—anemia ERLEADA™ 70% (0.4%), platelet 64% (0.5%); leukopenia ERLEADA™ 47% (0.3%); platelet 29% (0.6%); lymphopenia ERLEADA™ 41% (2%), platelet 21% (2%)
• Chemistry—hypercholesterolemia ERLEADA™ 76% (0.1%), placebo 46% (0.6%); hyperglycemia ERLEADA™ 70% (2%), placebo 55% (1%); hypertriglyceridemia ERLEADA™ 67% (2%), placebo 49% (0.8%); hyperkalemia ERLEADA™ 32% (2%), placebo 22% (0.5%)

Rash—was most commonly described as macular or maculo-papular. Adverse reactions were 24% with ERLEADA™ versus 6% with placebo. Grade 3 rash (defined as covering >30% body surface area [BSA]) was reported with ERLEADA™ treatment (5%) versus placebo (0.3%). The onset of rash occurred at a median of 82 days. Rash resolved in 81% of patients within a median of 60 days (range: 2 to 709 days) from onset of rash. Four percent of patients treated with ERLEADA™ received systemic corticosteroids. Rash occurred in approximately half of patients who were re-challenged with ERLEADA™.

Hyperthyroidism was reported for 8% of patients treated with ERLEADA™ and 2% of patients treated with placebo based on assessments of thyroid-stimulating hormone (TSH) every 4 months. Elevated TSH occurred in 50% of patients treated with ERLEADA™ and 7% of patients treated with placebo. The median onset was day 113. There were no Grade 3 or 4 adverse reactions. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted.

DRUG INTERACTIONS
Effect of Other Drugs on ERLEADA™
Co-administration of a strong CYP2C8 or CYP3A4 inhibitor is predicted to increase the steady-state exposure of the active moieties. No initial dose adjustment is necessary; however, reduce the ERLEADA™ dose based on tolerability (see Dosage and Administration (2.2)).

Effect of ERLEADA™ on Other Drugs—ERLEADA™ is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9 in humans. Concomitant use of ERLEADA™ with medications that are primarily metabolized by CYP3A4, CYP2C19, or CYP2C9 can result in lower exposure to these medications. Substitution for these medications is recommended when possible, or evaluate for loss of activity if medication is continued. Concomitant administration of ERLEADA™ with medications that are substrates of UDP-glucuronosyl transferase (UGT) can result in decreased exposure. Use caution if substrates of UGT must be co-administered with ERLEADA™ and evaluate for loss of activity.

P-gp, BCRP, or OATP1B1 Substrates—Apalutamide is a weak inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (OATP1B1) clinically. Concomitant use of ERLEADA™ with medications that are substrates of P-gp, BCRP, or OATP1B1 can result in lower exposure of these medications. Use caution if substrates of P-gp, BCRP, or OATP1B1 must be co-administered with ERLEADA™ and evaluate for loss of activity if medication is continued.

*PSA doubling time ≤10 months.

Study Design: SPARTAN was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial of patients with non-metastatic CRPC (N=1,007). Patients had a PSA doubling time ≤10 months and serum testosterone levels ≤50 ng/dL. All patients in the SPARTAN trial received a concomitant GnRH analog or had a bilateral orchectomy. All patients enrolled were confirmed to be non-metastatic by blinded central imaging review. Patients were randomized 2:1 to receive ERLEADA™ 240 mg orally once daily + ADT or placebo orally once daily + ADT. The primary endpoint was metastasis-free survival (MFS), defined as the time from randomization to the time of first evidence of blinded independent central review-confirmed distant metastasis, defined as new bone or soft tissue lesions or enlarged lymph nodes above the iliac bifurcation, or death due to any cause, whichever occurred first.1

ADT = androgen-deprivation therapy; CRPC = castration-resistant prostate cancer; GnRH = gonadotropin-releasing hormone; HR = hazard ratio.


Please see brief summary of full Prescribing Information for ERLEADA™ on subsequent pages.

Janssen Biotech, Inc.
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Brief Summary of Prescribing Information for ERLEADA™ (apalutamide)

ERLEADA™ (apalutamide) tablets, for oral use

See package insert for Full Prescribing Information

INDICATIONS AND USAGE

ERLEADA is indicated for the treatment of patients with non-metastatic, castration-resistant prostate cancer (NM-CRPC).

CONTRAINDICATIONS

Pregnancy

ERLEADA can cause fetal harm and potential loss of pregnancy [see Use in Specific Populations].

WARNINGS AND PRECAUTIONS

Falls and Fractures

Falls and fractures occurred in patients receiving ERLEADA. Evaluate patients for fracture and fall risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone targeted agents.

In a randomized study (SPARTAN), falls occurred in 18% of patients treated with ERLEADA compared to 5% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure. Fractures occurred in 12% of patients treated with ERLEADA and in 7% of patients treated with placebo. Grade 3–4 fractures occurred in 3% of patients treated with ERLEADA and in 1% of patients treated with placebo. The median time to onset of fracture was 314 days (range: 20 to 953 days) for patients treated with ERLEADA. Routine bone density assessment and treatment of osteoporosis with bone targeted agents were not performed in the SPARTAN study.

Seizure

Seizure occurred in patients receiving ERLEADA. Permanently discontinue ERLEADA in patients who develop a seizure during treatment. It is unknown whether anti-epileptic medications will prevent seizures with ERLEADA. Advise patients of the risk of developing a seizure while receiving ERLEADA and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others.

In a randomized study (SPARTAN), two patients (0.2%) treated with ERLEADA experienced a seizure. Seizure occurred from 354 to 475 days after initiation of ERLEADA. No seizures occurred in patients treated with placebo. Patients with a history of seizure, predisposing factors for seizure or receiving drugs known to decrease the seizure threshold or to induce seizures were excluded. There is no clinical experience in re-administering ERLEADA to patients who experienced a seizure.

ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:

• Falls and Fractures [see Warnings and Precautions].
• Seizure [see Warnings and Precautions].

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

SPARTAN, a randomized (2:1), double-blind, placebo-controlled, multicenter clinical study, enrolled patients who had non-metastatic, castration-resistant prostate cancer (NM-CRPC). In this study, patients received either ERLEADA at a dose of 240 mg daily or a placebo. All patients in the SPARTAN study received a concomitant gonadotropin-releasing hormone ( GnRH) analog or had a bilateral orchietomy. The median duration of exposure was 16.9 months (range: 0.1 to 42 months) in patients who received ERLEADA and 11.2 months (range: 0.1 to 37 months) in patients who received placebo.

Overall, 8 patients (1%) who were treated with ERLEADA died from adverse reactions. The reasons for death were infection (n=4), myocardial infarction (n=3), and cerebral hemorrhage (n=1). One patient (0.3%) treated with placebo died from an adverse reaction of cardiac pulmonary arrest (n=1). ERLEADA was discontinued due to adverse reactions in 11% of patients, most commonly from rash (3%). Adverse reactions leading to dose interruption or reduction of ERLEADA occurred in 33% of patients; the most common (<1%) were rash, diarrhoea, fatigue, nausea, vomiting, hypertension, and hematoma. Serious adverse reactions occurred in 25% of ERLEADA-treated patients and 22% in patients receiving placebo. The most common serious adverse reactions (>2%) were fracture (3%) in the ERLEADA arm and urinary retention (4%) in the placebo arm.

Table 1 shows adverse reactions occurring in ≥10% on the ERLEADA arm in SPARTAN that occurred with a 2% absolute increase in frequency compared to placebo. Table 2 shows laboratory abnormalities that occurred in ≥1% of patients, and more frequently (>5%) in the ERLEADA arm compared to placebo.
**DRUG INTERACTIONS**

**Effect of Other Drugs on ERLEADA**

Strong CYP2C8 or CYP3A4 Inhibitors

Co-administration of a strong CYP2C8 or CYP3A4 inhibitor is predicted to increase the steady-state exposure of the active moieties (sum of unbound apalutamide plus the potency-adjusted unbound N-desmethyl-apalutamide). No initial dose adjustment is necessary however, reduce the ERLEADA dose based on tolerability (see Clinical Pharmacology (12.3) in Full Prescribing Information). Mild or moderate inhibitors of CYP2C8 or CYP3A4 are not expected to affect the exposure of apalutamide.

**Effect of ERLEADA on Other Drugs**

CYP3A4, CYP2C9, CYP2C19, and UGT Substrates

ERLEADA is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9 in humans. Concomitant use of ERLEADA with medications that are primarily metabolized by CYP3A4, CYP2C19, or CYP2C9 can result in lower exposure to these medications. Substitution for these medications is recommended when possible or evaluate for loss of activity if medication is continued. Concomitant administration of ERLEADA with medications that are substrates of UDP-glucuronosyl transferase (UGT) can result in decreased exposure. Use caution if substrates of UGT must be co-administered with ERLEADA and evaluate for loss of activity (see Clinical Pharmacology (12.3) in Full Prescribing Information).

**P-gp, BCRP or OATP1B1 Substrates**

Apalutamide is shown to be a weak inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (OATP1B1) clinically. At steady-state, apalutamide reduced the plasma exposure to fexofenadine (a P-gp substrate) and rosuvastatin (a BCRP/OA TP1B1 substrate). Concomitant use of ERLEADA with medications that are substrates of P-gp, BCRP, or OATP1B1 can result in lower exposure of these medications. Use caution if substrates of P-gp, BCRP or OATP1B1 must be co-administered with ERLEADA and evaluate for loss of activity if medication is continued (see Clinical Pharmacology (12.3) in Full Prescribing Information).

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary**

ERLEADA is contraindicated for use in pregnant women because the drug can cause fetal harm and potential loss of pregnancy. ERLEADA is not indicated for use in females, so animal embryo-fetal developmental toxicology studies were not conducted with apalutamide. There are no human data on the use of ERLEADA in pregnant women. Based on its mechanism of action, ERLEADA may cause fetal harm when administered during pregnancy.

**Lactation**

**Risk Summary**

ERLEADA is not indicated for use in females. There are no data on the presence of apalutamide or its metabolites in human milk, the effect on the breastfed child, or the effect on milk production.

**Females and Males of Reproductive Potential**

**Contraception**

**Males**

Based on the mechanism of action and findings in an animal reproduction study, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA. (see Use in Specific Populations).
CDK4/6 Inhibitors: Game Changers in the Management of Hormone Receptor–Positive Advanced Breast Cancer?

Mirat Shah, MD\(^1\), Maria Raquel Nunes, MD\(^2\), Vered Stearns, MD\(^3,4\)

ABSTRACT: The cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors palbociclib, ribociclib, and abemaciclib are rapidly transforming the care of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (HR+/HER2−) advanced breast cancer. Current clinical questions include how to choose among these agents and how to sequence them with other therapies. Areas of active inquiry include identifying predictive biomarkers for CDK4/6 inhibitors, deciding whether to continue CDK4/6 inhibitors after disease progression, creating novel treatment combinations, and expanding use beyond HR+/HER2− advanced breast cancer. Here, we review the current use of and potential next directions for CDK4/6 inhibitors in the treatment of patients with HR+ breast cancer.

Introduction
Despite the availability of many therapies, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (HR+/HER2−) advanced breast cancer is rarely curable. The current treatment paradigm for HR+/HER2− advanced breast cancer involves sequencing endocrine therapy, targeted therapy, and/or chemotherapy to prolong patients’ lives, delay disease progression, and minimize cancer-related symptoms. The cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors are rapidly transforming this treatment landscape. There are currently three CDK4/6 inhibitors that have been approved by the US Food and Drug Administration: palbociclib, ribociclib, and abemaciclib. How to choose among these agents and how to sequence them with other therapies are currently the most pressing questions. The possibility of using biomarkers to predict response, novel treatment combinations with CDK4/6 inhibitors, and the potential activity of these agents beyond the setting of HR+/HER2− advanced breast cancer are areas of active research. We will review the current role of CDK4/6 inhibitors in the treatment of patients with HR+ breast cancer, as well as promising future applications.

Mechanism of Action of CDK4/6 Inhibitors
The CDK4/6 inhibitors act at the G1-to-S cell cycle checkpoint. This checkpoint is tightly controlled by the D-type cyclins and CDK4 and CDK6. When CDK4 and CDK6 are activated by D-type cyclins, they phosphorylate the retinoblastoma-associated protein (pRb). This suspends pRb’s suppression of the E2F transcription factor family and ultimately allows the cell to proceed through the cell cycle and divide. In HR+ breast cancer, cyclin D overexpression is common and loss of pRb is rare, making the G1-to-S checkpoint an ideal therapeutic target. The CDK4/6 inhibitors prevent progression through this checkpoint, leading to cell cycle arrest.[1]

Approved CDK4/6 Inhibitors for HR+/HER2− Advanced Breast Cancer
Table 1 summarizes the evidence from the pivotal trials that led to the FDA approvals of palbociclib, ribociclib, and abemaciclib.

Palbociclib
Palbociclib was approved for use with an aromatase inhibitor (AI) as first-line treatment of HR+/HER2− advanced breast cancer in postmenopausal women, based on the phase II study PALOMA-1/TRIO-18 and the phase III study PALOMA-2. Palbociclib was approved for use with fulvestrant as second- or later-line treatment of HR+/HER2− advanced breast cancer based on the phase III study PALOMA-3.

In PALOMA-1/TRIO-18, 165 women with HR+/HER2− untreated advanced breast cancer were randomized to receive either palbociclib and letrozole or letrozole alone. Previous treatment with an AI more than 12 months before enrollment was allowed. The study’s primary endpoint was median progression-free survival (PFS). Patients who received palbociclib and letrozole had a median PFS of 20.2 months, compared with only 10.2 months with letrozole alone (hazard ratio, 0.488; 95% CI, 0.319–0.748; \( P = .0004 \)).[2] This study led to accelerated approval of palbociclib in February 2015. Median overall survival (OS) was 37.5 months with palbociclib and letrozole and 34.5 months with letrozole alone (HR, 0.897; 95% CI, 0.623–1.294; \( P = .281 \)). This difference was not significant, but the study was not powered to show a difference in OS.[3]

In PALOMA-2, 666 treatment-naïve patients with HR+/HER2− advanced breast cancer were randomized to receive palbociclib and letrozole or placebo and letrozole. Median PFS was 24.8 months in the patients who received palbociclib and letrozole and 14.5 months in those who received placebo and letrozole (hazard ratio, 0.58; 95%
Table 1. Summary of Clinical Trial Data for CDK4/6 Inhibitors for HR+/HER2– Advanced Breast Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>Arms</th>
<th>Description</th>
<th>Median PFS Hazard Ratio (95% CI)</th>
<th>ORR</th>
<th>Median OS Hazard Ratio (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>First-line</td>
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<tr>
<td>PALOMA-1/</td>
<td>II</td>
<td>2</td>
<td>Palbociclib/letrozole vs letrozole</td>
<td>20.2 vs 10.2 mo 0.488 (0.319–0.748)</td>
<td>55.0% vs 39.0%</td>
<td>375 vs 34.5 mo 0.897 (0.623–1.294)</td>
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<tr>
<td>TRIO-18</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>PALOMA-2</td>
<td>III</td>
<td>2</td>
<td>Palbociclib/letrozole vs placebo/letrozole</td>
<td>24.8 vs 14.5 mo 0.58 (0.46–0.72)</td>
<td>55.3% vs 44.4%</td>
<td>Pending</td>
</tr>
<tr>
<td>MONALEESA-2</td>
<td>III</td>
<td>2</td>
<td>Ribociclib/letrozole vs placebo/letrozole</td>
<td>25.3 vs 16.0 mo 0.568 (0.457–0.704)</td>
<td>52.7% vs 37.1%</td>
<td>Pending</td>
</tr>
<tr>
<td>MONALEESA-7</td>
<td>III</td>
<td>2</td>
<td>Ribociclib/OFs/Al or tamoxifen vs placebo/OFs/Al or tamoxifen</td>
<td>23.8 vs 13.0 mo 0.553 (0.441–0.694)</td>
<td>51.0% vs 36.0%</td>
<td>Pending</td>
</tr>
<tr>
<td>MONARCH-3</td>
<td>III</td>
<td>2</td>
<td>Abemaciclib/Al vs placebo/Al</td>
<td>NR vs 14.7 mo 0.543 (0.409–0.723)</td>
<td>59.0% vs 44.0%</td>
<td>Pending</td>
</tr>
<tr>
<td>Second-line</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PALOMA-3</td>
<td>III</td>
<td>2</td>
<td>Palbociclib/fulvestrant vs placebo/fulvestrant</td>
<td>9.5 vs 4.6 mo 0.46 (0.36–0.59)</td>
<td>24.6% vs 15.0%</td>
<td>Unknown</td>
</tr>
<tr>
<td>MONARCH-2</td>
<td>III</td>
<td>2</td>
<td>Abemaciclib/fulvestrant vs placebo/fulvestrant</td>
<td>16.4 vs 9.3 mo 0.553 (0.449–0.681)</td>
<td>48.1% vs 21.3%</td>
<td>Pending</td>
</tr>
<tr>
<td>Later-line</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>MONARCH-1</td>
<td>II</td>
<td>1</td>
<td>Abemaciclib</td>
<td>6.0 mo</td>
<td>19.7%</td>
<td>177 mo</td>
</tr>
</tbody>
</table>

AI = aromatase inhibitor; CDK4/6 = cyclin-dependent kinase 4 and 6; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; OFS = ovarian function suppression; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.

CI, 0.46–0.72; P = .001). This led to regular approval of palbociclib in March 2017. OS data are still maturing.

In PALOMA-3, 521 women of any menopausal status with HR+/HER2– advanced breast cancer whose disease had progressed on prior endocrine therapy or recurred within 12 months of stopping adjuvant endocrine therapy were randomized to receive either palbociclib and fulvestrant or placebo and fulvestrant. Approximately half the patients had received two or more lines of endocrine therapy in the metastatic setting and approximately one-third had received chemotherapy in the metastatic setting. Final analysis demonstrated a median PFS in the palbociclib and fulvestrant group of 9.5 months, compared with 4.6 months in the placebo and fulvestrant group (hazard ratio, 0.46; 95% CI, 0.36–0.59; P < .001), which led to the approval of palbociclib in combination with fulvestrant for use after progression while receiving endocrine therapy.

Ribociclib
Ribociclib was approved in March 2017 for first-line treatment of HR+/HER2– advanced breast cancer in postmenopausal women, based on the results of the phase III MONALEESA-2 study. In this study, treatment-naïve patients with HR+/HER2– advanced breast cancer received letrozole with ribociclib or placebo. Prior AI therapy was allowed if it had been discontinued 12 months before enrollment. At the 18-month follow-up, median PFS had not been reached in the ribociclib-treated arm, compared with a median PFS of 14.7 months in the placebo group (hazard ratio, 0.56; 95% CI, 0.43–0.72; P < .001). Updated analysis showed a median PFS of 25.3 months in the ribociclib group vs 16.0 months in the placebo group. OS data are not available yet.

MONALEESA-3 is a phase III study assessing ribociclib in combination with fulvestrant for both second-line and first-line treatment of HR+/HER2– advanced breast cancer in both postmenopausal women and men. This study has completed recruitment but results are not yet available.

Abemaciclib
Abemaciclib was approved in February 2018 in combination with an AI for first-line therapy of HR+/HER2– advanced breast cancer in postmenopausal women, based on results from the MONARCH-3 study. Abemaciclib was approved in September 2017 for second- or later-line therapy in combination with fulvestrant, based on the results of MONARCH-2, and as a single agent for third- or later-line therapy for women and men, based on MONARCH-1.

MONARCH-3, a phase III study, compared an AI with abemaciclib or placebo in treatment-naïve patients with HR+/HER2– advanced breast cancer. Interim results after 18 months of follow-up demonstrated that median PFS was not reached in the abemaciclib arm, compared with a median PFS of 14.7 months in the placebo arm (hazard ratio, 0.543; 95% CI, 0.409–0.723; P < .001). Abemaciclib was approved in February 2018 in combination with an AI for first-line therapy of HR+/HER2– advanced breast cancer in postmenopausal women, based on results from the MONARCH-3 study.

Abemaciclib was approved in September 2017 for second- or later-line therapy in combination with fulvestrant, based on the results of MONARCH-2, and as a single agent for third- or later-line therapy for women and men, based on MONARCH-1.
Comparative Efficacy of CDK4/6 Inhibitors for HR+/HER2− Advanced Breast Cancer

Palbociclib, ribociclib, and abemaciclib are approved in combination with an AI for first-line therapy of HR+/HER2− advanced breast cancer. These drugs have never been directly compared and are considered equivalent in efficacy. Palbociclib and ribociclib demonstrated similar prolongations of PFS when compared with AI-only therapy in PALOMA-1/PALOMA-2 and MONALEESA-2, respectively. Data regarding abemaciclib with an AI vs an AI only are comparatively immature. Only results from 18 months of follow-up have been reported thus far; however, the hazard ratio is similar to that seen in studies with palbociclib and ribociclib, suggesting similar efficacy. All three agents are appropriate choices in combination with an AI for first-line treatment.

The safety profiles of these agents do not absolutely favor one agent over another. . . . If a patient is intolerant of one agent, it is reasonable to try another

Palbociclib and abemaciclib are both approved in combination with fulvestrant for second- or later-line treatment of HR+/HER2− advanced breast cancer, and either combination is an appropriate choice in this setting. There are no direct comparisons of these two agents and they are likely equivalent in efficacy. Of note, the patients who received abemaciclib-fulvestrant in MONARCH-2 had a much longer PFS (16.4 months) than did patients who received palbociclib-fulvestrant in PALOMA-3 (9.5 months). This likely reflects differences in the characteristics of the patient populations enrolled. The patients in MONARCH-2 had received only one prior line of endocrine therapy, and 59% had received only adjuvant or neoadjuvant endocrine therapy. No patients had received chemotherapy in the metastatic setting. In contrast, about half the patients enrolled in PALOMA-3 had received two or more lines of endocrine therapy in the metastatic setting, and about one-third had received chemotherapy in the metastatic setting, indicating a population that was more endocrine-resistant and possibly more treatment-resistant. Consequently, the median PFS for patients in the control (fulvestrant alone) arm of MONARCH-2 was much longer than for patients in the control arm of PALOMA-3 (9.3 vs 4.6 months). Ribociclib with fulvestrant will likely have activity similar to that of the palbociclib-fulvestrant and abemaciclib-fulvestrant combinations.

CDK4/6 Inhibitors in Premenopausal Women

The combination of palbociclib or ribociclib with an AI is only approved for postmenopausal women. Many providers are treating premenopausal women with a CDK4/6 inhibitor, an AI, and ovarian function suppression with gonadotropin-releasing hormone agonist, based on studies showing that an AI with ovarian suppression is efficacious for premenopausal women with HR+/HER2− advanced breast cancer.[13] Several ongoing studies specifically include premenopausal women receiving palbociclib or ribociclib and endocrine therapy with ovarian function suppression (eg, FATIMA [ClinicalTrials.gov identifier: NCT02917005], COMPLEMENT-1 [NCT02941926]).

MONALEESA-7 was the first of these trials that included premenopausal women to be reported. In this phase III study, premenopausal women with HR+/HER2− advanced breast cancer were treated with first-line ribociclib vs placebo, along with goserelin and tamoxifen or a nonsteroidal AI. The improvement in PFS seen in the ribociclib arm (23.8 vs 13.0 months [hazard ratio, 0.553; 95% CI, 0.441–0.694; P < .001]) was similar to that seen in postmenopausal women in MONALEESA-2.[14]

In PALOMA-3, premenopausal women were included and received goserelin. A subgroup analysis of the PALOMA-3 study showed that premenopausal women derived a benefit similar to that seen in the overall study population.[15] The combination of palbociclib and fulvestrant is approved regardless of menopausal status.

Safety of CDK4/6 Inhibitors

The CDK4/6 inhibitors as a class are generally well tolerated. The most common class-wide adverse effects include nausea, diarrhea, fatigue, neutropenia, leukopenia, anemia, and thrombocytopenia. Palbociclib and ribociclib most commonly cause neutropenia, while diarrhea is the most common adverse effect of abemaciclib, perhaps because of its greater affinity for CDK4 over CDK6.[16] The safety profiles of these agents do not absolutely favor one agent over another.
er, and patient-specific concerns related to toxicity should be taken into account. If a patient is intolerant of one agent, it is reasonable to try another.

Palbociclib, administered at a dosage of 125 mg daily for 3 weeks on and 1 week off, was associated with grade 3/4 neutropenia in 55% to 65% of patients across clinical studies. Febrile neutropenia occurred in only 0% to 2% of patients, and permanent discontinuation of therapy was infrequent.[4,17] Complete blood count (CBC) should be monitored frequently early in therapy, and neutropenia should be managed with appropriate dose interruption and/or dose reduction. Palbociclib-induced neutropenia occurs via a unique mechanism, in which cell cycle arrest occurs without apoptosis of hematopoietic precursor cells.[18] This unique mechanism allows rapid reversal with dose interruption and/or dose reduction, unlike with chemotherapy-induced neutropenia. Detailed safety analysis ofPALOMA-3 showed that neutropenia occurred early (median time to onset, 6 days in MONARCH-2) and was managed with antidiarrheals, followed by dose interruption and dose reduction if needed. More than 70% of the patients in MONARCH-2 who experienced diarrhea did not need dose reduction. Grade 3/4 neutropenia occurred in approximately 25% of patients across studies; this adverse effect can also be managed with dose interruption/dose reduction.

For all three agents, we recommend initiating the approved dose for most patients and then making adjustments for toxicities. Patients should be counseled that dose adjustments may be necessary but that they can still have benefit on a lower dose. Specific guidance about monitoring parameters is provided in Table 2.

### Sequencing CDK4/6 Inhibitors With Existing Therapies for HR+/HER2– Advanced Breast Cancer

There are already a number of treatment options for patients with HR+/HER2– advanced breast cancer, including the selective estrogen receptor modulator tamoxifen, nonsteroidal AIs such as anastrozole and letrozole, the selective estrogen receptor degrader fulvestrant, the steroidal AI exemestane (with or without the mammalian target of rapamycin [mTOR] inhibitor everolimus), and chemotherapy. Usually, patients receive sequential endocrine therapies until they develop resistance or experience a visceral crisis that requires chemotherapy.[20] Clinicians must now decide whether to use CDK4/6 inhibitors as part of first- or later-line therapy (approved

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose and Schedule</th>
<th>Pregnancy Test*</th>
<th>CBC and Differential</th>
<th>Liver Tests (AST, ALT, and Total Bilirubin)</th>
<th>Serum Electrolytes (K, Ca, Mg, Phos)</th>
<th>ECG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palbociclib</td>
<td>125 mg daily, 3 wk on, 1 wk off</td>
<td>Baseline</td>
<td>Baseline, every 2 wk for 2 mo, monthly for next 4 mo, then every 3 mo^2</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Ribociclib</td>
<td>600 mg daily, 3 wk on, 1 wk off</td>
<td>Baseline</td>
<td>Baseline, every 2 wk for 2 mo, monthly for 4 mo</td>
<td>Baseline, every 2 wk for 2 mo, monthly for 4 mo</td>
<td>Baseline, monthly for 6 mo</td>
<td>Baseline, day 14 of cycle 1, day 1 of cycle 2</td>
</tr>
<tr>
<td>Abemaciclib</td>
<td>150 mg twice daily OR 200 mg twice daily</td>
<td>Baseline</td>
<td>Baseline, every 2 wk for 2 mo, monthly for 2 mo</td>
<td>Baseline, every 2 wk for 2 mo, monthly for 2 mo</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

*In women of childbearing potential.

*When given with fulvestrant.

*When given alone.

^If no more than grade 1 or 2 neutropenia in the first 6 mo.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = complete blood cell count; CDK4/6 = cyclin-dependent kinase 4 and 6; ECG = electrocardiogram; NA = not applicable.
in both settings) and how to sequence therapies after progression. Clinical evidence to guide these decisions is immature or lacking.

Receiving a CDK4/6 inhibitor during any line of therapy probably confers a survival benefit compared with never receiving one. However, whether receiving a CDK4/6 inhibitor in the first line adds a survival advantage is unknown, and the OS results from PALOMA-2, MONALEESA-2, and MONARCH-3 are eagerly anticipated. Our recommendations for sequencing the CDK4/6 inhibitors with existing therapies are summarized in the Figure.

First-line endocrine therapy
We generally recommend that patients with HR+/HER2− advanced breast cancer receive a CDK4/6 inhibitor along with an AI for first-line treatment, pending OS data. CDK4/6 inhibitors are well tolerated by most women, and even without an OS benefit, a prolonged PFS may delay the onset of more severe disease symptoms and have other benefits. However, select patients with a long disease-free interval, low-volume disease, and/or bone-only disease will likely have a long progression-free interval with endocrine therapy alone. While it is possible that they would do even better with the addition of a CDK4/6 inhibitor, patients should be counseled regarding the treatment schedule for the agents being considered, the need for laboratory and other monitoring, and safety profiles.

The combination of a CDK4/6 inhibitor and an AI is efficacious even for women with visceral disease. Between 45% and 60% of patients enrolled across all first-line studies had visceral disease. In subgroup analyses, these patients derived a benefit similar to that seen in the overall study populations. The combination of a CDK4/6 inhibitor and an AI may be considered even when a rapid tumor response is needed, given its robust ORR (50% to 60% in the first line), but chemotherapy should still be used for a true visceral crisis.[21]

Second-line endocrine therapy
In patients whose disease progresses while receiving a CDK4/6 inhibitor and an AI, we recommend fulvestrant for second-line treatment, although the clinical trials showing fulvestrant’s efficacy in this setting were conducted prior to CDK4/6 inhibitor use.[22,23] Exemestane can also be considered after treatment with a CDK4/6 inhibitor and an AI, or reserved for use in the next line, along with everolimus.[24] There is currently no evidence to support continuing the same CDK4/6 inhibitor or switching to a different CDK4/6 inhibitor after progression.

Patients who received endocrine therapy only (tamoxifen or an AI) as first-line treatment should receive a CDK4/6 inhibitor–based second-line treatment, although for patients with a very long progression-free interval, endocrine therapy alone can again be considered. Those whose disease has progressed while receiving adjuvant or neoadjuvant endocrine therapy or for whom ≤ 12 months has passed since their completion of adjuvant endocrine therapy can receive a CDK4/6 inhibitor with fulvestrant upfront, since they would meet inclusion criteria for PALOMA-3 and/or MONARCH-2.

Third- and later-line endocrine therapy
For patients who received a CDK4/6 inhibitor and fulvestrant or fulvestrant alone for second-line treatment, we would recommend exemestane with the addition of everolimus in the third line, although the efficacy of this combination after receiving a CDK4/6 inhibitor with endocrine therapy is unknown.
CDK4/6 INHIBITORS FOR HR+ BREAST CANCER

KEY POINTS

- The cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors palbociclib, ribociclib, and abemaciclib are approved by the US Food and Drug Administration for first-line, second-line, and later-line treatment of patients with hormone receptor–positive/human epidermal growth factor receptor 2–negative (HR+/HER2–) advanced breast cancer.
- Efficacy data do not support the use of one agent over another; however, their safety profiles differ somewhat and may help select among agents.
- There are several options for sequencing the CDK4/6 inhibitors with other therapies for HR+/HER2– advanced breast cancer.
- Next steps for CDK4/6 inhibitors include finding predictive biomarkers beyond the estrogen receptor, determining whether to continue these agents beyond disease progression, creating novel combinations with other treatments, and using them for indications other than HR+/HER2– advanced breast cancer.

For patients who have not yet received a CDK4/6 inhibitor but who have received endocrine therapy and chemotherapy, abemaciclib as a single agent may be given, based on data from MONARCH-1. It may also be reasonable to try single-agent abemaciclib before chemotherapy for patients who have exhausted endocrine therapy, although this is different from the approved indication. We do recognize that the number of patients who reach third-or later-line therapy without receiving a CDK4/6 inhibitor will diminish over time and we do not recommend reserving therapy with a CDK4/6 inhibitor for use in this setting.

Next Directions for CDK4/6 Inhibitors

Many questions remain about integrating CDK4/6 inhibitors into clinical practice. These include whether there are biomarkers that may predict response to a CDK4/6 inhibitor, how to determine if a CDK4/6 inhibitor should be continued or switched after progression, whether CDK4/6 inhibitors may be combined with therapies other than endocrine therapies, and whether the use of these agents can be expanded to HR+/HER2– early-stage breast cancer and HR+/HER2+ disease.

Predictive biomarkers for CDK4/6 inhibitors

Approximately 20% of patients will not respond to CDK4/6 inhibitors initially, and all patients will ultimately develop resistance. A better understanding of biomarkers of intrinsic and acquired resistance may help guide therapy. Despite extensive research, estrogen receptor positivity remains the best predictive biomarker for initial response to CDK4/6 inhibitors. PALOMA-1/TRIO-18 initially enrolled two cohorts of patients with HR+/HER2– advanced breast cancer: an unselected group; and a group with either amplification of the cyclin D1 gene (CCND1), loss of the p16 gene (INK4A/CDKN2A), or both. The presence of these alterations was not associated with increased benefit from the addition of palbociclib. This was also confirmed in PALOMA-2, where expression levels (whether high or low) of genes in the cyclin D-CDK4/6-Rb pathway did not correlate with benefit from palbociclib plus letrozole.[25] In PALOMA-3, mutations of PIK3CA were detectable in circulating DNA, but not predictive of benefit from palbociclib. Mutations in the ESR1 gene (which encodes estrogen receptor-a) are detectable in 25% to 40% of tumors that become resistant to AI therapy,[26,27] but these were not predictive of benefit or resistance with palbociclib in PALOMA-3.[26] In MONALEESA-2, benefit with ribociclib was maintained irrespective of baseline Rb, Ki-67, or p16 protein expression; or CDKN2A or CCND1 messenger RNA expression levels.[28] Several ongoing studies with palbociclib (PYTHIA [NCT02536742, NCT03195192]) and ribociclib (NCT03195192) are designed specifically to look at gene- and protein-based predictive biomarkers in an effort to better understand intrinsic and acquired resistance.

Continuing CDK4/6 inhibitors after disease progression

It is not known whether a CDK4/6 inhibitor should be continued beyond the development of disease progression. In two ongoing studies, patients with HR+/HER2– advanced breast cancer whose disease had progressed while receiving a CDK4/6 inhibitor and an AI will receive palbociclib and fulvestrant (NCT02738866) or be randomized to receive ribociclib and fulvestrant or fulvestrant alone (NCT02632045) to determine whether there is a benefit to continuing CDK4/6 inhibitor therapy in this setting.

Novel combinations with CDK4/6 inhibitors

Novel combinations with CDK4/6 inhibitors for patients with HR+/HER2– advanced breast cancer are also being studied. Preclinical data suggest a synergistic effect of inhibiting CDK4/6 and the phosphoinositide 3-kinase (PI3K)/AKT/mTOR pathway. Several studies are combining a CDK4/6 inhibitor with everolimus and exemestane (NCT02871791, TRINITI-1[NCT02732119], NCT01857193) or with novel inhibitors of the PI3K pathway (NCT02684032, NCT02389482, NCT03128619, NCT03006172, NCT01872260, NCT02088684, NCT02154776). The CDK4/6 inhibitors are also being combined with immunotherapy (programmed death 1 or programmed death ligand 1 inhibitors) in several clinical studies (PACE [NCT03147287], NCT02778685, NCT02779751).

CDK4/6 inhibitors for HR+/HER2– early-stage breast cancer

It is not known whether CDK4/6 inhibitors should be added to adjuvant treatment for patients with HR+/HER2– early-stage breast cancer. Several ongoing studies with palbociclib (PAL-LAS [NCT02513394]), ribociclib (EarLEE-1 [NCT03078751] and EarLEE-2 [NCT03081234]), and abemaciclib (monarchE [NCT03155997]) are comparing treatment with a CDK4/6 inhibitor plus endocrine therapy vs adjuvant endocrine therapy alone. These studies are enrolling patients with stage II or III disease to determine whether some patients at higher risk for recurrence may benefit from an adjuvant CDK4/6 inhibitor. If the results of these studies are positive, benefit for some patients will need to be balanced against the risks of overtreatment, as is the case with any adjuvant treatment; in addition, novel biomarkers of response could add value.
CDK4/6 inhibitors for HR+/HER2- advanced breast cancer

Preclinical data suggest that combining a CDK4/6 inhibitor with anti-HER2 therapy may be effective in this setting.[29] Ongoing clinical trials with palbociclib (PATRICIA [NCT02448420], PATINA [NCT02947685]), ribociclib (NCT02657343), and abemaciclib (monarcHER [NCT02675231]) are all examining the benefit of a CDK4/6 inhibitor added to HER2-directed therapy or HER2-directed therapy and endocrine therapy for patients with HR+/HER2+ advanced breast cancer.

Conclusion
The CDK4/6 inhibitors palbociclib, ribociclib, and abemaciclib are rapidly changing the treatment paradigm for patients with HR+/ HER2− advanced breast cancer. They have demonstrated meaningful improvement in PFS when used for first- or later-line therapy, although OS data are still immature. All three CDK4/6 inhibitors appear to have equivalent efficacy; their somewhat different safety profiles may favor use of one over another in particular patients. We provide a possible framework that clinicians can use to sequence the CDK4/6 inhibitors with existing therapies; future data will better guide this approach. Next steps include identifying biomarkers beyond the estrogen receptor to predict response, determining whether to continue CDK4/6 inhibitors after disease progression, combining these agents with other therapies, and expanding their use into settings other than HR+/HER2− advanced breast cancer.

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Chemotherapy vs Abiraterone for the Initial Management of Metastatic Prostate Cancer

The Case for Chemotherapy

Pedro Isaacsson Velho, MD¹, Mario A. Eisenberger, MD²

The treatment landscape for metastatic prostate cancer has changed considerably with the approval of several life-prolonging systemic therapies. Among the various agents approved since 2004 are traditional chemotherapeutic compounds (docetaxel and cabazitaxel), immunotherapy (sipuleucel-T), a bone-targeted radiopharmaceutical (radium-223), and two novel androgen receptor (AR)-targeted therapies (abiraterone acetate and enzalutamide).[1] Docetaxel, the first chemotherapeutic agent to show a survival advantage in metastatic castration-resistant prostate cancer (CRPC), became the standard nonhormonal treatment in this setting.[2] In addition, two recent placebo-controlled randomized phase III trials reported significantly improved metastasis-free survival in patients with nonmetastatic CRPC: the SPARTAN study,[3] which led to US Food and Drug Administration (FDA) approval of the AR-targeted drug apalutamide, and the PROSPER study,[4] which led to the approval of enzalutamide in this setting.

In 2005, the Eastern Cooperative Oncology Group initiated a trial comparing standard androgen deprivation therapy (ADT) with or without 6 cycles of docetaxel in patients with metastatic hormone-sensitive prostate cancer (HSPC; the CHAARTED study). In a recent updated analysis with a median follow-up time of 53.7 months, the group reported a median overall survival (OS) for the combined treatment arm of 57.6 months compared with 47.2 months for ADT alone (hazard ratio [HR], 0.72; 95% CI, 0.59–0.89; *P* = .0018).[5] Subgroup analysis indicates that this survival benefit is significant primarily in the group of patients (513 patients) with high-volume disease, defined as presence of visceral metastases and/or 4

The Case for Abiraterone

Robert J. Jones, MBChB, PhD¹

In the modern era of cytotoxic chemotherapy for common solid tumors, advanced prostate cancer came late to the table. The principal reason for this was the already established role of androgen deprivation therapy (ADT), with its near 100% chance of success and its contrastingly acceptable toxicity profile, coupled with a philosophy of using “the most active and least toxic treatment first.” Although a role for chemotherapy was eventually established in the treatment of men with advanced prostate cancer in whom ADT was failing,[1] it seemed counterintuitive to use it in men who retained sensitivity to the relatively benign intervention of ADT. Initially establishing a niche among men in whom both ADT and docetaxel had failed, the new hormonal therapies abiraterone acetate and enzalutamide rapidly became a first-choice treatment for men with metastatic castration-resistant prostate cancer (CRPC), with most patients and physicians preferring to defer chemotherapy until abiraterone or enzalutamide had failed.[2-5] This shift occurred in the absence of any head-to-head trials comparing abiraterone or enzalutamide with docetaxel, and despite the substantially lower acquisition cost of docetaxel. In other words, patients and physicians made instinctive decisions as to which drug was more suited to their needs during the predominantly asymptomatic or minimally symptomatic stage of the disease after initial failure of ADT.

Despite this, it is still clear that, for most men with metastatic CRPC, there is benefit to be had from sequential use of docetaxel and abiraterone or enzalutamide. Until recently, for most men the preferred treatment pathway was ADT, followed by the addition of abiraterone or enzalutamide, and then docetaxel when this approach failed.

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or more bone lesions (≥ 1 appendicular lesions) (51.2 months for the combined arm vs 34.4 months for ADT alone; HR, 0.63; 95% CI, 0.50–0.79; P < .001). In the 277 patients classified as having low-volume disease, the OS difference between the two arms was not significant—the median survival in these patients was 58.3 and 59.8 months for the combined and ADT-alone arms, respectively. The combined arm was superior with regard to secondary study endpoints, including time to the development of castration resistance (either by prostate-specific antigen or clinical progression) and time to clinical progression.[5]

The STAMPEDE trial[6] was started in 2005 to test the same chemohormonal hypothesis, and the results reported were similar to those of CHAARTED. The STAMPEDE trial design also addressed the question of whether the addition of zoledronic acid would further improve outcomes, which was eventually shown to not be the case.[6] With a median follow-up of 43 months for 2,962 patients, the latest published report from STAMPEDE showed a significant OS difference in favor of the combined ADT + docetaxel arm (HR, 0.78; 95% CI, 0.66–0.93; P = .006). The median OS was 81 months (range, 30 months to not reached) for the combined arm vs 71 months (range, 32 months to not reached) for the ADT-alone arm. The combination arm also showed significantly improved failure-free survival. Toxicities observed in both CHAARTED and STAMPEDE included those previously reported with docetaxel and were mostly reversible.

A third study (GETUG-AFU 15), involving only 385 patients with mostly (> 50%) low-volume disease as defined in the CHAARTED trial, reported an OS of 58.9 months vs 54.2 months for the combined and ADT-alone arms, which was not significant (median follow-up of 50 months).[7] Toxicities were again similar to those reported in the other two trials.

More recently, two large prospectively randomized phase III studies[8,9] of patients with metastatic HSPC reported significant OS improvements with the addition of abiraterone to standard-of-care ADT. The first (LATITUDE) was a placebo-controlled double-blind study (abiraterone plus prednisone was blinded) that included 1,199 patients randomized to abiraterone + ADT (597 patients) or ADT alone (602 patients). With a median follow-up of 30.4 months, 28% of the patients had died in the abiraterone + ADT arm vs 39% in the ADT-alone arm, which represents a 38% lower risk of death with abiraterone use (HR, 0.62; 95% CI, 0.51–0.76; P < .001).[8]

In the second study (STAMPEDE—abiraterone segment), 1,917 men with metastatic or locally advanced prostate cancer were randomized to receive abiraterone + ADT or ADT alone. The combination arm had a significant improvement in the 3-year survival rate (83% vs 76% in the ADT-alone arm; HR, 0.61; 95% CI, 0.49–0.75).[9] Both studies also reported impressive differences in failure-free and progression-free survival, favoring the abiraterone arms. Toxicity was modest, especially when compared with docetaxel treatment. The survival benefit favoring abiraterone was reported across all extent-of-disease subgroups in these two studies.

The data summarized herein strongly support the notion that the standard treatment for metastatic HSPC should no longer be ADT alone. While previous experience in HSPC patients using combined endocrine manipulations with first-generation antiandrogens and older (less effective) chemotherapy regimens did not result in clinical benefit of the magnitude reported with contemporary systemic approaches, it is clear that the biological heterogeneity of this disease at the time of metastatic presentation remains an important consideration for the design of future trials and underscores the need for additional rationally combined approaches based on biology.

At the present time, the choice between the modalities that can be added to standard ADT remains a major challenge for patients and physicians alike. The results of clinical trials indicate a remarkable similarity in benefits. While it is certainly true that toxicities are more severe with chemotherapy than with abiraterone, they are usually acute and reversible after treatment is discontinued. The median follow-up time in the LATITUDE and STAMPEDE trials was less than 40 months.[8,9] In our opinion, additional follow-up information is necessary to properly evaluate adverse events with longer-term abiraterone plus prednisone use. It is possible that the chronic and incremental testosterone suppression and inhibition of CYP17-lyase and hydroxylase caused by abiraterone and chronic (> 5 years) exposure to 10 mg of prednisone may further increase the incidence and severity of toxicities associated with this type of treatment, such as decreases in bone and muscle mass; fatigue; obesity; a variety of chronic metabolic abnormalities; and, most importantly, the potential risk of progressive cognitive changes currently emphasized as a potential complication of long-term ADT.[10]

Current knowledge of the biology of prostate cancer clearly supports the use of chemotherapy and abiraterone.[11-13] Prostate cancer is remarkably dependent on AR signaling, and while AR-targeted approaches are highly effective, the emergence of resistance is predictable.[11,12] Drugs that further suppress intracrine androgen synthesis (abiraterone) and
novel AR antagonists (enzalutamide) result in significant benefits following disease progression after castration, supporting the notion that reactivation of AR signaling is an important mechanism of resistance to ADT. However, while the benefits are clinically meaningful, it is clear that they remain relatively short-lived; most patients with metastatic CRPC develop resistance and eventually die of their disease.

Prostate cancer is a biologically heterogeneous disease and includes various phenotypes that are variably sensitive to currently available AR antagonists, both as preexisting clones and emerging as a result of adaptation to long-term AR selective pressure.[11-13] Data illustrate that with sequential administration of novel AR-targeted therapies for metastatic CRPC (enzalutamide after abiraterone or vice versa), the second drug is only minimally effective, suggesting that clinically significant resistance emerges after exposure to the first AR-targeted drug. In fact, across trials, experience indicates that there are greater benefits with taxane-based chemotherapy after the first novel AR-targeted drug is no longer effective.[12] Therefore, it remains possible that the early use of abiraterone, while effective in delaying progression, may at least partly negate subsequent benefits of current AR-targeted drugs at the time castration resistance develops.

The lack of prospectively planned standardization of post-progression management of newly diagnosed metastatic HSPC patients represents a major challenge in the interpretation of all clinical trials designed to employ survival as the primary endpoint. In the LATITUDE trial,[8] protocol treatment was unblinded at the time of first interim analysis, at which point 78% of patients in the ADT-alone arm and 53% in the ADT + abiraterone arm developed evidence of disease progression. Based on post-hoc assessments, only 11% of patients assigned to the ADT-alone arm received subsequent abiraterone treatment. Thirty-four percent in the ADT + abiraterone arm and 40% in the ADT-alone arm were reported to receive docetaxel after disease progression.

The STAMPEDE study[6] represented a more complex multiarm, multistage platform design in which standardization of post-progression management was not prospectively defined. As in the LATITUDE study, post-progression management in the STAMPEDE trial was left to the discretion of the participating treating physician. Twenty-two percent of patients in the ADT-alone arm received abiraterone after progression; 37% in the ADT-alone arm and 46% in the ADT + abiraterone arm received docetaxel. Based on these data, it may be argued that the benefits of initial combined treatment (ADT + abiraterone and prednisone) compared with sequential treatment (ADT followed by abiraterone and prednisone) need to be better defined. Future trials should prospectively include crossover designs specifically aimed at minimizing the potential post-progression effects of other life-extending systemic treatments.[14]

Finally, the availability and cost of treatments are critical points of consideration in treatment decision making. Docetaxel is a widely used drug available in many countries. A recent analysis of the economic burden[15] associated with the use of single-agent docetaxel in men with metastatic CRPC showed an average of $1,799 per patient. The actual cost of each docetaxel cycle is approximately $1,700, while the cost for 1 month of treatment with abiraterone in the United States is approximately $10,000.[16] Abiraterone is now approved by the FDA for use in HSPC.[17,18]

In summary, at present the choice of chemohormonal therapy in metastatic HSPC can be supported biologically and clinically, primarily in patients with high disease burden as defined by the CHAARTED study. While more significant, the toxicities associated with docetaxel are short-lived and mostly reversible. Additionally, the overall economic burden of docetaxel treatment is substantially lower than that of treatment with abiraterone + prednisone.

Research focusing on the identification of biomarkers to facilitate patient and treatment selection, and on prospectively validated intermediate endpoints that correlate with survival, is urgently needed to further build on the significant advances in the treatment of men with metastatic HSPC.

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chieved sufficient follow-up to enable an estimate of FFS, with 38% and 39% reductions in the risk of metastatic prostate cancer who had metastatic disease at presentation.[7]

disease, but also men with high-risk locally advanced disease.[8]

Sheppord and recurrent prostate cancer. The abiraterone trial was randomized between docetaxel and abiraterone. In both trials, the tolerability of abiraterone was associated with a superior FFS (HR, 0.82–1.65, in favor of docetaxel), although there was no difference in toxicity. This analysis included patients with high-risk locally advanced disease.[8]

node-dominant acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multi-stage, platform randomized controlled trial. Lancet. 2016;387:1163-77.

high-risk metastatic prostate cancer at the time of diagnosis. “High-risk” disease was defined in this trial as two or more of the following three features: Gleason score ≥ 8, ≥ 3 bone metastases, and/or visceral disease. The coprimary endpoints were overall survival and radiographic progression–free survival (rPFS).[6]

Despite these recent advances, for most patients, metastatic prostate cancer remains a fatal condition. Patients’ expectations of treatment differ from one patient to another, and so it is unlikely that a unified treatment pathway will be right for all men. While survival is important, many will trade survival time for quality of life, and most strive for treatment that prolongs the high-quality phase of their survival.

Treatment objectives for men with metastatic HSPC

Due to its unique design features, there was a brief delay in rPFS in men receiving abiraterone in LATITUDE, with a 53% reduction in risk and a median improvement in rPFS of 18.2 months. Routine scanning was not performed in STAMPEDE, and so rPFS was not calculated. However, the risk of failure of any sort was reduced by 69% in those with metastatic disease who received abiraterone. In both trials, the tolerability of abiraterone was similar to what was seen in the metastatic CRPC setting, despite the lower dose of corticosteroids.

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Due to its unique design features, there was a brief period when patients entering the STAMPEDE trial were directly randomized between docetaxel and abiraterone. Although this was not a formally powered comparison, it offers the only head-to-head data in this setting. There was no difference in overall survival between the two treatments (hazard ratio [HR], 1.16; 95% CI, 0.82–1.65, in favor of docetaxel), although abiraterone was associated with a superior FFS (HR, 0.51; 95% CI, 0.39–0.67). At 1 and 2 years, there was no difference in toxicity. This analysis included patients with high-risk locally advanced disease.[8]

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The evidence

Two large trials inform our understanding of the use of abiraterone (in combination with low-dose prednisone) predominantly in patients with newly diagnosed advanced prostate cancer. Both trials completed accrual before docetaxel became standard treatment in this setting, and so both trials excluded men who had received prior docetaxel.

LATITUDE was a multicenter, double-blind, randomized, phase III trial conducted in 34 countries that compared abiraterone plus prednisone (5 mg once daily) with dual placebos in men with high-risk metastatic prostate cancer at the time of diagnosis. “High-risk” disease was defined in this trial as two or more of the following three features: Gleason score ≥ 8, ≥ 3 bone metastases, and/or visceral disease. The coprimary endpoints were overall survival and radiographic progression–free survival (rPFS).[6]

STAMPEDE is a multi-arm, multi-stage trial in men starting long-term ADT. As such, the trial has included multiple interventions in a group of men, which includes not only men presenting with metastatic disease, but also men with high-risk locally advanced and recurrent prostate cancer. The abiraterone comparison of STAMPEDE (arm G vs arm A) was an open-label trial comparing abiraterone plus prednisolone (5 mg once daily) with ADT alone. The primary endpoint was overall survival, and failure-free survival (FFS; defined, predominantly, as prostate-specific antigen [PSA] progression) was a key secondary endpoint in the final analysis. For the purposes of this debate, I will focus on the subgroup of the 52% of patients who had metastatic disease at presentation.[7]

Both trials have yielded striking and similar results, with 38% and 39% reductions in the risk of death in LATITUDE and STAMPEDE, respectively, in men with metastatic disease. Neither trial has achieved sufficient follow-up to enable an estimate of the median survival gain, but informal extrapolation of the survival curves leads to an estimated median survival gain in excess of 20 months. The true magnitude of the survival gain in LATITUDE may be compromised by crossover after unblinding for those men who were still progression-free and receiving placebo.

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CHEMOTHERAPY VS ABIRATERONE IN PROSTATE CANCER

＞Counterpoint. JONES CONTINUED FROM PAGE 226

However, the months between diagnosis and first progression will, for most, be among the highest-quality months of the remainder of their lives. This precious progression-free period is a time when most patients are enjoying a fully active and productive life. Therefore, a major objective of treatment intensification in metastatic hormone-sensitive prostate cancer (HSPC) is the prolongation of progression-free survival.

**Abiraterone is a more effective option in metastatic HSPC**

The data demonstrate that treatment with abiraterone achieves the objectives of prolonging both overall and progression-free survival to an extent rarely seen in solid tumor trials. The common methodology used throughout the STAMPEDE trial permits high-quality indirect comparison. Docetaxel reduced the risk of FFS by 39%, compared with 69% for abiraterone.[9] Even in the undersized direct comparison, there was a significantly greater effect on FFS with abiraterone compared with docetaxel. This seemingly greater effect of abiraterone may be explained by its direct effect on PSA transcription, resulting in a spurious exaggeration of the effect when compared with the less direct effects of docetaxel on PSA production. However, even with the more conservative measure of rPFS used in the LATITUDE trial, the magnitude of the benefit is greater than the effect on PSA-driven endpoints seen in the docetaxel comparisons of STAMPEDE, GETUG-AFU 15, and CHAARTED.[9-11]

Indirect comparison of the effects on overall survival suggest that the 38% to 39% risk reduction observed with abiraterone is greater than the 23% reduction seen in the meta-analysis of the docetaxel trials.[12]

**Abiraterone is less toxic than docetaxel**

There is no debate that, during treatment, docetaxel will be associated with a greater burden of toxicity and a higher risk of severe toxicity or death compared with abiraterone. Indeed, the higher proportion of elderly and lower-performance-status men enrolled in the abiraterone trials compared with the docetaxel trials would support the position that abiraterone remains effective even in men who are less suitable for treatment with docetaxel.

**Abiraterone will prove to be more cost-effective**

The high cost of abiraterone when compared with the low acquisition cost of docetaxel is a clear factor against its use in 2018. However, even at this cost, given the sizable effect on overall survival and, more importantly, the likely gain in quality-adjusted life-years (due to the high proportion of time gained in the pre-progression state), abiraterone is likely to demonstrate good value in high-income healthcare systems, at least when compared with ADT alone. As patent expiries loom for abiraterone around the world, it will inevitably be the case that the price will drop very substantially in coming years, meaning that abiraterone may well become more cost-effective than docetaxel, despite the prolonged duration of therapy.

**A future for metastatic HSPC**

Despite their differences, the trials of abiraterone and docetaxel have irreversibly changed the way we view and treat metastatic prostate cancer, clearly demonstrating that early intervention results in significantly superior outcomes. We can anticipate very rapid evolution in this field: trials including sequential use of docetaxel and abiraterone or other androgen receptor–targeted therapies, as well as the combination of enzalutamide and abiraterone, have already completed accrual in this setting, and emerging agents in metastatic CRPC will, in all likelihood, rapidly transition to the early phase of the disease. As we move into the era of precision medicine and genomics, it will inevitably make sense to use such approaches at the time of initial diagnosis. In the meantime, many patients have a choice of treatments available to them, a choice that will be guided by their own expectations of treatment, as well as the differing profiles of the drugs.

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＞Counterpoint. JONES CONTINUED ON PAGE 247
Combination Controversies: Checkpoint Inhibition Alone or in Combination for the Treatment of Melanoma?

Allison Betof Warner, MD, PhD¹, Michael A. Postow, MD²,³

**ABSTRACT:** The immune checkpoint inhibitors ipilimumab, nivolumab, and pembrolizumab have dramatically improved outcomes for patients with metastatic melanoma; however, not all patients benefit from monotherapy with these agents. To address this issue, complementary combinations of immunotherapy are increasingly being explored as a strategy to improve outcomes. However, combinatorial approaches come with heightened risk of toxicity. In this review, we highlight combinations for which there are prospective data from clinical trials. The combinations discussed include ipilimumab plus anti–programmed death 1 agents, ipilimumab plus granulocyte-macrophage colony-stimulating factor, checkpoint inhibitor plus talimogene laherparepvec, ipilimumab plus chemotherapy, checkpoint inhibitor plus BRAF/MEK targeted therapy, and checkpoint inhibition plus radiation therapy. We discuss data regarding the efficacy and toxicity of combination therapy, and we identify clinical scenarios that may favor treatment with combination therapy.

**Background**

The immune system can eliminate cancer, so strategies to increase antitumor immunity have emerged as a primary therapeutic approach for the treatment of melanoma. While the immune system is complex and multifaceted, therapeutic approaches to antitumor immunity have largely focused on T cells. T-cell immunity is controlled by immune checkpoints. These are physiologic on/off switches that enable immune responses to potentially threatening antigens, while protecting the host from overzealous immune responses and autoimmunity.[1,2] For the treatment of melanoma, there are currently three checkpoint inhibitors that have been approved by the US Food and Drug Administration (FDA): ipilimumab, nivolumab, and pembrolizumab. These have two main targets: cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), which is targeted by ipilimumab, and programmed death receptor 1 (PD-1), which is targeted by nivolumab and pembrolizumab. All three of the approved checkpoint inhibitors are widely used in clinical practice.

Single-agent immune checkpoint inhibition has proved to be a successful strategy for the treatment of metastatic melanoma. Ipilimumab is also approved as adjuvant therapy for resected stage III disease. More recently, nivolumab was approved for adjuvant therapy based on an improvement in recurrence-free survival compared with ipilimumab in patients with resected stage IIIIB, IIIIC, or IV melanoma.

Despite the known efficacy of these agents, not all patients benefit from single-agent immune checkpoint inhibitor therapy, prompting further investigation into whether combining immune checkpoint inhibitors, either with each other or with other anticancer treatments, could improve outcomes. Combinations ideally should have complementary and not overlapping mechanisms of immune activation to maximize benefit and minimize toxicity.[3,4]

While combinatorial approaches hold considerable promise, it is important that the potential added risk of toxicity with a proposed combination therapy not outweigh the added benefit.[5] In this article, we take a practical approach to understanding the role of combination strategies for checkpoint inhibition in melanoma by examining data on the superiority of combinations vs single agents, and thereby trying to answer controversial questions of “which is better.” We focus on clinically relevant therapeutic strategies for which clinical trial data are available. A number of other combinations are being actively investigated—such as those that involve indoleamine 2,3-dioxygenase inhibitors or lymphocyte-activation gene 3—but these are not yet ready for the clinic due to the paucity of randomized data. The Figure shows the mechanisms of action of the various approaches we discuss. The Table lists ongoing phase III clinical trials of combinations of immune checkpoint inhibition with other approaches. In the many areas where much remains unknown, we highlight key questions in the field and propose strategies for remedying deficiencies in available knowledge.

**Ipilimumab Plus Anti–PD-1 vs Ipilimumab Alone vs Anti–PD-1 Alone**

CTLA-4 was the first immune checkpoint targeted for clinical intervention. CTLA-4 is expressed on the surface of T cells and regulates early activation, known as priming, of naive T cells during their first encounter with a tumor peptide, which is presented as part of the major histocompatibility complex by antigen-presenting cells in the draining lymph node.[6] Binding of CTLA-4 to its ligands on antigen-presenting cells inhibits T cells, so preventing this binding is one mechanism by which CTLA-4 blockade increases T-cell responses against tumors.[7] Ultimately, the anti–CTLA-4 monoclonal antibody ipilimumab was shown to improve overall survival...
A Table: Ongoing Phase III Trials of Melanoma Combination Therapies Involving Immune Checkpoint Inhibitors

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<th>Comparators</th>
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<td>Pembrolizumab ± T-VEC</td>
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| **IDO** = indoleamine 2,3-dioxygenase; **LAG-3** = lymphocyte-activation gene 3; **T-VEC** = talmogene laherparevec.

(OS) in patients with advanced melanoma,[8] and ipilimumab was approved by the FDA for the treatment of metastatic melanoma in March 2011.

While CTLA-4 blockade functions primarily, though not exclusively, in lymph nodes, PD-1 is thought to operate primarily within the tumor microenvironment, where it decreases the activity of peripheral T cells. Therefore, anti–PD-1 therapy has a mechanism of therapeutic checkpoint inhibition that complements rather than overlaps that of CTLA-4 blockade. In a phase 1 clinical trial of the combination of ipilimumab and nivolumab at escalating doses in patients with melanoma, response rates were favorable compared with each agent as monotherapy. However, an increase in immune-related adverse events (irAEs) with the combination compared with each agent as monotherapy was also reported.[9,10]

The phase II CheckMate 069 study of 142 patients with advanced untreated melanoma, which compared ipilimumab (3 mg/kg) plus nivolumab (1 mg/kg) vs ipilimumab alone, demonstrated an objective response rate (ORR) of 61% for combination therapy vs 11% for ipilimumab alone in patients with BRAF wild-type melanoma.[11] The risk of progression or death was reduced by 60% with combination therapy compared with ipilimumab alone (hazard ratio [HR], 0.40; 95% CI, 0.22–0.71; P < .002). In a subsequent exploratory OS analysis after a median of 24.5 months of follow-up, the 2-year OS rate in the ipilimumab + nivolumab arm was 63.8% (95% CI, 53.3%–72.6%) vs 53.6% in the ipilimumab-alone arm (95% CI, 38.1%–66.8%), and median OS was not yet reached in either arm.[12] Grade 3/4 toxicity was observed in 54% of patients treated with combination therapy and in 24% of patients treated with ipilimumab alone.

After the superiority of the combination over ipilimumab in short-term endpoints (progression-free survival [PFS]) had been demonstrated in CheckMate 069, the phase III trial (CheckMate 067) randomized 945 patients with advanced untreated melanoma to ipilimumab alone, nivolumab alone, or concurrent ipilimumab and nivolumab.[13] ORRs for the ipilimumab, nivolumab, and combination arms were 19%, 44%, and 58%, respectively. An updated survival analysis was recently published, with a minimum of 36 months of follow-up; this showed that the median OS was 19.9 months for ipilimumab, 37.6 months for nivolumab, and not yet reached for the ipilimumab + nivolumab arm (HR for death with ipilimumab plus nivolumab vs ipilimumab alone, 0.55; P < .001).[14] Three-year OS rates for ipilimumab, nivolumab, and combination therapy were 34%, 52%, and 59%, respectively. The study was not powered sufficiently to compare nivolumab alone against ipilimumab plus nivolumab.

Again, this study demonstrated that improved efficacy with combination therapy compared with ipilimumab alone comes with the detriment of higher toxicity. Grade 3/4 toxicity rates were 28.3% for ipilimumab, 16.3% for nivolumab, and 55% for combination therapy.[13] While 31% of patients receiving ipilimumab plus nivolumab stopped therapy because of adverse events (compared with 14.1% in the ipilimumab arm and 7.7% in the nivolumab arm), the ORR was 70% among those who discontinued therapy and median OS was not yet reached, raising questions about the optimal duration of combination immunotherapy.[15]

Given the impressive efficacy yet ongoing concerns about increased toxicity with the combination of checkpoint inhibitors targeting CTLA-4 and PD-1, there is considerable interest in altering schedules and/or dosing of CTLA-4 blockade to try to minimize irAEs while maintaining efficacy.[16,17] Specifically, altering the administration of ipilimumab by lowering the dose to 1 mg/kg in combination with anti–PD-1 therapy, or administering ipilimumab less frequently (ie, every 6 or 12 weeks), have been appealing strategies. In one single-arm nonrandomized study of reduced-dose ipilimumab (1 mg/kg) with standard-dose pembrolizumab, the response rate appeared similar to that seen with standard-dose ipilimumab (3 mg/kg) plus nivolumab (1 mg/kg). However, ipilimumab is known to have dose-dependent effects on OS that are not necessarily dependent on response rates, given that 10 mg/kg of ipilimumab was
A CUTELY LYMPHOBLASTIC LEUKEMIA IN ADULTS

recently shown to improve OS compared with 3 mg/kg, without an apparent difference in response rate or PFS.[18] Thus, clinicians must be cautious when considering reduced dosing of ipilimumab in combination with an anti–PD-1 agent based on response rate endpoints alone. Randomized trials with longer-term follow-up are needed to assess the true efficacy of these modifications.[19]

In summary, ipilimumab plus nivolumab is clearly superior to ipilimumab alone, but the question of whether combination ipilimumab plus nivolumab is superior to nivolumab alone remains a difficult dilemma for clinicians who must decide between these treatments for their patients. The exploratory data that demonstrate the highest efficacy for the combination are intriguing, but this advantage comes at the cost of higher toxicity, requiring appropriate patient selection and counseling.

Unfortunately, no biomarker has been shown to be specifically predictive of treatment benefit from nivolumab plus ipilimumab compared with nivolumab (or pembrolizumab) alone. Nonetheless, testing for tumor programmed death ligand 1 (PD-L1) expression and mutational burden have been explored as potential predictive indicators of response to immunotherapy—PD-L1 negativity and high mutational burdens being favorable for better outcomes.[20] Despite some exploratory signals that the relative benefits of nivolumab plus ipilimumab compared with nivolumab alone were greatest in patients who were defined as PD-L1–negative, a statistical test for interaction was not positive, suggesting that PD-L1 negativity is not statistically predictive of treatment benefit from combination immunotherapy compared with single-agent anti–PD-1 therapy.[13] Data for tumor mutational burden have not yet been reported in the setting of nivolumab plus ipilimumab. Therefore, while the hypotheses are provocative that perhaps patients with PD-

Figure. Mechanisms of Action of Immunotherapies Used in the Treatment of Melanoma.

APC = antigen-presenting cell; CTLA-4 = cytotoxic T-lymphocyte–associated antigen 4; GM-CSF = granulocyte-macrophage colony-stimulating factor; IDO = indoleamine 2,3-dioxygenase; LAG-3 = lymphocyte-activation gene 3; MHC = major histocompatibility complex; PD-1 = programmed death receptor 1; PD-L1 = programmed death ligand 1; TCR = T-cell receptor; T-VEC = talimogene laherparepvec.
L1-negative tumors or those with low mutational burden may derive greater benefit from nivolumab plus ipilimumab compared with single-agent anti–PD-1 therapy, the data are not strong enough to recommend using these markers to guide clinical practice.

Special considerations may be warranted for certain subgroups of patients. One example is patients with mucosal melanoma, who are generally believed to have a poor prognosis.[21] A pooled analysis of patients with mucosal melanoma (N = 86) who received ipilimumab plus nivolumab or nivolumab alone in a clinical trial was recently published.[22] Of these patients, the median PFS was 2.7 months in the ipilimumab arm, 3.0 months in the nivolumab arm, and 5.9 months in the combination arm. Combination immunotherapy response rates appeared lower in patients with mucosal melanoma (37%) than in patients with cutaneous melanoma (60%). Patients with mucosal melanoma had a response rate of 37% for combination immunotherapy vs a response rate of 23% for therapy with nivolumab alone. Notably, this absolute difference of 14 percentage points approximates the absolute difference in response rate between combination immunotherapy and nivolumab monotherapy seen in cutaneous melanoma. These data suggest that the choice of the combination of nivolumab plus ipilimumab for a patient with cutaneous melanoma should be largely based on the higher response rate and cannot simply be made based on the histology of the underlying melanoma subtype.

Similarly, particular attention has been paid to the efficacy of nivolumab plus ipilimumab in patients with brain metastases. At the American Society of Clinical Oncology (ASCO) 2017 Annual Meeting, data were presented from two phase II trials. One study consisted of 50 patients with asymptomatic melanoma brain metastases who had not received prior local brain therapy or immune checkpoint blockade.[23] Patients were randomized to ipilimumab plus nivolumab vs nivolumab alone. While not powered for a statistical comparison of OS, the 6-month OS rate was 59% for nivolumab alone vs 76% for ipilimumab plus nivolumab, suggesting an advantage to combination therapy for patients with intracranial metastases. Data from the CheckMate 204 study were also presented at the 2017 ASCO Annual Meeting; these demonstrated an intracranial ORR of 56% with the combination of ipilimumab plus nivolumab.[24] Although these are small studies, and longer-term follow-up with more patients is needed, these data suggest impressive efficacy for the combination of ipilimumab plus nivolumab in patients with brain metastases. In our practice, we generally prefer combination immunotherapy over single-agent anti–PD-1 therapy for patients with multiple brain metastases who are not candidates for stereotactic radiosurgery (SRS).

Most important to the choice of combination immunotherapy in any setting, however, is that patients are perceived to be capable of handling the possibility of irAEs and consequent treatment with corticosteroids. Patients who do not have supportive caregivers or who are perceived as having difficulty communicating with the care team may not be good candidates for combination immunotherapy, since management requires close communication and may necessitate adherence to immunosuppressive treatment regimens in the event of significant toxicity. Because the 3-year OS rates of nivolumab plus ipilimumab and nivolumab alone are similar, single-agent anti–PD-1 therapy remains an appropriate choice for many patients and is the standard control arm of most randomized clinical trials.

GM-CSF Plus Ipilimumab vs Ipilimumab Alone
Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a cytokine naturally secreted by macrophages, T cells, mast cells, natural killer cells, endothelial cells, and fibroblasts to stimulate stem cells to produce granulocytes and monocytes. The monocytes subsequently mature into macrophages and dendritic cells. From an oncologic perspective, GM-CSF augments the ability of dendritic cells to present antigen to lymphocytes, thereby boosting the antitumor activity of T- and B-lymphocytes.[25,26] Hodi and colleagues conducted a phase II randomized clinical trial in 245 patients who had advanced melanoma that had progressed on at least one prior therapy. Patients were randomized to receive either ipilimumab (10 mg/kg) plus sargramostim (GM-CSF; 250 μg subcutaneously on days 1–4 of a 21-day cycle) or ipilimumab (10 mg/kg) alone.[27] At a median follow-up of 13.3 months, median OS in the ipilimumab + sargramostim group was 17.5 months (95% CI, 14.9 months–not reached) vs 12.7 months in the ipilimumab-alone arm (95% CI, 10.0 months–not reached; P = .01). Grade 3–5 toxicity was significantly lower in the ipilimumab + sargramostim arm than in the ipilimumab-alone arm (P = .04). Although follow-up time was short, this study provided the first evidence of an OS advantage with combination immunotherapy. The toxicity data are also reassuring. Despite the positive findings from incorporating GM-CSF into treatment with high-dose ipilimumab, this trial’s findings have not led to significant clinical use of GM-CSF with CTLA-4 blockade. Reasons for the limited uptake may be related to the difficulty of GM-CSF administration and the increase in use of the ipilimumab + anti–PD-1 combination at around the same time that the GM-CSF + ipilimumab combination data became available. Clearly, additional larger studies are needed with longer follow-up before conclusive recommendations can be made about the use of GM-CSF in addition to checkpoint blockade.

Checkpoint Inhibition Plus Talimogene Laherparepvec vs Checkpoint Inhibition Alone
Talimogene laherparepvec (T-VEC) is an oncolytic virus derived from herpes simplex virus type 1 that is FDA-approved for the treatment of advanced melanoma. It is the first oncolytic virus to produce meaningful clinical benefit in a randomized clinical trial for patients with solid tumors.[28] Administration of oncolytic viruses in patients with melanoma enhanced tumor antigen–specific T-cell response and abrogated the immunosuppressive function of regulatory T cells, suppressor CD8+ T cells, and myeloid-derived suppressor cells, providing a rationale for exploring T-VEC in combination with checkpoint inhibition.[29,30] Data were recently presented from an open-label, randomized phase II trial of 198 patients with advanced, unresectable stage IIIIB–IV melanoma with injectable tumors who were given ipilimumab (3 mg/kg) with or without T-VEC.[31] The ORR was 38.8% for T-VEC plus ipilimumab vs 18.0% for ipilimumab alone (P = .002). In total, 28% of patients who received T-VEC plus ipilimumab and 18% of patients who received ipilimumab alone had grade 3/4 toxicity. These results are quite promising,
and additional data are expected that will further inform decisions about this combination. Given the higher response rate and no obviously increased toxicity for the T-VEC + ipilimumab combination, for patients with unresectable or metastatic melanoma who have injectable lesions and for whom treatment with ipilimumab is appropriate, we favor combining ipilimumab with T-VEC, although we acknowledge this is not an approved combination.

T-VEC has also been studied in combination with anti–PD-1 therapy, including in a recently reported phase Ib trial with pembrolizumab that demonstrated a 62% confirmed response rate in patients with injectable melanoma lesions and advanced disease.[32] Despite this promise in a nonrandomized study, randomized data for T-VEC plus pembrolizumab are needed; a phase III randomized trial of pembrolizumab with or without T-VEC is ongoing (ClinicalTrials.gov identifier: NCT02263508).

**Chemotherapy Plus Ipilimumab vs Ipilimumab Alone vs Chemotherapy Alone**

Although traditionally viewed as immunosuppressive, chemotherapy can potently release of antigen and pro-inflammatory damage-associated molecular patterns, which in theory could be used to increase the efficacy of immune checkpoint blockade.[33] However, experience with this approach in melanoma has been limited to date. A randomized phase II trial of 72 patients with unresectable metastatic melanoma who had not received previous chemotherapy showed improved OS in the combination arm (11.2 months vs 9.1 months; HR, 0.72; P < .001).[35] As expected, grade 3/4 toxicity was increased in the combination arm (56.3% vs 27.5%; P < .001). The response rate in the ipilimumab + dacarbazine arm was 15.2%, similar to the published response rates for ipilimumab monotherapy. The trial did not compare the combination against ipilimumab alone. For this reason, and given the higher toxicity of this combination compared with ipilimumab monotherapy, this combination is not generally recommended for clinical use.

**MAP Kinase Pathway–Directed Targeted Therapy Plus Immune Checkpoint Inhibition vs Targeted Therapy Alone**

For melanoma that harbors a BRAF mutation, small molecules that target the combination of BRAF and MEK have become standard of care. FDA-approved BRAF inhibitors include dabrafenib and vemurafenib, and the approved MEK inhibitors are trametinib and cobimetinib. One of the tenets of combination strategies is that each agent should address a separate mechanism of antitumor action. Thus, combining BRAF/MEK inhibition with immunotherapy is an intriguing approach to improving efficacy and durability of response. Additionally, preclinical experiments indicated that treatment with BRAF inhibitors could increase antigen presentation and T-cell activation and proliferation.[36,37] Inhibition of CTLA-4 enhanced this effect in preclinical models.[38] However, both strategies can cause dermatologic and hepatic toxicities.

Unfortunately, the first report of such a combination, a phase I study of vemurafenib (960 mg orally twice daily) plus concurrent ipilimumab (3 mg/kg) in patients with metastatic BRAF V600–mutated melanoma, showed significant dose-limiting hepatotoxicity as well as rash.[39] These effects persisted at a lower dose of vemurafenib (720 mg twice daily), and thus the trial was closed to accrual. It is noteworthy that all aminotransferase levels were reversible with discontinuation of the agents and/or treatment with glucocorticoids. Sequential dosing, with administration of ipilimumab followed by vemurafenib, also caused severe skin toxicity, providing additional evidence of increased toxicity when these agents are given in proximity.[40] In a subsequent study, triple therapy with ipilimumab plus dabrafenib plus trametinib resulted in colitis followed by intestinal perforation in 2 of 7 patients.[41] The results of these studies have diminished enthusiasm for combining ipilimumab with MAP kinase pathway inhibitors.

PD-1/PD-L1 inhibitors are likely to be better combinatorial partners with BRAF and MEK inhibitors. At the 2017 ASCO Annual Meeting, data were presented on the combination of the PD-L1 inhibitor atezolizumab plus cobimetinib plus vemurafenib in BRAF V600–mutant metastatic melanoma.[42] Of 34 treated patients, 15 (44.1%) had grade 3/4 adverse events; 3 had to discontinue treatment because of transaminitis, and 1 patient discontinued treatment because of rash. At the time of the meeting, the ORR was 85.3%. While these data are promising, high response rates can be seen with the...
tion of BRAF + MEK inhibitors without immunotherapy, and the true question remains how much the addition of anti–PD-1/ PD-L1 immunotherapy increases the duration of response. Clearly, data from ongoing randomized studies with longer follow-up are needed to determine the safety and efficacy of these combinations.

**Concurrent Immune Checkpoint Inhibition Plus Radiation Therapy vs Immune Checkpoint Inhibition Alone**

In addition to the systemic therapies discussed previously, radiation therapy (RT) is a mainstay of treatment for metastatic melanoma. Nearly half of patients with metastatic melanoma receive RT during their treatment, with palliative intent—to either relieve symptoms or prevent more serious complications (eg, impending cord compression, enlarging intracranial metastases). Because increasing numbers of patients are receiving immunotherapy, it is critical to understand the interactions between immune-based approaches and RT.

The role of RT in the era of immunotherapy for melanoma continues to evolve. For decades, scientists in the field of radiation biology have studied the abscopal effect, in which systemic effects in the nonirradiated field are observed following treatment with local RT. While radiation is generally thought to be immunosuppressive as a result of toxic effects on hematopoietic cells, studies have demonstrated that high-dose radiation causes tumor cell necrosis, releasing tumor-associated antigens that potentiate a systemic immune response.[43] Additionally, radiation has been shown to increase CD8+ T-cell infiltration, increase antigen presentation to dendritic cells, and promote pro-inflammatory cytokine signaling.[44,45] The mechanistic details of the interaction between RT and systemic immunity are reviewed elsewhere, and there is preclinical evidence to support the combination of RT with immunotherapy.[46,47] Here, we focus on available clinical data in melanoma.

**Extracranial irradiation**

The first prospective trial to evaluate checkpoint inhibition plus RT was a phase I trial of 22 patients with metastatic melanoma who were treated with RT targeting bone, liver, lung, and subcutaneous metastases, followed by ipilimumab (3 mg/kg).[48] Response rates and toxicity were similar to those seen in historical controls treated with ipilimumab monotherapy, suggesting that RT did not enhance the efficacy of ipilimumab in this setting.

In a separate pilot trial of 22 patients with metastatic melanoma, another group of investigators treated patients with ipilimumab (3 mg/kg) followed by RT within 5 days of the first dose of ipilimumab.[49] The median OS in this trial was 13.8 months, and nonirradiated tumor shrinkage was noted in 6 patients. Whether the shrinkage of nonirradiated tumors was purely attributable to ipilimumab alone (without RT) remains unknown, as nonrandomized studies are unable to assess for abscopal responses. Again, no added toxicity was seen above that expected from the individual therapies. To date, there has not been a randomized trial of ipilimumab with or without RT to definitively address whether the combination is superior to ipilimumab alone. We therefore cannot support adding RT to ipilimumab purely in hopes of eliciting an abscopal response. However, if a patient needs RT anyway, it appears safe to add RT to ipilimumab.

Anti–PD-1 therapy in combination with RT is also being explored. To date, no prospective clinical trial data are available. There are many ongoing clinical studies testing the combination of RT plus anti–PD-1 therapy (with or without additional ipilimumab; eg, ClinicalTrials.gov identifier: NCT02659540). At this time, there still are no prospective data that suggest adding RT to immune checkpoint inhibition improves the efficacy of checkpoint inhibition alone.

**Intracranial irradiation**

Over half of all patients with metastatic melanoma will develop brain metastases, and the majority of these metastases are often treated with SRS. Whether SRS enhances the efficacy of immune checkpoint inhibition for brain metastases is therefore an active area of interest. Since immunotherapy has efficacy in this patient population, there is controversy about adding SRS to the treatment regimen in these patients, making studies of SRS and immunotherapy especially important. Reports of combinations of immunotherapy with SRS are increasing, and the toxicity level is generally believed to be acceptable.[46] One group of investigators has reported biopsy-confirmed symptomatic necrosis of the brain following SRS and ipilimumab, but conclusions cannot be drawn from isolated case reports.[50]

Some retrospective analyses of patients who received the combination of ipilimumab plus SRS show improvements in OS with combination therapy compared with SRS alone, but others have not demonstrated the same improvement.[51-53] Additionally, in the patients with improved survival, it is unclear whether this improvement is simply a byproduct of the efficacy of systemic immunotherapy or a result of the combination approach.[54] In our practice, given safety data that generally indicate that SRS with immunotherapy has an acceptable toxicity profile, if a patient needs SRS and immunotherapy, we feel both are reasonable to pursue.

**Conclusions**

Advances in immunotherapy and the approval of immune checkpoint inhibitors have revolutionized the treatment of metastatic melanoma, but not all patients benefit from monotherapy with an immune checkpoint inhibitor. To overcome this, complementary combinations of immunotherapy are increasingly being explored as a strategy to improve outcomes. We have highlighted the combination strategies that have been studied in prospective trials and have attempted to identify clinical scenarios that would favor treatment with combination therapy. However, with so many potential combinatorial strategies, identifying optimal approaches and obtaining randomized data are paramount to maximize benefit and minimize toxicity. To maximize efficiency, cost-effectiveness, and potential benefit to patients, novel clinical trial designs are needed to explore the growing array of new immunotherapy combinations.

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Improving Adherence to Endocrine Therapy in Women With HR-Positive Breast Cancer

Julia P. Brockway, MD1, Charles L. Shapiro, MD2

ABSTRACT: Aromatase inhibitors (AIs) are the standard treatment for postmenopausal women with hormone receptor–positive breast cancers. One of the most common side effects of AIs is joint pain; it is also the most frequently cited reason for nonadherence and discontinuation before completion of the prescribed treatment course. Nonadherence and, in particular, discontinuation, can lead to increased rates of breast cancer mortality. The prevalence of AI-induced arthralgias is about 50%, and there are several interventions, including switching to a different AI, that can increase adherence. The healthcare professional plays a part in fostering adherence by communicating the side effects of AIs to patients before the initiation of treatment, as well as explaining the strategies for addressing these side effects, should they occur.

Introduction
Adjuvant endocrine therapy is the standard of care for women with estrogen receptor– and progesterone receptor–positive breast cancers. Endocrine therapies include aromatase inhibitors (AIs), such as the nonsteroidal compounds letrozole and anastrozole and the steroidal compound exemestane. All three AIs have comparable benefits and side effect profiles. The selective estrogen receptor modulator tamoxifen has anticancer activity in pre- and postmenopausal women. While AIs only have anticancer activity in postmenopausal women, they are superior to tamoxifen at reducing the risk of recurrence and improving overall survival.[1-3]

AIs and tamoxifen require long-term daily self-administration of oral medications for 5 years, and in some cases, 10 years. However, up to 28% of women in clinical trials, and as many as 73% in community practice settings, prematurely discontinue these drugs.[4-6] AI adherence in particular is suboptimal, ranging from 50% to 91% over 5 years of therapy,[6] and only 40% to 60% of women complete the recommended course of AIs.[7-9] A consequence of nonadherence and discontinuation is an increase in breast cancer mortality.[8-10]

Medication “adherence” is synonymous with medication “compliance.” Adherence is measured over time and reported as a percentage.[11] The preference for “adherence” over “compliance” is due to the former term’s less harsh and judgmental connotations regarding patients’ behavior.[12] Persistence is the duration of time from initiation to discontinuation of therapy, and is a continuous variable referring to the duration of treatment.[11,12] Persistence is a specific aspect of adherence.

There are several ways to measure adherence. One method is to review prescription refill data and the medication possession ratio (MPR). The MPR is the ratio of total days of medication divided by the entire duration of days that the drug is prescribed for, with adherence defined as > 80%.[8] Another method of measuring adherence is to use patient-reported data, which may take into account behaviors and experiences. The most straightforward and reliable way to measure adherence is to ask the patient if she is taking the medication.

Risk Factors Leading to Treatment Nonadherence and Discontinuation
There are many independent risk factors for treatment nonadherence and discontinuation, including adverse effects; disease stage; use of chemotherapy (ie, taxanes); comorbidities; demographic features such as age, lower socioeconomic status, and race; and psychosocial factors such as quality of life, emotional distress, attitude toward therapy, and perception of self-efficacy.[13-16]

Adverse effects are the most common reason for nonadherence to and discontinuation of endocrine therapy. A survey of 538 women with early-stage...
HOW AN EXPERT APPROACHES IT

breast cancer receiving endocrine treatments found that 18% of women discontinued therapy within 5 years, and 94% of them experienced adverse effects. Among those who discontinued AIs, two-thirds reported that they “did not like the adverse effects.”[15] Importantly, about 25% of the women in this study discontinued treatment without consulting a medical provider, thus missing an opportunity for guidance or shared decision making.

**Adverse Effects of Endocrine Therapy**

The adverse effects of endocrine therapy include hot flashes, vaginal dryness, dyspareunia, osteoporosis, and arthralgia/myalgia. For many of these side effects, there are proven interventions, including venlafaxine or gabapentin for hot flashes; vaginal moisturizers, dehydroepiandrosterone, the intravaginal laser MonaLisa Touch, and minimal doses of intravaginal estrogens for dyspareunia or vaginal dryness; and vitamin D and calcium supplementation, bisphosphonates, and denosumab for osteoporosis and osteopenia. Here, we will focus on arthralgia and myalgia, because mitigating these symptoms can prove especially challenging.

Arthralgia and myalgia are the most common side effects of AI treatment and contribute the most to nonadherence and discontinuation. The prevalence of AI-induced arthralgia is 50% (range, 20% to 73%).[17] Some studies combine data on arthralgia and myalgia, referring to the two together as ‘musculoskeletal symptoms.’[18] We have followed this practice here, using the term ‘AI-induced arthralgia’ to encompass myalgia as well. In one study of women with early-stage breast cancer receiving an adjuvant AI, more than half of those who discontinued treatment reported grade 2/3 arthralgia as the reason.[19]

The primary criteria defining AI-induced arthralgia are:

- Joint pain develops or worsens while a patient is taking an AI.
- If the AI is stopped for 3 weeks, the joint pain goes away. When the AI is subsequently restarted, the joint pain returns.[20]

Minor criteria include:

- The joints are affected symmetrically.
- The patient complains of pain in the hands or wrists, carpal tunnel syndrome, and/or decreased grip strength.
- Joint stiffness is worse in the morning.
- Exercise improves symptoms.

AI-induced arthralgia tends to occur soon after initiating treatment with an AI, with a median onset of 1.6 months (range, 0.4 to 10 months).[20] The mechanism(s) of AI-induced arthralgia are not entirely understood.[21] MRI findings show tenosynovitis with enhancement and thickening of the tendon sheaths, consistent with an inflammatory process.[22]

**Our Approach to Maximizing Treatment Adherence to AI Therapy**

In clinical practice, the biggest challenge of treating hormone receptor (HR)-positive breast cancer patients is helping them maintain adherence and complete the prescribed course of AI treatment. Some of the questions that clinicians often struggle with include: How do you know that the patient receiving an AI is experiencing AI-induced arthralgia, and what distinguishes it from osteoarthritis? What are the proven interventions for AI-induced arthralgia? Finally, what is the role of the healthcare provider in increasing adherence and decreasing discontinuation rates? Our experience mirrors the literature.[23]

Before starting AI therapy, weight management and increasing physical activity should be part of the routine care of every woman with breast cancer. Obesity increases breast cancer mortality, and increasing physical activity (i.e., from being sedentary), though not proven, may decrease breast cancer mortality. Increasing physical activity has a wealth of benefits beyond breast cancer, and may mitigate AI-induced arthralgia. It is beyond the scope of this article to discuss the ‘teachable moment’[24] and the ways to effect behavior modification. However, three points are worth mentioning. The first point is that women receiving AIs desire information from their oncology provider about AI-induced arthralgia, and are more likely to increase physical activity if their oncologists recommend it.[25] Second, if AI-induced arthralgia occurs, despite maintaining optimal physical activity, there are approaches to mitigate it. Finally, it should be noted that there is a placebo effect in all intervention trials. For example, as many as 50% of women reported improvements in joint pain while receiving a placebo in a randomized placebo-controlled trial of omega-3 fatty acids for AI-induced arthralgias. [26] From the patient’s point of view, it doesn’t matter whether it’s a therapeutic effect of an intervention or the placebo effect, as long as it relieves the joint pain.

Typically, we start endocrine treatment with the nonsteroidal compound anastrozole. If the patient has any preexisting arthritis, we note the sites of joint pain. As discussed previously, we describe the relatively rapid onset of AI-associated joint pain, and its typical pattern of affecting the joints symmetrically. To assess adherence, we directly ask the patient if she is taking her medication.[27]

If new joint symptoms appear while a patient is
taking an AI, do not respond to over-the-counter medications, and are of sufficient magnitude to affect activities of daily living, we recommend stopping the AI for 2 to 4 weeks. If the joint pain persists, it is not likely related to the AI. If the joint pain improves, we recommend a rechallenge with the same AI. If the joint pain reoccurs, then a causal relationship between the particular AI and the joint pain is established.

One of the simplest and most effective interventions is switching from one AI to another or to tamoxifen,[28,29]; about one-third of women who switch to another AI can tolerate the second AI for a median of nearly 14 months (range, 3 to 39 months).[30] For example, we would switch to the steroidal compound exemestane if anastrozole causes intolerable side effects. If exemestane results in joint pain, and relieves, then rechallenge if anastrozole causes intolerable side effects of nearly 14 months (range, 3 to 39 months).

For another AI can tolerate the second AI for a median of 2 to 4 weeks. If the joint pain persists, it is not related to other causes. The most effective way is to note what happens to the joint pain when the AI is stopped for about 2 to 4 weeks. If joint pain resolves, then rechallenge with the same AI. If joint pain reoccurs, causality is proven.

One of the simplest and most effective methods of maintaining adherence is in a patient who experienced AI-induced joint pain is to switch her to another AI. About 30% of women will stay on the second AI for a median of 14 months. Some women are intolerant of all three AIs and are then switched to tamoxifen.

There are several recent systematic reviews of other interventions, including high-dose vitamin D, omega-3 fatty acids, duloxetine, acupuncture, aero-

bic and resistance exercise training, yoga, and tai chi.[18,31] Many of the intervention trials have methodological problems, including small sample sizes, the inclusion of only retrospective or prospective cohorts, the use of different entry criteria for baseline level of joint pain, and the use of different instruments to measure the primary endpoint of joint pain, as well as secondary endpoints.

The results of acupuncture trials and exercise interventions, as well as studies on vitamin D, are mixed. [18] Higher doses of omega-3 fatty acids in randomized controlled trials were shown to be ineffective at reducing AI-induced arthralgia. [18] Recently, the results of a randomized placebo-controlled trial of duloxetine showed statistically and clinically significant reductions in joint pain in women receiving AIs.[32] At Mount Sinai, there is an ongoing randomized controlled trial of hyponis for women with AI-induced arthralgia. We encourage eligible patients to enroll in this trial. The uptake of the trial is high because it uses a nondrug intervention. We also often refer women with AI-induced arthralgia for acupuncture, despite the mixed trial results.

As healthcare providers, we tend to underestimate the role we play in maintaining adherence and reducing discontinuation. It is important to remember that adherence depends on a considerable degree on good physician/patient communication, as well as on the strength of the therapeutic relationship; good communication should include clear and careful explanations of risks, benefits, and alternatives to treatment. ☺

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KEY POINTS

- It should be established that a patient’s joint pain is caused by her aromatase inhibitor (AI) and not related to other causes. The most effective way is to note what happens to the joint pain when the AI is stopped for about 2 to 4 weeks. If joint pain resolves, then rechallenge with the same AI. If joint pain reoccurs, causality is proven.

- One of the simplest and most effective methods of maintaining adherence is in a patient who experienced AI-induced joint pain is to switch her to another AI. About 30% of women will stay on the second AI for a median of 14 months. Some women are intolerant of all three AIs and are then switched to tamoxifen.

- There are many trials of interventions to mitigate the pain of AI-induced arthralgia. Many of these are flawed methodologically, and are of low to moderate quality. Higher doses of vitamin D3 and omega-3 fatty acids are ineffective. However, there is recent evidence for duloxetine that shows both statistically significant and clinically meaningful reductions in AI-induced arthralgia.

- Healthcare providers have a role in increasing adherence and decreasing discontinuation rates. Adherence, in part, depends on good physician/patient communication with regard to the benefits of treatments, and available alternatives.

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REFERENCES


For previously treated metastatic NSCLC

IS TECENTRIQ® RIGHT FOR YOUR PATIENT?

Stratification factors from the OAK study\(^1\,\,2\)

<table>
<thead>
<tr>
<th>PD-L1 expression</th>
<th>Histology</th>
<th>Prior therapy</th>
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<tbody>
<tr>
<td></td>
<td>Non-squamous</td>
<td>Squamous</td>
</tr>
<tr>
<td>TC and IC &lt;1% or undetectable</td>
<td>74%</td>
<td>26%</td>
</tr>
<tr>
<td>TC or IC ≥1%</td>
<td></td>
<td></td>
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<tr>
<td>TC ≥50% or IC ≥10%</td>
<td>16%</td>
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In the OAK study, nearly half of patients had PD-L1 expression on <1% of TCs and ICs

The OAK study was a pivotal Phase III, multicenter, international, randomized, open-label trial in patients with metastatic NSCLC who progressed during or following a platinum-containing chemotherapy regimen (N=1225). The primary analysis was conducted on the first 850 randomized patients. Of the 850 patients, the median age was 64 years, 61% were male, 70% were white, and 82% were current or previous smokers. In addition, the baseline ECOG performance status was 0 (37%) or 1 (63%), 10% had a known EGFR mutation, 0.2% had known ALK rearrangements, and 75% had received only 1 prior platinum-based therapeutic regimen. Patients were randomized 1:1 to receive either TECENTRIQ 1200 mg IV q3w or docetaxel 75 mg/m\(^2\) IV q3w. The primary endpoint was overall survival (OS).\(^1\,\,2\)

**Indication**

TECENTRIQ is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving TECENTRIQ.

**Important Safety Information**

**Serious Adverse Reactions**

Please refer to the full Prescribing Information for important dose management information specific to adverse reactions.

**Immune-Related Pneumonitis**

- Immune-mediated pneumonitis or interstitial lung disease, including fatal cases, occurred with TECENTRIQ treatment
- In non-small cell lung cancer (NSCLC), pneumonitis occurred in 3.7% of patients
- Monitor patients for signs with radiographic imaging and symptoms of pneumonitis. Administer steroids for ≥Grade 2 pneumonitis. Withhold TECENTRIQ until resolution of Grade 2 pneumonitis. Permanently discontinue for Grade 3 or 4 immune-mediated pneumonitis

**Immune-Related Hepatitis**

- Immune-mediated hepatitis, including a fatal case in urothelial carcinoma (UC), and liver test abnormalities have occurred with TECENTRIQ treatment
- Across clinical trials, Grade 3 or 4 elevation occurred in ALT (2.5%), AST (2.3%), and total bilirubin (1.6%). In NSCLC, immune-mediated hepatitis occurred in 0.9% of patients
- Monitor patients for signs and symptoms of hepatitis. Monitor AST, ALT, and bilirubin prior to and periodically during treatment
- Administer corticosteroids for ≥Grade 2 transaminase elevations, with or without concomitant elevation in total bilirubin. Withhold TECENTRIQ for Grade 2, and permanently discontinue for Grade 3 or 4 immune-mediated hepatitis

**Immune-Related Colitis**

- Immune-mediated colitis or diarrhea have occurred with TECENTRIQ treatment
- Across clinical trials, colitis or diarrhea occurred in 19.7% of patients, including a fatal case of diarrhea-associated renal failure in UC. In patients with NSCLC, immune-mediated colitis or diarrhea occurred in 0.5% of patients
- Withhold TECENTRIQ for Grade 2 or Grade 3 colitis. Permanently discontinue for Grade 4 diarrhea or colitis
- Monitor patients for signs and symptoms of diarrhea or colitis. Withhold TECENTRIQ for Grade 2 or Grade 3 diarrhea or colitis. Permanently discontinue for Grade 4 diarrhea or colitis

**Immune-Related Endocrinopathies**

- Immune-related thyroid disorders, adrenal insufficiency, hypophysitis, and type 1 diabetes mellitus, including diabetic ketoacidosis, have occurred in patients receiving TECENTRIQ. Monitor patients for clinical signs and symptoms of endocrinopathies
**Important Safety Information (cont’d)**

**Immune-Related Endocrinopathies (cont’d)**

- In patients with NSCLC, hypo- and hyperthyroidism occurred in 4.2% and 1.1%, respectively. Monitor thyroid function prior to and periodically during treatment with TECENTRIQ. For symptomatic hypothyroidism, withhold TECENTRIQ and initiate hormone replacement as needed. Manage isolated hypothyroidism with replacement therapy and without corticosteroids. For symptomatic hyperthyroidism, withhold TECENTRIQ and initiate an anti-thyroid drug as needed.

- Across clinical trials, adrenal insufficiency occurred in 0.4% of patients. For symptomatic adrenal insufficiency, withhold TECENTRIQ and administer steroids.

- In UC, hypophysitis occurred in 0.2% of patients. Administer corticosteroids and hormone replacement as clinically indicated. Withhold for Grade 2 or Grade 3, and permanently discontinue for Grade 4 hypophysitis.

- New onset diabetes with ketoacidosis occurred in patients. Diabetes mellitus without an alternative etiology occurred in 0.3% of patients with NSCLC. Initiate treatment with insulin for type 1 diabetes mellitus. For Grade 3 hyperglycemia (fasting glucose >250-500 mg/dL), withhold TECENTRIQ.

**Other Immune-Related Adverse Reactions**

- Other immune-related adverse reactions, including meningoencephalitis, myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome, ocular inflammatory toxicity, and pancreatitis, including increases in serum amylase and lipase levels, have occurred in ≤1.0% of patients treated with TECENTRIQ.

- Symptomatic pancreatitis without an alternative etiology occurred in 0.1% of patients across clinical trials.

- Monitor patients for clinical signs and symptoms of meningitis or encephalitis, as well as symptoms of motor and sensory neuropathy. Permanently discontinue TECENTRIQ for any grade of meningitis or encephalitis, or any grade of myasthenic syndrome/myasthenia gravis or Guillain-Barré syndrome.

- Monitor patients for signs and symptoms of acute pancreatitis. Withhold TECENTRIQ for Grade 3 serum amylase or lipase levels (>2.0 ULN), or Grade 2 or 3 pancreatitis. Permanently discontinue for Grade 4 or any grade of recurrent pancreatitis.

**Infection**

- Severe infections, including sepsis, herpes encephalitis, and mycobacterial infection leading to retroperitoneal hemorrhage, occurred in patients receiving TECENTRIQ.

- In patients with NSCLC, infection occurred in 43% of patients treated with TECENTRIQ compared with 34% of patients treated with docetaxel. Grade 3 or 4 infection occurred in 9.2% of patients treated with TECENTRIQ compared with 2.2% with docetaxel. Two patients (1.4%) treated with TECENTRIQ died. Pneumonia was the most common cause of Grade 3 or higher infection, occurring in 7.7% of patients.

- Monitor patients for signs and symptoms of infection and treat with antibiotics for suspected or confirmed bacterial infections. Withhold TECENTRIQ for ≥Grade 3 infection.

**Infusion-Related Reactions**

- Severe infusion reactions have occurred in patients in clinical trials of TECENTRIQ.

- In patients with NSCLC, infusion-related reactions occurred in 16.6% of patients.

- Interrupt or slow the rate of infusion in patients with Grade 2 infusion-related reactions. Permanently discontinue TECENTRIQ in patients with Grade 3 or 4 infusion reactions.

**Embryo-Fetal Toxicity**

- Based on its mechanism of action, TECENTRIQ can cause fetal harm when administered to a pregnant woman. Advise pregnant women or women planning to become pregnant of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with TECENTRIQ and for at least 5 months after the last dose of TECENTRIQ.

**Nursing Mothers/Fertility**

- Because of the potential for serious adverse reactions in breastfed infants from TECENTRIQ, advise female patients not to breastfeed while taking TECENTRIQ and for at least 5 months after the last dose.

- Based on animal studies, TECENTRIQ may impair fertility in females of reproductive potential while receiving treatment.

**Most Common Adverse Reactions**

The most common adverse reactions in NSCLC (rate ≥20%) included fatigue (46%), decreased appetite (35%), dyspnea (26%), cough (20%), nausea (22%), musculoskeletal pain (22%), and constipation (20%).

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at 1-888-835-2555.

**Please see Brief Summary of Prescribing Information on adjacent pages.**

**References:**


Thyroid Disorders
Thyroid function was assessed routinely only at baseline and the end of the study. Monitor thyroid function prior to and periodically during treatment with TECENTRIQ. Asymptomatic patients with abnormal thyroid function tests can continue to receive TECENTRIQ for symptomatic benefit. For symptomatic hypothyroidism, withhold TECENTRIQ and initiate thyroid hormone replacement as needed. Manage isolated hyperthyroidism with antithyroid drug therapy and withhold TECENTRIQ. For symptomatic hyperthyroidism, withhold TECENTRIQ and initiate an anti-thyroid drug as needed. Resume treatment with TECENTRIQ when symptoms of hypothyroidism or hyperthyroidism are controlled and thyroid function is improving [see Clinical Studies (14.2) and Adverse Reactions (6.2)].

Across clinical trials, hypothyroidism and hyperthyroidism occurred in 3.9% (77/1978) and 1.0% (20/1978) of patients, respectively.

Urinary Tract Infection
In 523 patients with urothelial carcinoma who received TECENTRIQ, urinary tract infection occurred in 21.7% (112/523) of patients across clinical trials, including two patients with Grade 3 infection. One patient had Grade 2 and one patient had Grade 1 urinary tract infection. TECENTRIQ was held due to infection in 2.2% (11/523) of patients and temporary interruption of TECENTRIQ in 2.2% (11/523) of patients. Patients with Grade 3 or higher urinary tract infection included seven patients with Grade 3 and four patients with Grade 2 urinary tract infection.

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6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in specific sections of the label:

- Immune-Related Pneumonitis [see Warnings and Precautions (5.5)]
- Immune-Related Hepatitis [see Warnings and Precautions (5.5)]
- Immune-Related Colitis [see Warnings and Precautions (5.5)]
- Immune-Related Endocrinopathies [see Warnings and Precautions (5.4)]
- Other Immune-Related Adverse Reactions [see Warnings and Precautions (5.5)]
- Infection [see Warnings and Precautions (5.6)]
- Infusion-Related Reactions [see Warnings and Precautions (5.7)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Urothelial Carcinoma

Cisplatin-Ineligible Patients with Locally Advanced or Metastatic Urothelial Carcinoma

The safety of TECENTRIQ was evaluated in Study 4, a multicenter, open-label, single-arm trial that included 119 patients with locally advanced or metastatic urothelial carcinoma who were ineligible for cisplatin-containing chemotherapy and were either previously untreated or had disease progression at least 12 months after neoadjuvant or adjuvant chemotherapy [see Clinical Studies (14.1)]. Patients received 1200 mg of TECENTRIQ intravenously every 3 weeks until either unacceptable toxicity or disease progression. The median duration of exposure was 15.0 weeks (range 0, 67 weeks).

The most common adverse reactions (≥ 10%) were fatigue (52%), increased alanine transaminase (ALT) (30%), hypertension, decreased appetite, pyrexia, and proteinuria. The most common serious adverse reactions (≥ 2%) were urinary tract infection, anemia, diarrhea, malaise, nausea, dyspnea, and colitis. Thirty patients (25%) received an overall predose dose equivalent to > 40 mg daily for an immune-mediated adverse reaction [see Warnings and Precautions (5)].

Table 1 summarizes the adverse reactions that occurred in ≥ 10% of patients and Table 2 summarizes grade 3–4 laboratory abnormalities in patients treated with TECENTRIQ.

Table 1: All Grade Adverse Reactions in ≥ 10% of Patients with Urothelial Carcinoma in Study 4

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TECENTRIQ N = 119</th>
<th>Grades 3–4</th>
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<tr>
<td>General Disorders</td>
<td></td>
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<tr>
<td>Fatigue</td>
<td>52 (44%)</td>
<td>6 (5%)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>17 (14%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>14 (12%)</td>
<td>0.8%</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>24 (20%)</td>
<td>6 (5%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>22 (18%)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>16 (14%)</td>
<td>0.8%</td>
</tr>
<tr>
<td>Constipation</td>
<td>15 (13%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>15 (13%)</td>
<td>0.8%</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>24 (20%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Musclekeletal and Connective Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back/Neck pain</td>
<td>18 (15%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>13 (11%)</td>
<td>0</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>18 (15%)</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>17 (15%)</td>
<td>0.8%</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>17 (15%)</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>Respiratory, Thoracic, and Mediastinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>14 (12%)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>12 (10%)</td>
<td>0</td>
</tr>
</tbody>
</table>

6.1.1 Adverse Reactions Associated with Clinical Trials Experience

Table 2: Grade 3–4 Laboratory Abnormalities in Patients with Urothelial Carcinoma in Study 4 in ≥ 1% of Patients (continued)

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Grades 3–4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased Alkaline phosphatase</td>
<td>7 (7%)</td>
</tr>
<tr>
<td>Increased Creatinine</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Increased LDH</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Increased AST</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>2 (2%)</td>
</tr>
</tbody>
</table>

Previously Treated Patients with Locally Advanced or Metastatic Urothelial Carcinoma

The safety of TECENTRIQ was evaluated in Study 1, a multicenter, open-label, single-arm trial that included 310 patients in a single arm trial with locally advanced or metastatic urothelial carcinoma who had disease progression during or following at least one platinum-containing chemotherapy regimen or who had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen [see Clinical Studies (14.1)]. Patients received 1200 mg of TECENTRIQ intravenously every 3 weeks until unacceptable toxicity or either radiographic or clinical progression. The median duration of exposure was 12.3 weeks (range: 0.1, 46 weeks).

The most common adverse reactions (≥ 10%) were fatigue (52%), decreased appetite (26%), nausea (25%), urinary tract infection (22%), pyrexia (21%), and constipation (21%). The most common grade 3–4 adverse reactions (≥ 2%) were urinary tract infection, anemia, fatigue, dehydration, intestinal obstruction, urinary obstruction, hematuria, dyspnea, acute kidney injury, abdominal pain, venous thromboembolism, sepsis, and pneumonia.

Table 3 summarizes the adverse reactions that occurred in ≥ 10% of patients while Table 4 summarizes grade 3–4 selected laboratory abnormalities that occurred in ≥ 1% of patients treated with TECENTRIQ in Study 1.
The safety of TECENTRIQ was evaluated in Study 3, a multicenter, international, randomized, open-label trial in patients with metastatic NSCLC who progressed during or following a platinum-containing regimen, regardless of PD-L1 expression [see Clinical Studies (14.2)]. Patients received 1200 mg of TECENTRIQ (n=142) administered intravenously every 3 weeks until unacceptable toxicity or either radiographic or clinical progression or docetaxel (n=135) administered intravenously at 75 mg/m² every 3 weeks until unacceptable toxicity or disease progression. The median duration of exposure was 3.7 months (range: 0–19 months) in TECENTRIQ-treated patients and 2.1 months (range: 0–17 months) in docetaxel-treated patients.

The most common adverse reactions (≥20%) in patients receiving TECENTRIQ were fatigue (46%), decreased appetite (35%), dyspnea (32%), cough (30%), nausea (22%), musculoskeletal pain (22%), and constipation (20%). The most common Grade 3–4 adverse reactions (≥2%) were dyspnea, pneumonia, hypoxia, hypotension, fatigue, anemia, musculoskeletal pain, PAI, and AR. Nine patients (6.3%) who were treated with TECENTRIQ experienced either pulmonary embolism (2), pancytopenia, ulcer hemorrhage, carotid artery secondary to dysphagia, or cardiac infarction, or large intestinal perforation which led to death. TECENTRIQ was discontinued due to adverse reactions in 4% (6/142) of patients. Adverse reactions leading to interruption of TECENTRIQ occurred in 24% of patients; the most common (≥1%) were pneumonia, liver function test abnormality, upper respiratory tract infection, pneumonia, acute kidney injury, hypoxia, hypothyroidism, dyspnea, anemia, and fatigue. Serious adverse reactions occurred in 37% of patients. The most frequent serious adverse reactions (≥2%) were pneumonia, dyspnea, pleural effusion, pyrexia, and venous thromboembolism. Table 5 summarizes adverse reactions that occurred in at least 10% of TECENTRIQ-treated patients and at a higher incidence than in the docetaxel arm. Table 6 summarizes selected laboratory abnormalities worsening from baseline that occurred in ≥10% of TECENTRIQ-treated patients and at a higher incidence than in the docetaxel arm.

Table 5: Adverse Reactions Occurring in ≥10% of TECENTRIQ-Treated Patients with NSCLC and at a Higher Incidence than in the Docetaxel Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3–4] (Study 3))

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TECENTRIQ</th>
<th>Docetaxel</th>
<th>Percentage (% of Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>18</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>18</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>35</td>
<td>21</td>
<td>12</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>16</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Back pain</td>
<td>14</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>14</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>32</td>
<td>7</td>
<td>24</td>
</tr>
<tr>
<td>Cough</td>
<td>30</td>
<td>1</td>
<td>25</td>
</tr>
</tbody>
</table>

Table 6: Selected Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of TECENTRIQ-Treated Patients with NSCLC and at a Higher Incidence than in the Docetaxel Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3–4] (Study 3))

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>TECENTRIQ</th>
<th>Docetaxel</th>
<th>Percentage (% of Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size (%) of Patients with Worsening Laboratory Test from Baseline 4% (6/142)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>48</td>
<td>13</td>
<td>32</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>48</td>
<td>5</td>
<td>49</td>
</tr>
<tr>
<td>Alkaline Phosphatase increased</td>
<td>42</td>
<td>2</td>
<td>24</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>33</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>31</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>19</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>Haptoglobin</td>
<td>18</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>13</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Total Bilirubin increased</td>
<td>11</td>
<td>0</td>
<td>5</td>
</tr>
</tbody>
</table>

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Among 275 patients in Study 1, 114 patients (41.5%) tested positive for treatment-emergent (treatment-induced or treatment-enhanced) anti-therapeutic antibodies (ATA) at one or more post-dose time points. Among 135 patients in Study 3, 73 patients (54.1%) tested positive for treatment-emerging ATAs at one or more post-dose time points. Among 111 patients in Study 4, 53 patients (47.7%) tested positive for treatment-emerging ATAs at one or more post-dose time points. In Study 1, Study 3, and Study 4, the presence of ATAs did not appear to have a clinically significant impact on pharmacoenergetics, safety, or efficacy. Immunogenicity results are only applicable to patients with ECOG 0, patients with adequate organ function, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of incidence of ATAs to TECENTRIQ with the incidence of antibodies to their proteins may be misleading.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, TECENTRIQ can cause fetal harm when administered to a pregnant woman [see Nonclinical Toxicology (12.1)]. There are no available data in animals on the use of TECENTRIQ during human pregnancy. Animal studies have demonstrated that if the PD-L1/PD-1 pathway is blocked can lead to increased risk of immune-related reaction of the developing fetus resulting in fetal death (see Data). If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential risk to the fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in women 15–44 years is 2% to 4% and 15% to 20%, respectively.
Initiation of ADT in a Man With Locally Advanced Prostate Cancer and Multiple Cardiovascular Risk Factors

Francisco J. Castro-Alonso, MD1, Jennifer Dominguez-Pineda, MD1, Guillermo Rosales-Sotomayor1, Thomas W. Flaig, MD2, María T. Bourlon, MD, MS1

The Case
A 65-year-old man presented with locally advanced, high-risk prostate cancer. His medical history was remarkable for type 2 diabetes mellitus (T2DM) treated with metformin, 500 mg BID. He was also overweight and had dyslipidemia and hypertension, although he was not receiving medical therapy for any of these problems. He was an active smoker with a 27 pack-year history.

His prostate-specific antigen (PSA) level was 32 ng/mL; no other recent PSA measurements were available. Digital rectal examination revealed a fixed prostate (cT4) not amenable to surgical resection; his prostate biopsy showed an acinar adenocarcinoma in 8 of 12 cores, with a Gleason score of 4+4=8. He underwent a bone scan and CT scanning of the chest, abdomen, and pelvis, which showed no evidence of metastatic disease. He was offered treatment with external beam radiation therapy (EBRT) and androgen deprivation therapy (ADT) with degarelix.

Upon ADT initiation, his blood pressure (BP) was 140/90 mm Hg and his body mass index (BMI) was 27.2 kg/m². Laboratory workup revealed a fasting glucose level of 123 mg/dL and a glycosylated hemoglobin (HbA₁c) of 7.1%. His lipid profile showed: triglycerides, 180 mg/dL; total cholesterol, 170 mg/dL; high-density lipoprotein cholesterol (HDL-C), 30 mg/dL; and low-density lipoprotein cholesterol (LDL-C), 140 mg/dL. His serum creatinine level was 0.7 mg/dL and his calculated creatinine clearance, adjusted for overweight, was 103 mL/min. An electrocardiogram was normal.

According to the American College of Cardiology (ACC)/American Heart Association (AHA) Cardiovascular (CV) Risk Calculator,[1] the patient’s 10-year risk for atherosclerotic cardiovascular disease (CVD)—defined as coronary death, nonfatal myocardial infarction, or fatal or nonfatal stroke—was 49.6%. This CV risk calculation mandated strict metabolic control for the management of his CV risk factors.

Which of the following is the best way to manage cardiovascular comorbidities in this patient?

A. Lifestyle interventions only
B. Lifestyle interventions + moderate-intensity statin + BP target < 140/90 mm Hg
C. Lifestyle interventions + high-intensity statin + BP target < 140/90 mm Hg
D. Lifestyle interventions + high-intensity statin + BP target < 130/80 mm Hg
E. Lifestyle interventions + high-intensity statin + BP target < 130/80 mm Hg + aspirin

Answer and full discussion appear on page 244.
**Discussion**

Prostate cancer is an exquisitely hormone-sensitive malignancy, and ADT is the mainstay of treatment in locally advanced and metastatic disease.[2,3] The therapeutic benefits of ADT are offset by a plethora of side effects, among which CVD is of greatest concern.[4] The association between ADT and fatal and nonfatal CVD is attested to by large retrospective and observational studies.[5,6] These data led to a joint statement by the AHA, the American Cancer Society, the American Urological Association, and the American Society for Radiation Oncology to raise awareness about CV consequences of ADT.[7] The aforementioned findings were not confirmed in a recent meta-analysis of randomized trials.[8] Potential reasons for this discrepancy may be the selection of a healthier population in clinical trials, underpowered post-hoc analysis, and short follow-up.[9]

The mechanism of action of the type of hormonal therapy prescribed may impact CVD risk. Hormonal treatment can be accomplished by reducing testosterone production (surgical orchietomy or medical castration) or by blocking the interaction of androgen receptors with testosterone. The Swedish National Data Service reported an increased risk of incident CVD with gonadotropin-releasing hormone (GnRH) agonists and orchietomy, and a decreased risk with anti-androgens.[10] In the meta-analysis by Zhao et al, GnRH agonists, and GnRH agonists plus anti-androgens, were associated with CVD, but not anti-androgens alone or orchietomy.[5] A meta-analysis by Bosco et al showed an increased risk of nonfatal CVD with GnRH agonists, anti-androgens, and orchietomy.[6] Recently, orchietomy was reported to be associated with higher rates of CV events in older patients and those with a history of CV comorbidities within 1.5 years of initiating ADT.[11] With regard to GnRH antagonists vs agonists, reports are divergent. A nationwide French database reported no difference in CVD risk between GnRH agonists and antagonists.[12] However, post-hoc pooled data from six randomized trials showed that GnRH antagonists were associated with a significantly lower risk of cardiac events, compared with GnRH agonists. These same data led clinicians to the conclusion that it may be safer to prescribe antagonists in men at high risk for CVD.[13] These data supported our decision to start hormonal therapy with degarelix, a GnRH antagonist, in this case.

Several potential pathophysiologic mechanisms link ADT with CVD. Pro-atherogenic metabolic

---

**Table. Summary of ACC/AHA and ADA Recommendations**

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Recommendations</th>
<th>Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM, aged 40–75 yr, LDL-C &gt; 190 mg/dL without clinical atherosclerotic CVD</td>
<td>High-intensity statin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No recommendations for or against specific LDL-C or non–HDL-C targets</td>
</tr>
<tr>
<td>Aged 40–75 yr, LDL-C 70–189 mg/dL without clinical CVD or DM</td>
<td>High-intensity statin&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1 (BP 130–139/80–89 mm Hg)</td>
<td>Moderate-intensity statin&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Stage 2 (BP ≥ 140/90 mm Hg)</td>
<td>Moderate-intensity statin&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>LDL-C &lt; 70 mg/dL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LDL-C ≥ 70 mg/dL</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>High-intensity statin: atorvastatin 40–80 mg/dL, rosuvastatin 20–40 mg/dL, or simvastatin 80 mg/dL.  
<sup>b</sup>Moderate-intensity statin: atorvastatin 10–20 mg/dL, rosuvastatin 5–10 mg/dL, or simvastatin 20–40 mg/dL.  
<sup>c</sup>A HbA<sub>1c</sub> target of <6.5% may be reasonable in younger patients with no comorbidities. Less stringent HbA<sub>1c</sub> goals (<8%) may be appropriate for patients with comorbidities (hypoglycemia and/or drug adverse effects).

BP = blood pressure; CVD = cardiovascular disease; DM = diabetes mellitus; HbA<sub>1c</sub> = hemoglobin A<sub>1c</sub>; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LI = lifestyle interventions; Rx = pharmacological.

changes, similar to those of metabolic syndrome, have been described in patients receiving ADT. These include sarcopenia obesity (decrease in lean body mass and subcutaneous fat increase), dyslipidemia (increase in triglycerides, total cholesterol, LDL-C, and HDL-C), insulin resistance, and increased fasting plasma glucose levels.[14,15] However, in some respects, the metabolic changes seen with ADT are different from metabolic syndrome: an increase in subcutaneous rather than visceral fat, and an increase in HDL-C levels instead of the decrease typically seen in metabolic syndrome.[14]

The greatest risk of a first CV event after the initiation of ADT is within the first year of treatment. These early events may not be due solely to accelerated atherosclerosis, since this develops more chronically than acutely.[10] Testosterone at physiologic levels has many antithrombotic effects, including stimulation of nitric oxide production, reduction of thromboxane A2 release from platelets, and increased expression of tissue plasminogen activator.[16-18] Testosterone has also been noted to have a potential antiarrhythmic effect—shortening the QT interval.[19] Therefore, testosterone depletion may impact a man’s health through multiple physiologic channels. In addition, ADT has been associated with cytokine derangements in the tumor microenvironment, resulting in increased IFN-γ production by T lymphocytes (activated by stimulation of GnRH receptors in these cells), with subsequent plaque instability and rupture.[9]

Guidelines suggest that every patient starting ADT for prostate cancer should be screened and assessed for CVD and CV risk factors. Preexisting CVD may further increase ADT’s deleterious side effects. In the Swedish population study, men with a history of two or more CVD events in the year prior to ADT initiation had the highest CVD risk.[10] In a retrospective cohort of patients with high-risk prostate cancer, the addition of ADT to radiation therapy was associated with increased risk of all-cause mortality among men with previous congestive heart failure or myocardial infarction, but not in men without these prior events.[20]

Clinicians must weigh the benefit of starting ADT against the potential CV toxicity on an individual patient basis. An internist, a primary care physician, a cardiologist, or a cardio-oncologist should be part of the tumor board or management team whenever possible.[14] Evaluating the patient’s personal history of preexisting CVD is of utmost importance. There are no specific recommendations for the management of CVD in prostate cancer patients undergoing ADT. Similar to the “ABCDE” steps for controlling CV risk factors in cancer survivors, an “ABCDE” mnemonic was developed for prostate cancer patients: Awareness/Aspirin, Blood pressure, Cholesterol/Cigarettes, Diabetes/Diet, and Exercise.[21,22] This mnemonic emphasizes the importance of adhering to the established guidelines (ACC/AHA, American Diabetes Association, the Obesity Society) regarding the detection and management of CV comorbidities.

Lifestyle interventions include, but are not limited to: smoking cessation; 150 minutes per week of moderate-intensity physical activity; and a diet rich in fruits, vegetables, and whole grains, and low in saturated fat. While these interventions are recommended, they may be insufficient by themselves to achieve this patient’s metabolic goals. A recent meta-analysis showed that an exercise program can overcome many ADT adverse effects, but may not have a noticeable impact on many important cardiometabolic parameters, such as triglycerides, LDL-C, and fasting glucose level. [23] Thus, Answer A is incorrect, since lifestyle interventions alone will likely be insufficient to modify this patient’s metabolic risk factors.

According to the 2013 ACC/AHA Guidelines on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults,[24] this patient fits in the statin benefit group of individuals aged 40–75 years with diabetes, LDL-C of 70–189 mg/dL, and an estimated 10-year atherosclerotic CVD risk of ≥ 7.5%. Dyslipidemia treatment for such persons consists of therapy with a high-intensity statin. Therefore, Answer B is incorrect, because moderate-intensity statin therapy will be insufficient for achieving the desired cholesterol reductions.

According to the 2017 ACC/AHA Guideline for the Prevention, Detection, Evaluation, and Management of High BP in Adults,[25] this patient has stage 2 hypertension (≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic). Therefore, at least one BP-lowering medication should be initiated. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are attractive options in patients with T2DM since they decrease CVD mortality in this population.[22,26] Because this man’s 10-year atherosclerotic CVD risk is ≥ 10%, a BP target of less than 130/80 mm Hg is recommended. Thus, Answer C is incorrect.

In 2016, the US Preventive Services Task Force published its latest statement on aspirin use in CVD prevention.[27] The patient in this case fits in the group of adults aged 60 to 69 years with a ≥ 10% atherosclerotic CVD risk; in this group, the decision to initiate low-dose aspirin should be individualized. This man has a low bleeding risk and a high CVD risk because of his comorbidities and impending initiation of ADT. There is also interesting evidence about aspirin use and its benefit in cancer-specific mortality in prostate cancer patients, especially high-risk patients.[28,29] Thus, as-

**KEY POINTS**

- **Androgen deprivation therapy (ADT)** for prostate cancer is associated with increased risk of fatal and nonfatal cardiovascular (CV) events.
- The type of ADT used, preexisting CV events, and CV comorbidities modify the magnitude of this risk.
- Currently for those patients with CV risk factors, strict comorbidity management as delineated by national guidelines is indicated.
- An “ABCDE” mnemonic may help with remembering the various useful interventions in comorbidity management: Awareness/Aspirin, Blood pressure, Cholesterol/Cigarettes, Diabetes/Diet, and Exercise.
pirin use is recommended, and Answer D is incorrect.

According to current national guideline recommendations, summarized in the Table, Answer E is the correct answer in this case. The patient has a 10-year atherosclerotic CVD risk > 10% and must start lifestyle interventions, high-intensity statin therapy, BP lowering with a goal of < 130/80 mm Hg, and low-dose aspirin. Several other interventions are worthwhile in the management of CV comorbidities, since they are tightly interconnected with CV outcomes. These include weight management (lowering BMI and abdominal perimeter) and T2DM treatment goals. Adherence to published clinical guidelines is highly recommended in patients with prostate cancer and metabolic comorbidities who will be starting hormonal therapy. [30, 31]

Outcome of This Case

The importance of lifestyle interventions was explained to the patient and he was sent to a tobacco cessation clinic. Antihypertensive treatment was started with enalapril 10 mg/d; strict BP monitoring was advised to achieve the goal of < 130/80 mmHg. His metformin dose was increased to 850 mg TID, and he achieved a fasting glucose level of 80–130 mg/dL and Hba1c of < 7.0%. He was also started on high-intensity statin therapy (rosuvastatin 20 mg/d) and aspirin. His last lipid profile showed triglycerides of 156 mg/dL, total cholesterol of 126 mg/dL, HDL-C of 32 mg/dL, and LDL-C of 62 mg/dL. The patient completed EBRT and 24 months of hormonal therapy with degarelix. His last scans showed him to be disease-free, and his last PSA level was 0.01 ng/dL.

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REFERENCES

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Robert Chapkin on relationships between the gut microbiome, diet, and colorectal cancer

We have become very familiar with reports in the media comparing the health effects of Western diets, typically heavy in animal fats and proteins, with Asian and Mediterranean diets, which include more fish and place greater emphasis on consumption of fruits, vegetables, and whole grains. There is a growing body of evidence that bioactive molecules deriv- ed from pesco-vegetarian meals offer better protection against colorectal cancer than meat-based diets. More recent research has delved even deeper into the beneficial and detrimental effects of dietary components at the molecular level—examining how what we eat and drink influences the quantity and diversity of gut bacteria, and, in turn, evaluating the ways in which the gut microbiota may impact colorectal cancer risk. ONCOLOGY recently interviewed cell biologist and nutritional biochemist Robert Chapkin, MSc, PhD, Distinguished Professor and Allen Endowed Chair in Nutrition & Chronic Disease Prevention in the department of nutrition and food science at Texas A&M University in College Station, Texas, to discuss both his work and the current state of the science in this pioneering area of cancer research.

1 Could you please provide some background on the beginnings of research into the relationship between gut microbiota and colon cancer? What are one or two pivotal studies in this area?

Dr. Chapkin: Only recently has it been appreciated that intestinal microbiota influences the development of colorectal tumors in preclinical models and human subjects. There have been many studies highlighting the interplay between host genetics, gut microbes, and intestinal tumor initiation/progression. However, the seminal works of Arthur,[1] Tao,[2] and O’Keefe[3] stand out in my mind.

The Arthur laboratory findings provided novel insight into the complex effects of inflammation on microbial composition/activity and the host’s (intestinal mucosa) ability to protect itself from microorganisms with genotoxic capabilities. Also, from a mechanistic perspective, the Tao lab findings demonstrated that Frizzled proteins (receptors that regulate Wnt signaling, required for colonic stem cell maintenance, self-renewal, and repair of the epithelial lining) can be activated by toxin B produced by pathogenic bacteria (Clostridium difficile). These findings demonstrate that colonic stem cells are the target of some microbial toxins.

Lastly, the O’Keefe lab findings demonstrated that dietary fiber and fat content have a remarkable effect on the colonic microbiota and its metabolic activity in high-risk vs low-risk cancer populations. His work supports the claim that total fiber intake needs to exceed 50 g per day to prevent colon cancer.

2 What key principles (eg, inflammation) or hypothesis models (eg, bacterial driver/passenger or keystone/pathogen models) are important to understanding how the gut microbiome modulates intestinal cells, immune cells, and malignant cells in the gut?

Dr. Chapkin: There is ample evidence that the microbiome (eg, patchy bacterial biofilms) in the gut can modulate host immune cell function, promoting low-grade chronic inflammation. This, combined with intestinal barrier deterioration induced by (1) colorectal cancer–initiating genetic lesions, and (2) crosstalk between microbiota and diets low in fiber, results in the invasion of secreted microbial products (eg, oncotoxins), which can drive tumor growth. Intriguingly, the protective effects of dietary fiber on cancer development may...
be based on dramatic shifts in microbial community function—particularly short-chain fatty acid production—which stimulate gut mucosal metabolism and increase epithelial barrier function. These findings suggest that precision (personalized) nutrition might be utilized to favorably modulate an individual’s microbiota to reduce cancer risk.

A review you coauthored in Seminars in Cancer Biology cites studies showing that some microbiota produce DNA-damaging toxins, and that others are known to activate tumor-promoting pathways.[4] You describe multiple “omics” techniques and analyses that could shed light on targetable microbiota/microenvironment interactions of potential use in colorectal cancer prevention and treatment. Could you please highlight two or three of the more promising approaches?

**DR. CHAPKIN:** A major gap in the field lies in the methodological limitations of assessing the multivariate relationships among the microbial metagenome (DNA), metatranscriptome (messenger RNA), metabolome (small molecules), and the host transcriptome and metabolome in the gut over time. Our collaborative interdisciplinary team, made up of biologists, engineers, bioinformaticians, and clinician scientists, is developing novel latent variable Bayesian data fusion and network-based algorithms to predict disease risk. The goal is to establish “molecular fingerprints,” which is a first step in identifying host/microbial targets that are amenable to interventions to optimize health and reduce the risk of chronic sequelae of inflammation and cancer.

Even your earliest undergraduate and graduate work in the early to mid 1980s was focused on cell biology and nutrition. Could you please share with our readers what drew you to this fascinating field of study?

**DR. CHAPKIN:** I have always been interested in using cutting-edge experimental tools to determine how and why nutrition, or diet, modifies disease risk. Since only a small fraction of biomedical research funding is devoted to the generation of new knowledge related to cancer prevention, my lab has always had to push the mechanistic boundaries of dietary chemoprevention. Fortunately, our interest in the (1) synergistic effects of systemic and luminal metabolites on intestinal stem cells, (2) development of a novel noninvasive methodology using exfoliated cells (exfoliome) to monitor host/microbe interactions, (3) effects of dietary/microbial bioactives on plasma membrane structure and function, and (4) investigation of the role of dietary and microbial ligands as modifiers of inflammation and colon cancer development, has been well received by the scientific community.

**Financial Disclosure:** The author has no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

**REFERENCES**

To reduce the risk of radiographic progression in metastatic CRPC†

83% reduction in the risk of radiographic progression or death‡
with XTANDI + GnRH therapy* vs placebo + GnRH therapy*†

• HR = 0.17 (95% CI, 0.14-0.21); P < 0.0001

Overall survival, co-primary endpoint§: 23% reduction in risk of death with
XTANDI + GnRH therapy* vs placebo + GnRH therapy* (HR = 0.77 [95% CI, 0.67-0.88])†

Indication
XTANDI (enzalutamide) capsules is indicated for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC).

Important Safety Information

Contraindications
XTANDI is not indicated for women. XTANDI can cause fetal harm and potential loss of pregnancy.

Warnings and Precautions

Seizure occurred in 0.5% of patients receiving XTANDI in clinical studies. In a study of patients with predisposing factors, seizures were reported in 2.2% of patients. See section 5.1 of the Prescribing Information for the list of predisposing factors. It is unknown whether anti-epileptic medications will prevent seizures with XTANDI. Permanently discontinue XTANDI in patients who develop a seizure during treatment.

Posterior Reversible Encephalopathy Syndrome (PRES) In postapproval use, there have been reports of PRES in patients receiving XTANDI. PRES is a neurological disorder which can present with rapidly evolving symptoms including seizure, headache, lethargy, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably MRI. Discontinue XTANDI in patients who develop PRES.

Adverse Reactions

The most common adverse reactions (≥ 10%) that occurred more commonly (≥ 2% over placebo) in the XTANDI patients from the two placebo-controlled clinical trials were asthenia/fatigue, back pain, decreased appetite, constipation, arthralgia, diarrhea, hot flush, upper respiratory tract infection, peripheral edema, dyspnea, musculoskeletal pain, weight decreased, headache, hypertension, and dizziness/vertigo.

In the bicalutamide-controlled study of chemotherapy-naïve patients, the most common adverse reactions (≥ 10%) reported in XTANDI patients were asthenia/fatigue, back pain, musculoskeletal pain, hot flush, hypertension, nausea, constipation, upper respiratory tract infection, diarrhea, and weight loss.

In the placebo-controlled study of patients taking XTANDI who previously received docetaxel, Grade 3 and higher adverse reactions were reported among 47% of XTANDI patients and 53% of placebo patients. Discontinuations due to adverse events were reported for 16% of XTANDI patients and 18% of placebo patients. In the placebo-controlled study of chemotherapy-naïve patients, Grade 3-4 adverse reactions were reported in 44% of XTANDI patients and 37% of placebo patients. Discontinuations due to adverse events were reported for 6% of both study groups. In the bicalutamide-controlled study of chemotherapy-naïve patients, Grade 3-4 adverse reactions were reported in 38.8% of XTANDI patients and 37.6% of bicalutamide patients. Discontinuations due to adverse events were reported for 7.6% of XTANDI patients and 6.3% of bicalutamide patients.

Lab Abnormalities: In the two placebo-controlled trials, Grade 1-4 neutropenia occurred in 15% of XTANDI patients (1% Grade 3-4) and 6% of placebo patients (0.5% Grade 3-4). Grade 1-4 thrombocytopenia occurred in 6% of XTANDI patients (0.3% Grade 3-4) and 5% of placebo patients (0.5% Grade 3-4). Grade 1-4 elevations in ALT occurred in 10% of XTANDI patients.
CI, confidence interval; GnRH therapy, gonadotropin-releasing hormone therapy; HR, hazard ratio; mCRPC, metastatic castration-resistant prostate cancer.

*Or after bilateral orchiectomy.1
†As seen in the PREVAIL trial (Study 2): a multinational, double-blind, randomized, phase 3 trial that enrolled 1717 patients with metastatic CRPC who progressed on GnRH therapy or after bilateral orchiectomy, and who had not received prior cytotoxic chemotherapy. All patients continued on GnRH therapy.1,3
‡Radiographic progression was assessed by blinded Independent Central Review (ICR) per Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria for bone lesion progression and/or Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) for soft tissue/visceral disease progression.1,3
§An updated survival analysis was conducted when 784 deaths were observed. The median follow-up time was 31 months. Results from this analysis were consistent with those from the prespecified interim analysis.1

II Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.2

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(0.2% Grade 3-4) and 16% of placebo patients (0.2% Grade 3-4). Grade 1-4 elevations in bilirubin occurred in 3% of XTANDI patients (0.1% Grade 3-4) and 2% of placebo patients (no Grade 3-4).

Infections: In the study of patients taking XTANDI who previously received docetaxel, 1% of XTANDI patients compared to 0.3% of placebo patients died from infections or sepsis. In the study of chemotherapy-naïve patients, 1 patient in each treatment group (0.1%) had an infection resulting in death.

Falls (including fall-related injuries) occurred in 9% of XTANDI patients and 4% of placebo patients in the two placebo-controlled trials. Falls were not associated with loss of consciousness or seizure. Fall-related injuries were more severe in XTANDI patients, and included non-pathologic fractures, joint injuries, and hematomas.

Hypertension occurred in 11% of XTANDI patients and 4% of placebo patients in the two placebo-controlled trials. No patients experienced hypertensive crisis. Medical history of hypertension was balanced between arms. Hypertension led to study discontinuation in < 1% of patients in each arm.

Drug Interactions

Effect of Other Drugs on XTANDI Avoid strong CYP3A4 inhibitors, as they can increase the plasma exposure to XTANDI. If co-administration is necessary, increase the dose of XTANDI.

Effect of XTANDI on Other Drugs Avoid CYP3A4, CYP2C9, and CYP2C19 substrates with a narrow therapeutic index, as XTANDI may decrease the plasma exposures of these drugs. If XTANDI is co-administered with warfarin (CYP2C9 substrate), conduct additional INR monitoring.

Please see adjacent pages for Brief Summary of Full Prescribing Information.

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Seizure
Seizure occurred in 0.5% of patients receiving XTandi in clinical studies. In these trials patients with predisposing factors for seizure were generally excluded. Seizure occurred from 31 to 603 days after initiation of XTandi. Patients experiencing seizures were permanently discontinued from therapy and all seizure events resolved. In a single-arm trial designed to assess the risk of seizure in patients with pre-disposing factors for seizure, 8 of 106 (7.6%) XTandi-treated patients experienced a seizure. Three of the 8 patients experienced a second seizure during continued treatment with XTandi after their first seizure resolved. It is unknown whether anti-epileptic medications will prevent seizures with XTandi. Patients in the study had one or more of the following predisposing factors: the use of medications that may lower the seizure threshold (e.g., 54), history of traumatic brain or head injury (e.g., 28), history of cerebrovascular accident or transient ischemic attack (e.g., 24), and Alzheimer’s disease, meningo, or leptomeningeal disease from prostate cancer. Unexplained loss of consciousness within the last 12 months, past history of seizure, presence of a space occupying lesion of the brain, history of arteriovenous malformation, or history of brain injury (all < 5%). Approximately 17% of patients had more than one risk factor.

Advise patients of the risk of developing a seizure while receiving XTandi and of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others.

Permanently discontinue XTandi in patients who develop a seizure during treatment.

Posterior Reversible Encephalopathy Syndrome (PRES)
There have been reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving XTandi. PRES is a neurological disorder which can present with rapidly evolving symptoms including seizure, headache, lethargy, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). Discontinue XTandi in patients who develop PRES.

ADVERSE REACTIONS
Clinical Trial Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Three randomized clinical trials enrolled patients with metastatic prostate cancer that has progressed on androgen deprivation therapy. A 150 mg orally once daily, all patients continued androgen deprivation therapy. Patients were allowed, but not required, to receive concomitant medications.

The most common adverse reactions (> 10%) that occurred more commonly (≥ 2% over placebo) in the XTandi-treated patients from the two randomized placebo-controlled trials were asthenia/tiredness back pain, decreased appetite, constipation, arthralgia, diarrhea, hot flush, upper respiratory tract infection, peripheral edema, dyspnea, muscular skeletal pain, weight decreased, headache, hypertension, and dizziness/vertigo.

The most common adverse reactions (≥ 10%) that were reported in Study 3 were asthenia/tiredness, back pain, decreased appetite, constipation, arthralgia, diarrhea, hot flush, upper respiratory tract infection, peripheral edema, dyspnea, muscular skeletal pain, weight decreased, headache, hypertension, and dizziness/vertigo.

Study 1: XTandi versus Placebo in Metastatic CRPC Following Chemotherapy
Study 1 enrolled 1715 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy, of whom 1715 received at least one dose of study drug. The median duration of treatment was 17.5 months with XTandi and 4.6 months with placebo. Grade 3-4 adverse reactions were reported in 44% of XTandi-treated patients and 37% of placebo-treated patients. Discontinuations due to adverse events were reported for 6% of XTandi-treated patients and 8% of placebo-treated patients. The most common adverse reaction leading to treatment discontinuation was fatigue/asthenia, which occurred in 1% of patients on each treatment arm. Table 2 includes adverse reactions reported in Study 2 that occurred at ≥ 2% higher frequency in the XTandi arm compared to the placebo arm.

Study 2: XTandi versus Bicalutamide in Chemotherapy-Naive Metastatic CRPC
Study 2 enrolled 373 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy, of whom 372 received at least one dose of study drug. The median duration of treatment was 11.6 months with XTandi.
and 5.8 months with bicalutamide. Discontinuations with an adverse event as the primary reason were reported for 7.8% of XTANDI-treated patients and 6.3% of bicalutamide-treated patients. The most common adverse reactions leading to treatment discontinuation were back pain and paternal fracture, which occurred in 3.8% of XTANDI-treated patients for each event and in 2.1% and 1.6% of bicalutamide-treated patients, respectively. Table 3 shows overall and common adverse reactions (> 10%) in XTANDI-treated patients.

<table>
<thead>
<tr>
<th>Table 3. Adverse Reactions in Study 3</th>
<th>XTANDI N = 183</th>
<th>Bicalutamide N = 169</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1-4 (%)</td>
<td>Grade 1-4 (%)</td>
</tr>
<tr>
<td>Overall</td>
<td>94.6</td>
<td>38.8</td>
</tr>
<tr>
<td>General Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenic Conditions</td>
<td>31.7</td>
<td>1.6</td>
</tr>
<tr>
<td>Musclekeletal And Connective Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back Pain</td>
<td>19.1</td>
<td>2.7</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot Flushing</td>
<td>14.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14.2</td>
<td>7.1</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>14.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Constipation</td>
<td>12.6</td>
<td>1.1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11.1</td>
<td>0.0</td>
</tr>
<tr>
<td>Infections And Infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>12.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Investigational</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight Loss</td>
<td>10.9</td>
<td>0.5</td>
</tr>
</tbody>
</table>

The following additional adverse reactions have been identified during post approval use of XTANDI. Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

- Body as a Whole: Hypersensitivity (tongue edema, lip edema, and pharyngeal edema)
- Gastrointestinal Disorders: vomiting
- Neurological Disorders: posterior reversible encephalopathy syndrome (PRES)

Skull and Subcutaneous Tissue Disorders: rash

DRUG INTERACTIONS

Drugs that Inhibit CYP3A8

Co-administration of a strong CYP3A8 inhibitor (e.g., ritonavir) increased the composite area under the plasma concentration-time curve (AUC) of enzalutamide plus N-desmethyl enzalutamide by 2.2-fold. Co-administration of XTANDI with a strong CYP3A8 inhibitor should be avoided if possible. If co-administration of XTANDI with a strong CYP3A8 inhibitor cannot be avoided, reduce the dose of XTANDI.

Drugs that Inhibit CYP3A4

Co-administration of rifampin (strong CYP3A4 inducer and moderate CYP2C9 inhibitor) decreased the composite AUC of enzalutamide plus N-desmethyl enzalutamide by 37%. Co-administration of strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifabutin, rifampin, ritampen) with XTANDI should be avoided if possible. St John’s wort may decrease enzalutamide exposure and should be avoided. If co-administration of a strong CYP3A4 inducer with XTANDI cannot be avoided, increase the dose of XTANDI.

Effect of XTANDI on Drug Metabolizing Enzymes

Enzalutamide is a substrate of CYP3A4, CYP2C9, and CYP2C19 and a moderate CYP2C9 and CYP2C19 inducer. At steady state, XTANDI reduced the plasma exposure to midazolam (CYP3A4 substrate), warfarin (CYP2C9 substrate), and omaprazole (CYP2C19 substrate). Concomitant use of XTANDI with narrow therapeutic index drugs that are metabolized by CYP3A4 (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus), CYP2C9 (e.g., phenytoin, warfarin) and CYP2C19 (e.g., 5-methylenopyrimidin) should be avoided, as enzalutamide may decrease their exposure. If co-administration with warfarin cannot be avoided, conduct additional INR monitoring.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

XTANDI is contraindicated for use in pregnant women because the drug may cause fetal harm and potential loss of pregnancy. XTANDI is not indicated for use in females. There are no human data on the use of XTANDI in pregnant women. In animal reproduction studies, oral administration of enzalutamide in pregnant mice during organogenesis caused adverse developmental effects at doses lower than the maximum recommended human dose.

Animal Data

In an embryo-fetal developmental toxicity study in mice, enzalutamide caused developmental toxicity when administered at oral doses of 10 or 30 mg/kg/day through the period of organogenesis (gestational days 6-15). Findings included embryo-fetal lethality (increased post-implantation loss and fetal losses) and decreased anogenital distance at ≥ 10 mg/kg/day, and cleft palate and absent palate bone at 30 mg/kg/day. Doses of 30 mg/kg/day caused maternal toxicity. The doses tested in mice (1, 10 and 30 mg/kg/day) resulted in systemic exposures (AUC) approximately 0.4, 0.4 and 1.1 times, respectively, the exposures in patients. Enzalutamide did not cause developmental toxicity in rabbits when administered throughout the period of organogenesis (gestational days 6-18) at dose levels up to 10 mg/kg/day (approximately 0.4 times the exposures in patients based on AUC).

Lactation

Risk Summary

XTANDI is not indicated for use in females. There is no information available on the presence of XTANDI in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Enzalutamide and/or its metabolites were present in milk of lactating rats.

Females and Males of Reproductive Potential

Contraception

Males

Based on findings in animal reproduction studies, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the final dose of XTANDI.

Infertility

Based on animal studies, XTANDI may impair fertility in males of reproductive potential.

Pediatric Use

Safety and effectiveness of XTANDI in pediatric patients have not been established.

Geriatric Use

Of 1671 patients who received XTANDI in the two randomized placebo-controlled clinical trials, 75% were 65 and over, while 31% were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Patients with Renal Impairment

A dedicated renal impairment trial for XTANDI has not been conducted. Based on the population pharmacokinetic analysis using data from clinical trials in patients with metastatic CRPC and healthy volunteers, no significant difference in enzalutamide clearance was observed in patients with pre-existing mild to moderate renal impairment (30 mL/min ≤ creatinine clearance [CrCL] ≤ 85 mL/min) compared to patients and volunteers with baseline normal renal function (CrCL > 90 mL/min). No initial dosage adjustment is necessary for patients with mild to moderate renal impairment. Severe renal impairment (CrCL < 30 mL/min) and end-stage renal disease have not been assessed.

Patients with Hepatic Impairment

Dedicated hepatic impairment trials compared the composite systemic exposure of enzalutamide plus N-desmethyl enzalutamide in volunteers with baseline mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C, respectively) to systemic exposure controls with normal hepatic function. The composite AUC of enzalutamide plus N-desmethyl enzalutamide was similar in volunteers with mild, moderate, or severe baseline hepatic impairment compared to volunteers with normal hepatic function. No initial dosage adjustment is necessary for patients with baseline mild, moderate, or severe hepatic impairment.

OVERDOSE

In the event of an overdose, stop treatment with XTANDI and institute general supportive measures taking into consideration the half-life of 5.8 days. In a dose escalation study, no seizures were reported at ≤ 240 mg daily, whereas 12 seizures were reported at each of 350 mg, 480 mg, and 600 mg daily. Patients may be at increased risk of seizure following an overdose.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of enzalutamide. Enzalutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in either the in vitro mouse lymphoma thymidine kinase (Tk) gene mutation assay or the in vivo mouse lymphoma assay.

Based on nonclinical findings in repeat-dose toxicity studies, which were consistent with the pharmacological actions of enzalutamide, male fertility may be impaired by treatment with XTANDI. In a 26-week study in rats, atrophy of the prostate and seminal vesicles was observed at ≥ 10 mg/kg/day (equal to or above human exposure based on AUC). In 4-, 13-, and 39-week studies in dogs, hyperprostaglandinemia and atrophy of the prostate and epididymides were observed at ≥ 4 mg/kg/day (0.3 times the human exposure based on AUC).

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Immunizing Cancer Patients: Which Patients? Which Vaccines? When to Give?

Monika K. Shah, MD1,2, Mini Kamboj, MD3,4

ABSTRACT: Patients receiving treatment for cancer should be considered for age- and indication-appropriate vaccinations, and the responsibility for administration of these vaccines is shared between the oncologist and the primary care provider. Certain vaccine-preventable diseases have higher incidence rates among cancer patients and are associated with worse clinical outcomes. The Centers for Disease Control and Prevention and the Advisory Committee on Immunization Practices recommend certain vaccines for routine use in adults, including those with cancer. This article provides guidance to oncology clinicians on vaccine recommendations and safety of use in their patients.

Introduction
The number of cancer survivors in the United States is predicted to exceed 20 million by 2026, largely due to advances in treatment and early detection of cancer, along with the aging and overall growth of the population.[1] The Centers for Disease Control and Prevention (CDC), under guidance from the Advisory Committee on Immunization Practices (ACIP), recommends certain vaccines for routine use in all persons, stratified by age and clinical indication.[2] Patients receiving treatment for cancer should be considered for age- and indication-appropriate vaccinations, and the responsibility for administration of these vaccines is shared between the oncologist and the primary care provider. Although vaccine effectiveness may be lower in patients immunocompromised because of cancer or its therapy—in comparison with the effectiveness in immunocompetent persons—vaccination can still reduce morbidity and mortality.

Inactivated vaccines are prepared from fractional or whole components of bacteria or viruses, or their products, and are typically protein- or polysaccharide-based. Polysaccharide vaccines are typically less immunogenic and can be conjugated to proteins to enhance the immune response. Live-attenuated vaccines use a weakened form of the pathogen to induce an immune response. Recombinant vaccines consist of genetically engineered antigens and are typically inactivated, but can occasionally be live-attenuated. Both inactivated and recombinant vaccines can contain adjuvants to increase the immune response.[3,4]

This article will address several important vaccination considerations in adult patients with cancer. Stem cell transplantation recipients require primary re-immunization strategies that are addressed in other reviews. [5,6] In general, inactivated and recombinant (non-live) vaccines can be safely given to immunocompromised patients (see Table). Live-attenuated vaccines should not be administered to patients who are considered to be highly immunocompromised.

Immunocompromised Patients With Cancer
Highly immunocompromised cancer patients are those who have received chemotherapy and/or radiation therapy within the preceding 3 months, those who have generalized malignancy or hematologic malignancy, and those who have received the equivalent of ≥ 20 mg prednisone daily for ≥ 2 weeks, as well as stem cell transplant recipients within 2 years of transplant (or beyond 2 years if there is ongoing evidence of graft-vs-host disease).[7] Patients who receive regimens containing anti-B-cell antibodies are also highly immunosuppressed and unable to mount effective vaccine responses, and thus should have routine vaccinations delayed for at least 6 months. Other biologic agents, including both targeted agents and immune checkpoint blockade therapy (immunotherapy), have variable immunomodulatory and immunosuppressive effects. The degree and duration of immunosuppression are dependent on the individual drug, dose, and therapeutic context of administra-
Timing of Vaccination

When feasible, vaccines should be administered prior to planned immunosuppressive chemotherapy. Inactivated vaccines should ideally be given at least 2 weeks prior to starting chemotherapy, or 3 months after completion. Live-attenuated vaccines should be administered ≥ 4 weeks prior to the onset of such therapy, or ≥ 3 months after immune restoration. For patients undergoing elective splenectomy as part of their cancer therapy, indicated vaccines should be administered at least 2 weeks prior to the procedure.[8]

Influenza Vaccines

Adult patients undergoing treatment for cancer are at a higher risk for developing serious complications from influenza, with 3 to 4 times higher odds of hospitalization compared with age-matched controls. [9] Despite their limited effectiveness in preventing influenza, existing studies suggest that inactivated influenza vaccines are safe, and offer protection to cancer patients by reducing influenza-related hospitalizations, interruption of chemotherapy cycles, and risk of death.[10-13] Antibody responses to vaccines are generally lower in patients receiving chemotherapy.

Table. Recommendations for Routine Vaccinations in Adults With Underlying Cancer

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Safety</th>
<th>Schedule</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza</td>
<td></td>
<td>One dose annually</td>
<td>High dose recommended for age 65 yr and above</td>
</tr>
<tr>
<td>Trivalent inactivated</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quadrivalent inactivated</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-dose inactivated</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Live-attenuated (FluMist)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell culture–based (Flucelvax Quadrivalent)</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recombinant (Flublok Tri- and Quadrivalent)</td>
<td>✓</td>
<td></td>
<td>Use for severe egg allergy; age indication: ≥ 18 yr</td>
</tr>
<tr>
<td>Pneumococcal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13-valent pneumococcal conjugate (PCV-13; Prevnar-13)</td>
<td>✓</td>
<td>One dose of PCV-13 followed by one dose of PPSV-23 at least 8 weeks after PCV-13</td>
<td></td>
</tr>
<tr>
<td>23-valent pneumococcal polysaccharide (PPSV-23; Pneumovax)</td>
<td>✓</td>
<td>(additional booster for Pneumovax may be recommended*)</td>
<td></td>
</tr>
<tr>
<td>Zoster</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recombinant zoster vaccine (RZV; Shingrix)</td>
<td>✓</td>
<td>Two doses 2–6 mo apart</td>
<td>Age indication: &gt; 50 yr; if previously vaccinated with ZVL, wait 2 mo</td>
</tr>
<tr>
<td>Live zoster vaccine (ZVL; Zostavax)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetanus, diphtheria, and pertussis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tdap</td>
<td>✓</td>
<td>Once in adulthood, if not previously vaccinated</td>
<td></td>
</tr>
<tr>
<td>Td</td>
<td>✓</td>
<td>Td booster every 10 yr (following Tdap)</td>
<td></td>
</tr>
</tbody>
</table>

✓ = safe.
X = contraindicated.

Certain patients or survivors with cancer may have anatomical or functional asplenia and, if this is their sole immune deficit, they are not considered to be highly immunocompromised and may be able to receive live-attenuated vaccines.
The high-dose influenza vaccine (https://www.cdc.gov/flu/protect/vaccine/qa_fluzone.htm) is not currently recommended by the ACIP.[21] At MSKCC, the high-dose influenza vaccine is routinely used only for patients ≥ 65 years. The benefit of second doses of standard or high-dose vaccine to achieve superior immune and clinical responses remains unproven, and second doses are not currently given at our institution.

- Recombinant and cell culture–based vaccines utilize shorter and more rapidly scalable manufacturing processes, compared with other influenza vaccine formulations that utilize traditional egg-based manufacturing methods; the former thereby preserve genetic and antigenic similarity to circulating viruses. It is conceivable that retention of genetic identity between vaccine and circulating strains translates into a higher level of protection, and this has been substantiated by a single study in adults > 50 years, which demonstrated superior efficacy of quadrivalent recombinant vaccines compared with standard-dose egg-based vaccines during a single influenza season.[22] Until further data are available on the relative efficacy of recombinant vaccines compared with other high-dose formulations, and their benefits are confirmed to extend across different strains and seasons, their use at MSKCC remains solely for patients with a history of severe egg allergy.

- Adjuvanted influenza vaccines are another promising frontier in vaccine development that may enhance the immunogenicity in immunocompromised patients.[23] None of the existing randomized controlled trials of newer vaccine formulations have specifically assessed their performance in oncology populations.

Safety, contraindications, and timing of influenza vaccine in relation to chemotherapy

There is no specific concern regarding the safety of the inactivated influenza vaccine among cancer patients undergoing chemotherapy. Most reported adverse effects are mild and local. High-dose vaccines may be more reactogenic at the site of administration, but the general safety profile and incidence of Guillain-Barré syndrome matches what is seen with standard-dose vaccines. Immunization between September and December, or later, is likely to be beneficial in most influenza seasons. Based on limited evidence, the preferred timing for the influenza vaccine during treatment with chemotherapy is either more than 2 weeks before receiving chemotherapy or between chemotherapy cycles. Due to the unpredictable nature of the influenza season and unexpected delays in vaccine production, such precision in tim-
Influenza vaccine for patients receiving immunotherapy

Recent reports have questioned the safety of the influenza vaccine in patients receiving immunotherapy, postulating that it acts as an unrecognized antigenic trigger that amplifies immune-related adverse events (irAEs).[24,25] In our experience, the incidence of irAEs in vaccine recipients receiving anti–programmed death 1 (PD-1) therapy, or combination therapy with ipilimumab and an anti–PD-1, is no different from the irAE rates reported in clinical trials of immune checkpoint inhibitors. Based on these data and the robust T-cell and humoral response to influenza vaccine in patients treated with checkpoint blockade,[26] we believe that co-administration of influenza vaccine with US Food and Drug Administration–approved immune checkpoint blockade therapy is safe and effective.

Pneumococcal Vaccines

Patients undergoing chemotherapy for solid tumors are at a 40- to 50-fold higher risk for the development of invasive pneumococcal disease (IPD) compared with healthy adults,[27] with case fatality rates approaching 35%. Polysaccharide-based vaccines (Pneumovax) are poorly immunogenic in cancer patients despite the broad coverage against 23 capsular serotypes.[28] The highly immunogenic conjugate vaccines were first licensed in the United States in 2000 (Prevnar-7); capsular serotype coverage was expanded with approval of Prevnar-13 for adults in 2011. Among older adults, Prevnar-13 demonstrated a vaccine efficacy rate of 45% in reducing pneumonia, and a rate of 75% in reducing IPD.[29] With the advent of conjugate vaccines, a marked reduction in IPD rates has been observed among cancer patients—widely believed to be a consequence of the universal vaccination of children.[30] The ACIP recommends that both pneumococcal vaccines be administered to adults with generalized malignancy, regardless of age.[31]

Co-administration of the pneumococcal vaccine and the influenza vaccine is safe and effective. Unfamiliarity with the frequently changing administration schedules for the two pneumococcal vaccines, and lack of access to vaccination records, have been major barriers to improving vaccination rates among patients in the oncology setting. To facilitate influenza and pneumococcal vaccine uptake among patients at MSKCC, a nurse-initiated protocol was developed and implemented in 2017. Patients are assessed for eligibility for influenza vaccines and pneumococcal vaccines at each ambulatory visit as a mandatory component of the nursing care assessment. Both vaccines may be administered by nurses, as guided by a logic tool built into the electronic medical record (EMR), and without a specific physician order. The logic tool screens for past vaccination history, eligibility for each type of vaccine, and potential contraindications.[32] This program has led to a substantial increase in vaccine coverage.

Zoster Vaccines

Following primary infection, varicella zoster virus persists in latent form in sensory ganglia. Reactivation of virus can occur in those with impaired cell-mediated immunity and can cause herpes zoster infection (“shingles”), postherpetic neuralgia, and other serious complications associated with varicella reactivation. Cancer patients have a higher overall incidence of zoster, compared with age-matched controls, particularly those with hematologic malignancies.[33] Two zoster vaccines are now licensed for use in the United States. The older vaccine, Zostavax (ZVL), is live-attenuated and therefore has had limited use in the oncology setting. The new recombinant subunit vaccine, Shingrix (RZV), is superior to ZVL and is available for adults ≥ 50 years of age, including those with a previous episode of zoster or those who have previously received ZVL, and is considered to be the preferred zoster vaccine by the ACIP.

Studies have demonstrated that RZV is highly effective at preventing herpes zoster infection and postherpetic neuralgia in all age groups, including the elderly (91% in adults ≥ 70 years old, 97% in adults 50–69 years old).[34-36] The ACIP has made no specific recommendations for RZV use in immunocompromised cancer patients, citing lack of efficacy data. However, a recent study found significant efficacy among autologous stem cell transplant recipients who received the vaccine 50 to 70 days post-transplant. The vaccine was about 68% effective at preventing herpes zoster reactivation and 89% effective at preventing postherpetic neuralgia; it reduced overall complications by nearly 78%.[37] Further studies to evaluate the efficacy of this vaccine in patients who have solid or hematologic malignancies are underway, as are studies assessing immune responses in patients who have previously received ZVL. At MSKCC, we offer RZV to patients we deem eligible, based on currently published data and ACIP recommendations; these are primarily adult patients ≥ 50 years who are not considered highly immunocompromised. We suggest administering the first dose of the vaccine prior to the

KEY POINTS

- Indicated vaccines are ideally administered before cancer treatment is initiated.
- Live vaccines are contraindicated due to risk of severe vaccine-induced infection.
- Injectable influenza vaccine is given annually, and both pneumococcal vaccines should be administered according to the recommended schedule from the Centers for Disease Control and Prevention.
- The newer recombinant zoster vaccine (RZV) is the safer and preferred vaccine.
- Family members and close contacts of cancer patients can be safely immunized with most, but not all, live vaccines.
onset of cancer-directed therapy or ≥ 3 months after chemotherapy. We vaccinate with RZV even patients who have previously received ZVL; the ACIP recommends waiting at least 2 months between the vaccines.

Other Routine Vaccines
All patients should be up to date on tetanus and diphtheria toxoid (Td) immunization. Adults who have never received the tetanus-diphtheria-pertussis (Tdap) vaccine should receive this as soon as possible; that dose can replace one of the Td booster doses. Human papillomavirus (HPV) vaccine should be offered to all immunocompromised young adults with cancer (through 26 years of age) if they have not previously received the series. Meningococcal, pneumococcal, and *Haemophilus influenzae* type b (Hib) vaccines should be given to cancer patients with anatomical or functional asplenia, to reduce the risk of sepsis caused by these organisms. Two different types of vaccines (against serogroups A, C, W, and Y and serogroup B) are available to target different serogroups of *Neisseria meningitidis*. Hepatitis A and B vaccines can be considered in cancer patients if another indication for vaccination is present. Live-attenuated vaccines—such as measles, mumps, and rubella (MMR) and varicella— are contraindicated in highly immunocompromised cancer patients.

Travel Vaccines
Recent studies have highlighted the fact that international travel is common among patients living with cancer, even highly immunocompromised patients. [38,39] Some vaccines that are considered prior to travel are based on specific epidemiologic risks that may be encountered at the travel destination(s). Country-specific vaccine recommendations are available from the CDC.[40] Live-attenuated yellow fever vaccine, oral typhoid vaccine, and oral cholera vaccine cannot be given to highly immunocompromised patients. Certain countries require proof of receipt of yellow fever vaccination upon disembarkation, based on the individual traveler’s prior travel history, irrespective of actual risk at the destination. For patients who cannot safely receive yellow fever vaccine but who will be visiting a location where there is little epidemiologic risk of yellow fever, a waiver letter can be written by a certified provider of yellow fever vaccine. For patients who are planning a trip that may result in natural exposure to disease, attendant risks of travel should be carefully discussed; this can be done in conjunction with a travel medicine provider.[41]

Household Contacts, Including Children
All immunocompetent household members of highly immunocompromised cancer patients should receive age-appropriate vaccinations as recommended by the ACIP, including all inactivated vaccines, as well as most live-attenuated vaccines, to protect the health of the immunocompromised household member. Live-attenuated vaccines such as MMR and varicella can be given, but immunocompromised patients should avoid contact with persons who develop skin lesions after receipt of the varicella vaccine until the lesions clear. Rotavirus vaccine can also be safely given, but immunocompromised patients should avoid handling diaries of infants who have been vaccinated for 4 weeks after vaccination. LAIVs should not be given to household contacts of patients who have received stem cell transplantation. Live-attenuated oral polio vaccine, which is not available in the United States, cannot be safely given to household contacts; the inactivated polio vaccine should be used.[5] Most travel vaccines can also be given to household contacts as indicated. Live-attenuated travel vaccines, such as yellow fever and oral typhoid vaccinations, can be given. There are limited data on the use of oral cholera vaccine among household contacts.

Conclusion
Routine vaccination in cancer patients and their household contacts is an important strategy for reducing morbidity and mortality in this vulnerable population. Vaccine type and categorization of the underlying degree of immunocompromise are essential considerations in the timing and feasibility of administration of each recommended vaccine. Complications from influenza and pneumococcal disease are significantly higher in patients with cancer compared with the general adult population, and we have found improved vaccine uptake with integrated EMR logic tools in our oncology patient population. The new recombinant zoster vaccine is highly promising, and forthcoming efficacy data in immunosuppressed patients will help guide possible expanded use.

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REFERENCES
TARGETING CANCER STEMNESS PATHWAYS

CANCER STEM CELLS

Not all cancer cells within a tumor are equal

Despite current advances in cancer therapy, tumor recurrence and metastases remain clinical challenges. A potential new approach to address these is the targeting of a subset of the tumor cell population known as cancer stem cells (CSCs). CSCs are highly tumorigenic, have high metastatic potential, and are resistant to conventional cancer therapies.

Stemness of CSCs may drive tumor growth

Stemness is defined by the ability to self-renew and differentiate. Unlike normal stem cells, which differentiate into healthy, mature cell types, CSCs differentiate into cancer cells. The stemness of CSCs is maintained by various signaling pathways that are overactivated, including JAK/STAT, Wnt/β-catenin, Nanog, and Notch, depending on the tumor type.

Stemness may enable CSCs to metastasize and regrow tumors. This makes CSCs phenotypically different from non-stem cancer cells and may confer therapy resistance. Stemness can be acquired by non-stem cancer cells as they dedifferentiate in response to multiple stimuli, possibly including conventional cancer therapies.

The CSC model may help explain tumor recurrence

In the clonal evolution model, all cells within a malignant tumor have similar tumorigenic activity. By contrast, in the CSC model only a subset of tumor cells, CSCs, have tumor-initiating capability. This may help to explain why early tumor shrinkage is often poorly predictive of overall survival. While conventional therapies kill the bulk of non-stem cancer cells, resulting in tumor shrinkage, CSCs may remain viable and later reestablish the tumor, leading to relapse.

A key implication of the CSC model for cancer treatment is that both CSCs and non-stem cancer cells should be targeted to reduce tumor recurrence and metastasis.

The next generation of cancer therapeutics is in development with investigational agents designed to inhibit stemness pathways.

Targeting Stemness

Boston Biomedical is developing the next generation of cancer therapeutics with drugs designed to inhibit cancer stemness pathways. Clinical trials are underway with the goal of reducing recurrence and metastasis.

References: