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16% of patients treated with ERLEADA
Falls
In a randomized study (SPARTAN) of patients with nmCPC, ischemic cardiovascular events occurred in 4% of patients treated with ERLEADA® and 2% of patients treated with placebo. Across the SPARTAN and TITAN studies, 5 patients (0.3%) treated with ERLEADA® and 2 patients (0.2%) treated with placebo died from an ischemic cardiovascular event. Patients with current evidence of unstable angina, myocardial infarction, or congestive heart failure within 6 months of randomisation were excluded from the SPARTAN and TITAN studies. Ischemic cardiovascular events, including events leading to death, occurred in patients receiving ERLEADA®.

Monitor for signs and symptoms of ischemic heart disease. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Consider discontinuation of ERLEADA® for Grade 3 and 4 events.

Fractures — In a randomized study (SPARTAN) of patients with nmCPC, fractures occurred in 12% of patients treated with ERLEADA® and in 6% of patients treated with placebo. Evaluate patients for fracture risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents.

Falls — In a randomized study (SPARTAN), falls occurred in 16% of patients treated with ERLEADA® compared with 9% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure. Falls occurred in patients receiving ERLEADA® with increased frequency in the elderly. Evaluate patients for fall risk.

Seizure — In 2 randomized studies (SPARTAN and TITAN), 5 patients (0.4%) treated with ERLEADA® and 1 patient treated with placebo (0.1%) 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.

Embryo-Fetal Toxicity — The safety and efficacy of ERLEADA® have not been established in females. Based on its mechanism of action, ERLEADA® can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise females 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 (8.1, 8.3)].

ADVERSE REACTIONS

Adverse Reactions — The most common adverse reactions (≥10%) that occurred more frequently in the ERLEADA®-treated patients (≥2% over placebo) from the randomized placebo-controlled clinical trials (TITAN and SPARTAN) were fatigue, asthenia, rash, decreased appetite, fall, weight decreased, hypertension, hot flush, diastema, and fracture.

Laboratory Abnormalities — All Grades (Grade 3-4)
• Hematology — In the TITAN study, while blood cell decreased ERLEADA® 27% (0.4%), placebo 19% (0.6%). In the SPARTAN study, anemia ERLEADA® 70% (0.4%), placebo 64% (0.5%); leukopenia ERLEADA® 47% (0.3%), placebo 29% (0.6%); lymphopenia ERLEADA® 41% (2%), placebo 21% (2%).
• Chemistry — In the TITAN study: hypertriglyceridemia ERLEADA® 7% (1%), placebo 12% (2%). In the SPARTAN study: hypercholesterolemia ERLEADA® 76% (0.7%), placebo 46% (0%); hyperglycemia ERLEADA® 76% (2%), placebo 59% (1%); hyperuricemia ERLEADA® 67% (2%), placebo 69% (0.8%); hyperkalemia ERLEADA® 32% (2%), placebo 22% (0.5%).

Rash — In 2 randomized studies, rash was most commonly described as macular or maculopapular. Adverse reactions of rash were 26% with ERLEADA® vs 8% with placebo. Grade 3 rashes (defined as coating ≥30% body surface area (BSA)) were reported with ERLEADA® treatment (6%) vs placebo (0.5%). The onset of rash occurred at a median of 83 days. Rash resolved in 78% of patients within a median of 7 days from onset of rash. Rash was commonly managed with oral antihistamines, topical corticosteroids, and 19% of patients received systemic corticosteroids. Dose reduction or dose interruption occurred in 14% and 28% of patients, respectively. Of the patients who had dose interruption, 59% experienced recurrence of rash upon reintroduction of ERLEADA®.

Hypothyroidism — In 2 randomized studies, hypothyroidism was reported for 8% of patients treated with ERLEADA® and 2% of patients treated with placebo (0.1%) experienced a decreased thyroid-stimulating hormone (TSH) every 4 months. Elevated TSH occurred in 2% of patients treated with ERLEADA® and 7% of patients treated with placebo. The median onset was at the first scheduled assessment. 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 CYP3A4 or CYP3A5 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 (2.3)].

Effect of ERLEADA® on Other Drugs — ERLEADA® is a strong inducer of CYP3A4 and CYP3A5, and a weak inducer of CYP2C9 in humans. Concomitant use of ERLEADA® with medications that are primarily metabolized by CYP3A4, CYP2C19, or CYP3A4 can result in lower exposure to these medications. Substitution for these medications is recommended when possible or evaluative for loss of activity if medication is continued. Concomitant administration of ERLEADA® with medications that are substrates of 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 substrate of P-glycoprotein (P-gp) and a weak inhibitor of organic anion transporting polypeptide 1B1 (OATP1B1). 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.

Please see Brief Summary of full Prescribing Information for ERLEADA® on subsequent pages.

* All patients who enrolled in the TITAN study started ADT for mCSPC ≤6 months prior to randomization.

Study Design: TITAN was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial of patients with mCSPC (N=1052). Patients had de novo mCSPC or relapsed metastatic disease after initial diagnosis of localized disease. All patients in the TITAN trial received a concurrent GnRH analog or had a bilateral orchietomy. Patients with visceral (i.e., liver or lung) metastases as the only sites of metastases were excluded. Patients were randomized 1:1 to receive ERLEADA® 240 mg orally once daily + ADT or placebo orally once daily + ADT. The dual primary endpoints were overall survival and radiographic progression-free survival. 1,2

NEW INDICATION

Now approved for the treatment of patients with metastatic castration-sensitive prostate cancer (mCSPC).

In the TITAN study:

ERLEADA® + ADT reduced the risk of death by 33% vs placebo + ADT1

(Median overall survival was not estimable in either arm; HR=0.67; 95% CI: 0.51, 0.89; P=0.0053)

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10/4/19 9:32 AM
ERLEADA® (apelutamide) tablets

Eight 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 cardiopulmonary arrest (n=1). ERLEADA was discontinued due to adverse reactions in 11% of patients, most commonly from rash (3%). Additional reactions leading to dose interruption or reduction of ERLEADA occurred in 23% of patients treated with ERLEADA as compared to 7% of patients treated with placebo. The most frequent severe adverse reactions (>2%) were rash (3%) in the ERLEADA arm and urinary retention (4%) in the placebo arm.

Table 3 shows adverse reactions occurring in ≥31% on the ERLEADA arm in SPARTAN that occurred with a ≥2% absolute increase in frequency compared to placebo. Table 4 shows laboratory abnormalities that occurred in ≥15% of patients, and more frequently (>5%) in the ERLEADA arm compared to placebo.

Table 3: Adverse Reactions in SPARTAN (nmCRPC)

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>ERLEADA</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse reaction</td>
<td>All Grades</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue1/2</td>
<td>39 1 28 0.3</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia4</td>
<td>16 0 8 0</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash2</td>
<td>25 5 6 0.3</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite6</td>
<td>12 0.1 9 0</td>
<td></td>
</tr>
<tr>
<td>Peripheral edema4</td>
<td>11 0 9 0</td>
<td></td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fall4</td>
<td>16 2 9 0.8</td>
<td></td>
</tr>
<tr>
<td>Fracture2</td>
<td>12 3 7 0.8</td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight decreased4</td>
<td>16 1 6 0.3</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>25 14 20 12</td>
<td></td>
</tr>
<tr>
<td>Hot flush</td>
<td>14 0 9 0</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>20 1 15 0.5</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>18 0 16 0</td>
<td></td>
</tr>
</tbody>
</table>

1 Includes fatigue and asthenia
2 Includes rash, maculopapular, rash generalised, urticaria, rash pruritic, rash macular, conjunctivitis, erythema multiforme, rash papular, skin exfoliation, genital rash, rash erythematous, stomatitis, drug eruption, miliaria, rash pustular, papule, papular, skin erosion, dermatitis, and rash vascular
4 Per the Common Terminology Criteria for Adverse Reactions (CTCAE), the highest severity for these events is Grade 3
5 Includes appetite disorder, decreased appetite, early satiety, and hypophagia
6 Includes peripheral edema, generalized edema, edema, edema genital, pleural edema, peripheral swelling, scrotal edema, lymphedema, swelling, and localized edema

Additional clinically significant adverse reactions occurring in 2% or more of patients treated with ERLEADA included hypothyroidism (8.1% versus 2% on placebo), pruritus (6.2% versus 2% on placebo), and heart failure (2.2% versus 1% on placebo).

Table 4: Laboratory Abnormalities Occurring in ≥15% of ERLEADA-Treated Patients and at a Higher Incidence than Placebo (Between Arm Difference ≥ 5% All Grades) in SPARTAN (nmCRPC)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ERLEADA N=803</th>
<th>Placebo N=398</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>Grade 3-4</td>
<td>All Grades</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>70 0.4 64 0.5</td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>47 0.3 29 0</td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>41 2 21 2</td>
<td></td>
</tr>
</tbody>
</table>

In the combined data of two randomized, placebo-controlled clinical studies, rash associated with ERLEADA was most commonly described as macular or maculo-papular. Adverse reactions of rash were reported for 26% of patients treated with ERLEADA versus 8% of patients treated with placebo. Grade 3 rashes (defined as covering >30% body surface area [BSA]) were reported with ERLEADA treatment (6%) versus placebo (0.5%).

The onset of rash occurred at a median of 83 days of ERLEADA treatment. Rash was resolved in 76% of patients within a median of 78 days from onset of rash. Rash was commonly managed with oral antihistamines, topical corticosteroids, and 19% of patients received systemic corticosteroids. Dose reduction or dose interruption occurred in 14% of patients treated with ERLEADA versus 5% of patients treated with placebo. The median onset was at the first scheduled assessment. There were no Grade 3 or 4 adverse reactions. Thyroid replacement therapy was initiated in 5% of patients treated with ERLEADA. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted [see Drug Interactions].

DRUG INTERACTIONS

Effect of Other Drugs on ERLEADA

Strong CYP2C9 or CYP3A4 Inhibitors

Co-administration of a strong CYP2C9 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 Dosage and Administration (2.2) in full Prescribing Information]. Mild or moderate inhibitors of CYP2C9 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 UGT 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 DAT1B1 Substrates

Apalutamide was 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/DAT1B1 substrate). Concomitant use of ERLEADA with medications that are substrates of P-gp, BCRP, or DAT1B1 can result in lower exposure to these medications. Use caution if substrates of P-gp, BCRP or DAT1B1 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

The safety and efficacy of ERLEADA have not been established in females. Based on its mechanism of action, ERLEADA can cause fetal harm and loss of pregnancy [see Clinical Pharmacology (12.1) in full Prescribing Information]. There are no human data on the use of ERLEADA in pregnant women. ERLEADA is not indicated for use in females, so animal embryo-fetal developmental toxicity studies were not conducted with apalutamide.

Lactation

Risk Summary

The safety and efficacy of ERLEADA have not been established in females. There are no data on the presence of apalutamide or its metabolites in human milk, the effect on the breastfeeding child, or the effect on milk production.
Brief Summary of Prescribing Information for ERLEADA® (apalutamide) tablet. For oral use

See package insert for Full Prescribing Information

INDICATIONS AND USAGE

ERLEADA® is indicated for the treatment of patients with:
- Metastatic castration-sensitive prostate cancer (mCSPC)
- Non-metastatic castration-resistant prostate cancer (nmCRPC)

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Ischemic Cardiovascular Events

Ischemic cardiovascular events, including events leading to death, occurred in patients receiving ERLEADA. Monitor for signs and symptoms of ischemic heart disease. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Consider discontinuation of ERLEADA for Grade 3 and 4 events.

In a randomized study (SPARTAN) of patients with nmCRPC, ischemic cardiovascular events occurred in 4% of patients treated with ERLEADA and 3% of patients treated with placebo. In a randomized study (TITAN) in patients with mCSPC, ischemic cardiovascular events occurred in 4% of patients treated with ERLEADA and 2% of patients treated with placebo. Across the SPARTAN and TITAN studies, 6 patients (0.5%) treated with ERLEADA and 2 patients (0.2%) treated with placebo died from an ischemic cardiovascular event. Patients with current evidence of unstable angina, myocardial infarction, or congestive heart failure within six months of randomization were excluded from the SPARTAN and TITAN studies.

Fractures

Fractures occurred in patients receiving ERLEADA. Evaluate patients for fracture 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) of patients with non-metastatic castration-resistant prostate cancer, 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 374 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.

In a randomized study (TITAN) of patients with metastatic castration-sensitive prostate cancer, fractures occurred in 9% of patients treated with ERLEADA and in 6% of patients treated with placebo. Grade 3-4 fractures were similar in both arms at 2%. The median time to onset of fracture was 56 days (range: 2 to 111 days) for patients treated with ERLEADA. Routine bone density assessment and treatment of osteoporosis with bone-targeted agents were not performed in the TITAN study.

Falls

Falls occurred in patients receiving ERLEADA with increased frequency in the elderly. Evaluate patients for fall risk.

In a randomized study (SPARTAN), falls occurred in 16% of patients treated with ERLEADA compared to 9% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure.

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. Consider 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 two randomized studies (SPARTAN and TITAN), five patients (0.4%) treated with ERLEADA and one patient treated with placebo (0.1%) experienced a seizure. Seizure occurred from 159 to 600 days after initiation of ERLEADA. 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.

Embryo-Fetal Toxicity

The safety and efficacy of ERLEADA have not been established in females. Based on its mechanism of action, ERLEADA can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise males with female partners of

ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:
- Ischemic Cardiovascular Events [see Warnings and Precautions].
- Fractures [see Warnings and Precautions].
- Falls [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.

ERLEADA® (apalutamide) tablets

The most common adverse reactions (≥10%) that occurred more frequently in the ERLEADA-treated patients (≥1% over placebo) from the randomized placebo-controlled clinical trials (TITAN and SPARTAN) were fatigue, arthralgia, rash, decreased appetite, fall, weight decreased, hypotension, hot flush, diarrhea, and fracture.

Metastatic Castration-sensitive Prostate Cancer (mCSPC)

TITAN, a randomized (1:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had mCSPC. In this study, patients received either ERLEADA at a dose of 240 mg daily or placebo. All patients in the TITAN study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had prior bilateral orchietomy. The median duration of exposure was 20 months (range: 0 to 34 months) in patients who received ERLEADA and 18 months (range: 0.1 to 34 months) in patients who received placebo.

Ten patients (2%) who were treated with ERLEADA died from adverse reactions. The reasons for death were ischemic cardiovascular events (n=3), acute kidney injury (n=2), cardio-respiratory arrest (n=1), sudden cardiac death (n=1), respiratory failure (n=1), cerebrovascular accident (n=1), and large intestinal ulcer perforation (n=1). ERLEADA was discontinued due to adverse reactions in 8% of patients; most commonly from rash (2%). Adverse reactions leading to dose interruption or reduction of ERLEADA occurred in 23% of patients; the most frequent (>1%) were rash, fatigue, and hypotension. Serious adverse reactions occurred in 20% of ERLEADA-treated patients and 20% in patients receiving placebo.

Table 1 shows adverse reactions occurring in ≥10% on the ERLEADA arm in TITAN that occurred with a ≥2% absolute increase in frequency compared to placebo. Table 2 shows laboratory abnormalities that occurred in ≥15% of patients, and more frequently (≥5%) in the ERLEADA arm compared to placebo.

Table 1: Adverse Reactions in TITAN (mCSPC)

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>ERLEADA N=526</th>
<th>Placebo N=527</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthropathy</td>
<td>17</td>
<td>0.4</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>28</td>
<td>6</td>
</tr>
<tr>
<td>Pruritus</td>
<td>11</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot flush</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18</td>
<td>8</td>
</tr>
</tbody>
</table>

1 Includes fatigue and anemia

2 Includes rash, maculo-papular, generalized, urticaria, rash pruritus, rash macular, conjunctivitis, erythema multiforme, rash pustular, skin exfoliation, genital rash, erythematous, stomatitis, drug eruption, mouth ulceration, rash pustular, blister, papule, pemphigoid, skin erosion, dermatitis, and rash vesicular

3 Par the Common Terminology Criteria for Adverse Reactions (CTCAE), the highest severity for these events is Grade 3

Additional adverse reactions of interest occurring in 2%, but less than 10% of patients treated with ERLEADA included diarrhea (9% versus 6% on placebo), muscle spasm (3% versus 2% on placebo), dysgeusia (3% versus 2% on placebo), drug eruption, and hot flush. Other adverse reactions of interest occurring in ≥2% over placebo were:

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ERLEADA N=524</th>
<th>Placebo N=527</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood cell decreased</td>
<td>27</td>
<td>0.4</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertiglyceridemia</td>
<td>17</td>
<td>3</td>
</tr>
</tbody>
</table>

Does not reflect fasting values

Non-metastatic Castration-resistant Prostate Cancer (nmCSPC)

SPARTAN, a randomized (2:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had nmCSPC. 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: 8.1 to 42 months) in patients who received ERLEADA and 11.2 months (range: 6.1 to 27 months) in patients who received placebo.
ERLEADA® (apalutamide) tablets

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].

Infertility

Males

Based on animal studies, ERLEADA may impair fertility in males of reproductive potential [see Nonclinical Toxicology (13.1) in full Prescribing Information].

Pediatric Use

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

Geriatric Use

Of the 1327 patients who received ERLEADA in clinical studies, 19% of patients were less than 65 years, 41% of patients were 65 years to 74 years, and 40% were 75 years and over.

No overall differences in effectiveness were observed between older and younger patients.

Of patients treated with ERLEADA (n=1073), Grade 3-4 adverse reactions occurred in 39% of patients younger than 65 years, 41% of patients 65-74 years, and 49% of patients 75 years or older. Falls in patients receiving ERLEADA with androgen deprivation therapy was elevated in the elderly, occurring in 8% of patients younger than 65 years, 10% of patients 65-74 years, and 19% of patients 75 years or older.

OVERDOSAGE

There is no known specific antidote for apalutamide overdose. In the event of an overdose, stop ERLEADA, undertake general supportive measures until clinical toxicity has been diminished or resolved.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Ischemic Cardiovascular Events

• Inform patients that ERLEADA has been associated with ischemic cardiovascular events. Advise patients to seek immediate medical attention if any symptoms suggestive of a cardiovascular event occur [see Warnings and Precautions].

Falls and Fractures

• Inform patients that ERLEADA is associated with an increased incidence of falls and fractures [see Warnings and Precautions].

Seizures

• Inform patients that ERLEADA has been associated with an increased risk of seizure. Discuss conditions that may predispose to seizures and medications that may lower the seizure threshold. Advise patients of the risk of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others. Inform patients to contact their healthcare provider right away if they experience a seizure [see Warnings and Precautions].

Rash

• Inform patients that ERLEADA is associated with rashes and to inform their healthcare provider if they develop a rash [see Adverse Reactions].

Dosage and Administration

• Inform patients receiving concomitant gonadotropin-releasing hormone (GnRH) analog therapy that they need to maintain this treatment during the course of treatment with ERLEADA.

• Instruct patients to take their dose at the same time each day (once daily). ERLEADA can be taken with or without food. Each tablet should be swallowed whole.

• Inform patients that in the event of a missed daily dose of ERLEADA, they should take their normal dose as soon as possible on the same day with a return to the normal schedule on the following day. The patient should not take extra tablets to make up the missed dose [see Dosage and Administration (2.1) in full Prescribing Information].

Embryo-Fetal Toxicity

• Inform patients that ERLEADA can be harmful to a developing fetus. 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. Advise male patients to use a condom if having sex with a pregnant woman [see Warnings and Precautions].

Infertility

• Advise male patients that ERLEADA may impair fertility and not to donate sperm during therapy and for 3 months following the last dose of ERLEADA [see Use in Specific Populations].

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Ryan M. Phillips, MD, PhD, Matthew P. Deek, MD, Theodore L. DeWeese, MD, and Phuoc T. Tran, MD, PhD

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Metastasis-Directed Therapy In Prostate Cancer: Why, When, and How?

Ryan M. Phillips MD, PhD†, Matthew P. Deek, MD†, Theodore L. DeWeese MD, and Phuoc T. Tran, MD
†Authors contributed equally to this work

ABSTRACT: Metastatic prostate cancer remains a life-limiting disease; while we have seen significant advances in systemic approaches which form the backbone of management, no curative paradigm yet exists. Metastasis-directed therapy (MDT) with stereotactic ablative radiotherapy (SABR) has emerged as a promising complementary technique for the management of low-volume metastatic prostate cancer. Herein we will review the rationale, potential benefits, and practical considerations associated with this approach.

Why Treat Prostate Cancer Metastases with Ablative Radiation?
Rationale for Metastasis-Directed Therapy (MDT) in Prostate Cancer
Traditionally, the management of metastatic cancer has been chiefly through systemic treatments (excellent summary guidelines for systemic management are available[1,2]) while local therapies such as radiation have been used primarily for palliation of symptomatic lesions. Prostate cancer commonly spreads to the bones, causing pain and potentially leading to fractures at weight-bearing sites such as the femoral neck, acetabulum, or vertebral bodies. Radiation is highly effective at reducing pain caused by osseous metastases and can be delivered in one or multiple fractions of external beam radiotherapy (EBRT) or with the systemic radiopharmaceutical radium-223.[3,4]

Beyond palliation, radiation may also impact the course of metastatic disease. Three decades ago, Soloway and colleagues[5] correlated 2-year survival rates with extent of metastatic disease as determined by radionuclide bone scans in men with prostate cancer receiving androgen deprivation therapy (ADT). Most notably, those men with fewer than 6 lesions had a 2-year overall survival of 94%. Just 2 years later, in a retrospective study of 136 men with prostate cancer who received pelvic radiation, Kaplan and colleagues[6] observed that coincidental irradiation of 30-50 Gy to the lumbar spine was associated with a significantly decreased incidence of subsequent lumbar spine metastases. While the mechanism for this apparent protective effect of moderate-dose radiotherapy is not fully understood, hypotheses at the time included treatment of occult micrometastatic disease or alteration of the local microenvironment. These observations led to the notion that aggressive treatment of metastatic deposits with metastasis-directed therapy (MDT) using radiation may alter the natural history of metastatic disease and/or potentially be curative by limiting disease burden and preventing further spread.

The Clinical Argument for MDT in Oligometastatic Prostate Cancer
In their editorial “Oligometastases,” Hellman and Weichselbaum[7] discuss the opposing hypotheses of cancer metastasis as well-ordered and predictable based on knowable anatomic and physiologic data or, alternatively, as the manifestation of cancer as a systemic disease with widespread, initially undetectable micrometastases present at the time of diagnosis but maturing to clinical relevance over time; ultimately they propose that our understanding of cancer behavior is most consistent with a continuum spanning these extremes and with many intermediate states. Their formulation of a “clinical significant state of oligometastases” describes a point on this continuum where metastatic disease is present but potentially curable through consolidation of both the primary tumor and all metastases with local therapies (see Figure 1).

The oligometastatic state in prostate cancer includes de novo hormone naïve metastatic disease present at initial diagnosis, oligorecurrent disease following
The Radiobiologic Argument for Ablative Radiation

Many factors go into the choice of total dose and fractionation during the radiation planning process. Radiobiology best practices dictate that one of the most important aspects is assessing tissue radiosensitivity with respect to optimizing tumor control while minimizing toxicity to normal tissues. This is often done through the α/β constant, a component of the linear-quadratic model which describes cell kill in response to radiation therapy, both for tumor control and for normal tissue complications. Typically, cells with lower α/β ratios become dramatically more sensitive to radiation as the dose per fraction increases. In contrast, cells with higher α/β ratios exhibit a much more muted response to radiation and have a less steep slope on the cell survival curve as dose per fraction increases. The implication of this assumption is that if particular cancer cells have a low α/β, then treating with higher dose per fraction should yield the highest therapeutic ratio by optimizing tumor cell kill and minimizing normal tissue complications. Indeed, for prostate cancer there is good evidence that it has a very low α/β, lower than most surrounding normal tissues[8], and therefore a therapeutic advantage may exist for the use of moderately hypofractionated or intensely hypofractionated stereotactic ablative radiation therapy (SABR) regimens. While extrapolating the linear quadratic equation in these circumstances is fraught with inaccuracies, it is currently the best available model. Thus far, clinical data of SABR in the definitive treatment of prostate cancer have shown promising clinical results.

SABR as MDT Is Well-Tolerated and Clinically Effective

To date, prospective and retrospective studies[9-23] have been performed describing the safety and efficacy of SABR as MDT in oligometastatic prostate cancer (OMPC), including one randomized controlled trial[13] (Table 1). While the definitions, detection methods, and use of concurrent ADT vary across these studies, there is agreement across studies that SABR is well tolerated, with grade 3 toxicity occurring in few patients reported in the aforementioned studies and no grade 4 or 5 toxicity. Similarly, these studies consistently show lesion control rates of 97-100% at 1 year and 93-100% at 2 years.

The Biological Effective Dose (BED)

In radiologic practice, the biological effective dose (BED) is a concept that acknowledges tissues have differential responses to radiation therapy depending on dose per fraction, number of fractions, and inherent tissue radiosensitivity. The BED is modeled using the linear quadratic formula as follows: \( \text{BED} = n \times d (1 + d / (\alpha / \beta)) \) where \( n \) = number of fractions, \( d \) = dose per fraction, and \( \alpha / \beta \) is a constant representing cell kill specific for different tissues. By using a BED practioner is able to more accurately compare different radiation dosing schedules.

SABR May Facilitate Delay of ADT Initiation

Controversially, the favorable safety profile and durable lesion control afforded by SABR has led to interest in using this approach to forestall initiation of ADT, in so-called oligorecurrent men, in order to avoid unpleasant side effects including hot flashes, fatigue, and sexual dysfunction. The shining example of this approach is the STOMP trial, which randomized men with 3 or fewer extracranial prostate cancer metastases to surveillance alone or SABR to all detectable foci of disease.[13] With a median follow-up of 36 months they observed that median ADT-free survival in men receiving SABR was 21 months vs 13 months with surveillance alone. The clinical relevance of this finding remains a point of active disagreement amongst experts.[24] Those in favor of early ADT initiation may cite the TOAD trial [25], which showed an overall survival benefit (unadjusted hazard ratio [HR], 0.55; \( P = .05 \)) with immediate initiation of ADT as compared to a recommended 2 year delay. Those opposed may cite the overall lack of impact on development of metastases with early ADT in the analysis of US Department of Defense patients by Moul et al.[26] and the results of EORTC 30891[27], which showed similar prostate cancer-specific survival in men not suitable for local treatment receiving early vs delayed ADT. Despite the controversy, an ADT backbone is the standard of care in men with metastatic disease and other novel approaches including MDT are still being evaluated under the auspices of a clinical trial.
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A critical limitation of any numerical definition for the oligometastatic state is its reliance on detection methods which are not absolutely sensitive nor specific and which may provide conflicting information when compared with complementary modalities. While computed tomography (CT), magnetic resonance imaging, and 99mTc scintigraphy remain the backbone of prostate cancer staging, the diagnostic toolbox is expanding rapidly and include 18F-NaF, 11C-choline, 18F-fluorocholine, 18F-fluciclovine, and a variety of prostate-specific membrane antigen (PSMA)-targeted radiotracers including 18F-DCFBC, 18F-DCF-PY, 68Ga-PSMA-HBED-CC, and 177Lu-PSMA several recent reviews have detailed the evidence for and unanswered questions surrounding the use of these agents.[24,29-31] It should be noted that a major challenge in defining the role of targeted imaging in the diagnosis and management of oligometastatic prostate cancer are the limited data correlating radiologic findings with gold standard surgical pathology, especially regarding distant metastases which may not be amenable to resection.

As detection methods continue to evolve, technological differences between studies must be taken into consideration when evaluating outcomes of MDT; patients with five or fewer lesions detectable with leading-edge methods may represent a population with a lower disease burden than those identified using conventional imaging alone.

While numerical definitions remain the best approach to defining the oligometastatic state, there is significant interest in defining the biology that differentiates men whose disease may yet be arrested with local consolidation from those with as yet undetectable, but nevertheless widespread disease who would be best served by systemic therapy.[32, 33] While such definitions have not yet been identified for prostate cancer, the recent description of a molecular phenotype associated with a 94% 10-year overall survival in patients with de novo oligometastatic colon cancer who undergo resection of liver metastases.[34] provides evidence that these biological descriptions are feasible.

**Location Of Metastases**

Studies of MDT for OMPC have primarily addressed nodal or skeletal metastases. Visceral metastases, while rare, portend a worse prognosis and relatively poor response to systemic therapies.[35] Sites may include liver and lung, which are potentially amenable to SABR, but it is unclear whether these lesions represent individual deposits that may benefit from MDT or inherently unfavorable biology best approached systemically. It is also important to consider surgical resection as an alternative approach to MDT in the treatment of OMPC. Several studies have included patients who underwent surgical resection, albeit representing a small number compared to SABR.[13,17] The recent STOMP trial[13] included six patients who underwent surgery, five of

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**Selecting Patients for Metastasis Directed Therapy - Definitions of Oligometastatic Prostate Cancer**

Quantitative cutoffs based on the number of metastatic foci are often used to define the oligometastatic state for simplicity as well as association with disease outcome. [5, 28] Nine prospective clinical trials have numerically defined the oligometastatic state in prostate cancer; three allowed up to three metastases, two up to four, three up to five, and one up to 10. The literature of other published retrospective reviews generally included five or fewer metastatic foci.[9,17,19]

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which were salvage pelvic lymph node dissections and one a lung metastectomy. Surgical resection may be the preferred intervention based on tumor location with, for example, central lung lesions where SABR would result in high toxicity[36], large brain metastases where radiosurgery alone would result in lower rates of local control[37], or spine metastases threatening cord compression.

How Is MDT Using Ablative Radiotherapy Delivered?

Target Volumes, Dose, and Fractionation

Optimal ablative dosing is contingent on multiple factors including radiobiological properties of prostate cancer cells and dosimetric constraints of adjacent organs at risk. Studies reporting on the use of SABR for the definitive treatment of prostate cancer have utilized regimens with biological effective doses (BED) (see Box 1) ranging from 168 to 407 Gy[38-45] with some evidence suggesting BED of 200 Gy (either for SABR or conventionally fractionated RT) is associated with better disease control.[46]

STOMP, the only published prospective randomized trial of MDT in oligometastatic prostate cancer, utilized a dose of 30 Gy in 3 fractions.[13] Other retrospective and observational studies of MDT in oligometastatic prostate cancer utilized doses ranging from 16 to 50 Gy in 1 to 10 fractions (Table 2 with some suggestion that a BED higher than 100 Gy is associated with superior local control.[10, 11,17-19]

Toxicity from SABR is generally mild across several lesion locations. Every other day scheduling is often used as it has shown reduced toxicity compared to daily treatments in definitive treatment of the prostate[41], however even with daily treatments toxicity rates remain low (Table 1).

Specific Considerations by Treatment Site

Gross tumor volumes (GTV) (see Box 2) generally include all tumor seen on imaging. Clinical target volumes (CTV), such as with spinal or vertebral metastases, are typically based on consensus contour guidelines.[47] Planning target volumes (PTV) vary by institution based on set up uncertainties, but generally are on the order of 3-5 mm when daily image guidance is used (Table 2). Dose constraints for organs at risk (OAR) are based on American Association of Physicists in Medicine Task Group 101 recommendations or other SABR-based clinical trials and delineation of specific OARs are guided by established guidelines and atlases.[48,49]

All patients should be custom fitted with immobilization devices created at the time of simulation. Motion management is necessary for rib lesions and (the less common) pulmonary metastasis using either 4-dimensional CT or an active breath coordinator.

Concurrent ADT and Other Systemic Therapies

One goal of MDT in OMPC is to avoid systemic therapy and its associated side effects. However, a more aggressive approach may involve intensification aimed at simultaneously eradicating sites of microscopic metastatic disease in addition to local consolidation with SABR through the use of concurrent ADT, non-castrating antiandrogens such as enzalutamide, chemotherapy such as docetaxel, and even complimentary forms of systemic radiation such as radium-223. No level 1 evidence exists for this treatment paradigm, however retrospective data[19] suggests a possible improvement in distant progression-free survival with the concurrent use of ADT and SABR. Therefore, prospective studies are on-going to address this question.

Follow-Up After MDT

Guidelines following biochemical failure typically recommend follow up, with physical exam and prostate-specific antigen (PSA), every 3-6 months with imaging as indicated for symptoms. However, individuals treated with local rather than

**BOX TWO** Radiation Target Volumes

Gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV) are three different sets of radiation target volumes used in the radiotherapy planning process. The GTV, as its name implies, represents gross disease that can be seen on imaging or physical exam and typically encompasses the primary tumor and involved lymph nodes. The CTV is an expansion of the GTV to account for microscopic disease that cannot be seen with conventional imaging or examination. The PTV is an expansion of the CTV taking into account uncertainties in the planning and delivery of radiation such as daily set up variation and tumor motion.
systemic therapies warrant closer follow-up for several reasons. First, though studies of MDT in oligometastatic disease have shown promising results, these patients have known systemic disease and therefore are still at risk for disease progression. For instance, 30% of patients in STOMP treated with MDT progressed to polymetastatic disease within one year. [13] Additionally, patients who develop oligometastatic recurrence can be successfully treated with additional SABR. For example, 25% of patients in Decaestecker et al[17] who developed oligometastatic recurrence and were subsequently treated with additional SABR remained progression-free at last follow-up. Finally, while PSA monitoring is the current standard to assess treatment response, there is great potential in the future to use circulating tumor cells or circulating tumor DNA as an alternative or complementary method.

**Ongoing Studies and Future Directions**

As investigation into the curative potential of MDT in OMPC continues, several major questions remain unanswered. Can MDT alone produce durable clinical benefits and, if so, how can patients be most appropriately selected? Does MDT provide additive benefit when combined with ADT and other systemic therapies? Does MDT have clinical benefit in oligoprogressive CRPC? Can MDT be combined with immunotherapy to encourage a systemic antitumor response?

Multiple prospective randomized clinical trials are ongoing to answer these first two questions. Similar to STOMP, the Baltimore ORIOLE trial [NCT02680587][50] is evaluating progression, ADT-free survival, and immunologic correlates in men with OMPC randomized to receive observation or SABR. PCS IX (NCT02685397) is investigating the clinical benefit of adding SABR to systemic treatment with ADT and enzalutamide in patients with CRPC. CORE (NCT02759783) and STEREO-OS (NCT03143322) are randomizing patients with prostate, breast, or lung cancers with 1-3 oligometastases to standard of care systemic therapy with or without SABR. STORM (NCT03569241) is randomizing patients with oligorecurrent prostate cancer confined to the lymph nodes to MDT (salvage lymph node dissection or SABR) with six months of ADT ± whole pelvic radiotherapy. Finally, the Movember GAP6 international initiative is pooling tissue samples from clinical trials such as these in order to promote collaborative efforts to facilitate further biological understanding of the oligometastatic state in prostate cancer.[51]

There are encouraging but still preliminary data with oligoprogressive CRPC that MDT can have a role in advanced disease but more clinical experimentation is needed (reviewed in ref 52).

### Table 2: Radiotherapy Techniques For Metastasis-Directed Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose</th>
<th>Biological Effective Dose*</th>
<th>Expansions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tabata[21]</td>
<td>30-50 Gy in 10-25 fx</td>
<td>&gt;50</td>
<td>Not reported</td>
</tr>
<tr>
<td>Jereczek-Fossa[11]</td>
<td>33 Gy in 3 fx for nodes</td>
<td>&gt;154</td>
<td>GTV + 1-2mm</td>
</tr>
<tr>
<td>Muacevic[12]</td>
<td>16.5-22 Gy in 1 fx</td>
<td>&gt;107.25</td>
<td>Not reported</td>
</tr>
<tr>
<td>Ahmed[9]</td>
<td>Median 20 Gy (range, 8-24 Gy)</td>
<td>GTV or ITV + 5mm</td>
<td></td>
</tr>
<tr>
<td>Berkovic [10]</td>
<td>50 Gy in 10 fx</td>
<td>133</td>
<td>GTV + 3-5mm</td>
</tr>
<tr>
<td>Decaestecker[17]</td>
<td>50 Gy in 10 fx</td>
<td>&gt;130</td>
<td>GTV + 2mm for bone</td>
</tr>
<tr>
<td>Ponti[20]</td>
<td>12 Gy in 1 fx, 30 Gy in 3 fx for nodes and 30 Gy in 3 fx</td>
<td>&gt;60</td>
<td>GTV + 5-8mm</td>
</tr>
<tr>
<td>Aitken[15]</td>
<td>Not specified</td>
<td>Median 60 (range 36-180)</td>
<td>GTV +1-1.5mm or international consensus</td>
</tr>
<tr>
<td>Ost[13]</td>
<td>30 Gy in 3 fx</td>
<td>130</td>
<td>GTV +2 mm for bone lesions</td>
</tr>
<tr>
<td>Triggiano[22]</td>
<td>&gt; 5 Gy per fraction</td>
<td>&gt;80</td>
<td>GTV + 3 mm</td>
</tr>
<tr>
<td>Bouman- Wammes [16]</td>
<td>30 Gy in 3 fx</td>
<td>&gt;116.7</td>
<td>GTV + 3-5mm</td>
</tr>
<tr>
<td>Muldermans [18]</td>
<td>16 Gy x 1, 18 Gy x 1, 19 Gy x 1, 24 Gy x 1, 10 Gy x 3, 10 Gy x 5</td>
<td>&gt;101.33</td>
<td>Consensus guidelines for spine mets, GTV + 1cm for CTV nonspine osseus</td>
</tr>
<tr>
<td>Siva[14]</td>
<td>20 Gy x 1</td>
<td>153.33</td>
<td>GTV + 5mm</td>
</tr>
</tbody>
</table>

*Calculated using α/β = 3. CTV = clinical target volumes; fx = fraction(s); GTV = gross tumor volumes; ITV = internal target volumes; PTV = planning target volume.
either alone or in combination with systemic therapies. At present, the strongest indication for this approach would be pain relief for symptomatic lesions. The randomized phase II STOMP trial and an increasingly compelling volume of retrospective series and phase III trials suggest that SABR may also be a valuable tool in the definitive management of OMPC. Patients should be educated on the proposed benefits and ongoing clinical trial opportunities.

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INTERVIEW

Benjamin Levy, MD

The Next Generation of Lung Cancer Management

ONCOLOGY recently sat down with Benjamin Levy, MD, of Johns Hopkins University, to learn about his lung cancer research, recent advances in the field and their clinical applications.

Q: What is the most significant science coming out of the lung cancer community right now, and what does it mean for oncologists?

Dr. Levy: The most important research falls under the hub of personalized medicine. There is an expanding list of lung cancer genotypes that we have identified as relevant, and even more importantly, that we have discovered targeted therapies for. In addition, we are learning more about predictive markers for immunotherapy that may inform us on how to optimally treat patients. Both targeted therapy and immunotherapy are approved in advanced non-small cell lung cancer and we are learning more about the utility for these drugs in earlier stage disease.

Q: There is a lot of recent data about targeted therapies. Will you be discussing new results at the upcoming Chemotherapy Foundation Symposium?

Dr. Levy: Yes, we will probably want to make room for the KRAS Amgen 510 drug when we discuss rare lung genotypes, a session that will be tackled by Dr. Drilon. It should be exciting information and data that once again is transforming the way we treat patients.

Q: Could you describe some of the most clinically relevant research in your specialty?

Dr. Levy: My interest really is in targeted therapies, but specifically on how we diagnose patients with lung cancer in terms of their genotyping. There is a lot of movement in this space in terms of using liquid biopsies to both genotype lung cancer patients but also as a tool for monitoring in real time how patients are doing on targeted therapies. Looking at longitudinal assessments of the genotype within the plasma to help better understand patient response holds real promise. We are actively discussing how liquid biopsies should be leveraged in everyday clinical practice at our medical crossfire at CFS.

Q: So, liquid biopsies are being used
somewhat already, but you are looking at how that can be expanded into everyday practice, including in smaller community oncologist settings?

**Dr. Levy:** The new data we have with liquid biopsy suggests that every patient with advanced non-small cell lung cancer should potentially have a liquid biopsy in conjunction with their tissue biopsy.[1] We want to educate clinicians, both in academia and in the community on that, and are exploring future applications using data from the longitudinal assessment. This includes studying advanced patients who are on targeted therapy and following their ctDNA over time, as well as looking at results in the minimal residual disease in patients who are cured from their lung cancer from either surgery or radiation, or both. The question we are trying to answer is “Can we detect recurrences in the plasma earlier than we can on a CAT scan and does that translate into better outcomes?”

**Q:** And that’s where the blood biopsy really comes in?

**Dr. Levy:** That’s correct.

**Q:** Obviously chemotherapy is still used widely in most cancer types in one way or another. Do you see us moving away from chemotherapy eventually?

**Dr. Levy:** Chemotherapy is still utilized in a large majority of our patients, either as first-line or second-line, even for patients with genetic aberrations. But this is the whole movement in oncology, and specifically in thoracic oncology, developing novel drugs that allow us to move away from chemotherapy. Now, that includes targeted therapy, so that’s why it’s so important to identify the target up front, so that we can use the right drug for the right patient. Things like testing for PD-L1 is also important because that also can help drive immunotherapy decisions.

Now that we’ve got targeted therapies and immunotherapies as frontline options, many patients will unfortunately still progress, and we do use chemotherapies in those settings. That as the new big question… how can we get away from using chemotherapy in the refractory space, looking at either novel targeted therapies or immunotherapies, to move away from chemotherapy in advanced non-small cell lung cancer. Eventually. That’s the goal.

**So, liquid biopsies are being used somewhat already, but you I guess that’s why you’re seeing the development of drugs for resistance mutations that come in response to a targeted therapy?**

**Dr. Levy:** That’s right. That’s part of it, looking at patients who have a genetic aberration who are treated with a targeted therapy. Trying to understand mechanisms of resistance to that targeted therapy will help inform treatment decisions, and those treatment decisions hopefully will involve another therapy that specifically targets that mechanism of resistance, and then on and on. Beyond that, we hope to do the same thing after the second targeted therapy. This is kind of what we’re learning a bit in ALK-rearranged lung cancer. If patients are on targeted therapy once they progress, mechanisms of resistance may develop[2] that might inform treatment decisions and we can hopefully sequence patients with therapies other than chemotherapy.

**Q:** What other research has been most notable?

**Dr. Levy:** The growing list of targeted therapies, the growing list of immunotherapies, but also, of course, CAR-T cells are very important. This is a field of medicine that’s growing rapidly, not so much in the solid tumor space but certainly in the malignant heme space. And that’s where the blood biopsy really comes in.

Also we are still looking at the role of radiation in many of these solid tumor malignancies. For instance, in lung cancer, we’re learning more and more that radiation can be incorporated for patients who have stage IV disease. But for patients who have what we call “oligometastatic disease,” there may be a real role for radiation therapy. The themes of precision medicine and biomarker implementation are most important.

I want to add that, while it’s important to talk about the science, it’s also important to talk about how we approach the patients comprehensively. And that includes all facets of care – the emotional needs, the evaluation of a patient’s fitness, specifically looking at elderly patients, even looking at comorbidity, the importance of assessing heart-related issues for cancer patients, for example. Treating the whole patient is critical.

**DISCLOSURE:** Dr. Levy has consulted for Merck, Celgene, Takeda, Pfizer, Genentech, Eli Lilly, Guardant, and Astra Zeneca. For references visit cancernetwork.com/LungLevy10-19
As a physician a question I am frequently asked is, “Will there be a cure for cancer in my lifetime?” As a longtime clinician and researcher of cancer prevention, my answer has been consistent: “We already have a full-proof cure or prevention for about 40 percent of all cancers.” When people hear this their eyes brighten and they lean in. Yet when I say that this cure is to not smoke, their expression changes and they feel they’ve been duped.

Yet it is education about the relative risks of lung cancer, oral cancer, laryngeal cancer, and other cancers that physicians need to emphasize to those who are, so far, cancer free. The media have generally done a poor job of communicating relative risk. Rather than using scare tactics—such as the misleading statistic that “radon is the second leading cause of lung cancer,” we need to speak directly to our patients about the very high risk of cancer from cigarette smoking. Low dose CT scanning to screen for lung cancer is a puny approach to the pandemic. It’s secondary prevention at best, and can lead to problems from false positive assessments and resulting invasive procedures. And although we can save one life for every 300 that are regularly screened with annual low dose CT, about one in 900 of those screened is developing cancer from the radiation exposure of frequent CT scans.[1]

As physicians, we need to directly engage with every one of our patients who smoke. A nonthreatening strategy to help a patient stop is to shift the focus from the person to the product. For example, the filter is consumer fraud. We need to debunk the myth that filtered cigarettes (which are purchased by 99% of patients who smoke) are in any way safer. In fact, those who buy filtered brands have to inhale more deeply to get the smoke through the filter, thus breathing in higher concentrations of carbon monoxide, cyanide, and other poisonous gases and increasing the risk of emphysema and heart disease. Similarly, “low tar” just means a few less cancer-causers and other poisons (“Would you buy a loaf of bread that was advertised as having only 1 ounce of aflatoxins or a can of tuna that has only 1 milligram of mercury?”); “lights” and “ultra-lights” just mean more sugar or other sweeteners; and menthol is just an anesthetic that deadens the throat to make the smoke seem less harsh.

Another topic to address with high school and college students is e-cigarettes, especially JUUL, which have become alarmingly popular. JUUL was designed to produce a more rapid absorption of nicotine and thus to result in earlier addiction. However, humor is a more effective approach than finger-wagging and scare tactics. For instance, matter-of-factly mentioning the inevitable yellow teeth and zoo breath of a teenager who smokes Marlboro or the goofy-looking image of a JUUL user sucking on a flash drive has a better chance of sinking in than talking about lung cancer or heart disease.

Overall, the keys to lung cancer prevention are the commitment of every physician and every medical school dean and every hospital administrator to make smoking prevention and smoking cessation (and relapse prevention) a top priority; environmental reinforcement through clean indoor air legislation and paid satirical mass media campaigns; and social reinforcement by family, friends, co-workers, employers, and one and all.

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.

For references visit cancernetwork.com/LungLevy10-19

Dr. Blum is a family physician, Professor, Gerald Leon Wallace, MD, Endowed Chair in Family Medicine, and Founding Director of the UA Center for the Study of Tobacco and Society, University of Alabama School of Medicine, Tuscaloosa, Alabama.
INTERVIEW

Recently, ONCOLOGY discussed the classification of diffuse large B-cell lymphoma (DLBCL) into distinct subtypes and treatment decisions based on molecular classifications. We spoke with Jennifer Crombie, MD, a medical oncologist at the Dana–Farber Cancer Institute in Boston, who specializes in the care of patients with lymphoma and takes part in clinical trials of lymphoma patients.

Q: Dr. Crombie, how is DLBCL generally diagnosed and what are the typical clinical and molecular characteristics of this tumor type?

Dr. Crombie: DLBCL is the most common subtype of non-Hodgkin lymphoma, representing about 30% to 40% of cases. Patients are typically diagnosed with an excisional lymph node biopsy or a biopsy of another affected organ. When pathologists look under the microscope, they can see a diffused proliferation of large neoplastic B cells. These B cells are identified by flow cytometry or immunohistochemistry that identifies pan-B-cell antigens such as CD19, CD20, and CD79a, as well as CD45. DLBCL is known to be an aggressive lymphoma, but it is also known to be both clinically and molecularly heterogeneous. [1] Patients can have a range of clinical presentations, with disease of only one lymph node to more advanced-stage disease with extranodal sites of involvement. Just like patients can have a range of clinical presentations, outcomes can also be extremely variable, with approximately 60% of patients being cured with frontline chemotherapy. The remaining patients with refractory or relapsed disease have much poorer outcomes.

Clinically, when we think about how to identify these patients to risk stratify them, we can use the International Prognostic Index. This has been the mainstay of risk stratification and incorporates a variety of clinical characteristics such as age, lactate dehydrogenase, performance status of the patient, and number of extranodal sites, as well as Ann Arbor staging. Using these criteria, we are able to stratify outcomes to frontline therapy. As far as the molecular characteristics, although there are a variety of genomic alterations, there is not a specific defining molecular feature, again highlighting the heterogeneity of this type of lymphoma.

Q: In the last several years, there have been studies that have identified a few different subtypes of DLBCL. Could you talk about the rationale for doing these studies and how these were done?

Dr. Crombie: As I mentioned, there is a wide range of clinical heterogeneity. There have been efforts to understand what biologic underpinnings could drive these differences in outcomes. The initial studies done almost 20 years ago used gene expression profiling, which is a laboratory test that looks at the expression of thousands of genes. This identified two molecularly distinct subtypes of DLBCL, and the genetic profiles were believed to reflect different stages of B-cell development. This is why this is known as “cell of origin.” The first subtype is germinal center B-cell–like (GCB)-DLBCL. These lymphomas express genes that define the GCB before it has left the germinal center. The other main subtype of DLBCL is the activated B-cell–like (ABC)-DLBCL. In this subtype, the transcriptional signature resembles B cells in the post-germinal center, which are blocked at the phase where they would have plasmablastic differentiation.

MEET OUR EXPERT

Jennifer Crombie, MD, is a Medical Oncologist, Dana Farber Cancer Institute and Instructor in Medicine at Harvard Medical School, Boston, Massachusetts.
Recently, researchers at the British Columbia Cancer Centre for Lymphoid Cancer in Vancouver and the Princess Margaret Cancer Centre–University Health Network in Toronto identified a novel subtype of DLBCL. Can you talk about whether they used similar approaches as other studies you described and place these results in the context of whether these subtypes are relatively fluid and more of a moving target?

Dr. Crombie: The authors of the study [2] used a similar approach to the initial gene expression profiling that identified cell of origin, but they used RNA sequencing rather than DNA microarrays. Specifically, they looked at 157 patients with germinal center B-cell lymphoma, including a subgroup that had double-hit and triple-hit lymphomas, and then identified a gene expression signature for the double-hit and triple-hit lymphomas. When they then applied this signature, which was based on 104 genes, they found that even patients who didn’t traditionally meet the criteria of double-hit or triple-hit lymphoma based on fluorescence in situ hybridization or identification of cytogenetic abnormalities shared the same transcriptional profile.

Similarly, they had an inferior outcome to frontline therapy. So, using this tool, the researchers were able to identify a group of patients who would otherwise have been missed as having a high-risk disease. Specifically, they found that patients with this double-hit signature had a high incidence of mutations within chromatin-modifier genes and few infiltrating T cells. This group of patients also had abnormalities in genes involved in oxidative phosphorylation. The authors wondered if adding therapies that could target these abnormalities could be beneficial in these high-risk patients. Then, to make it more clinically relevant, they went on to create a 30-gene NanoString-based assay that could classify these patients in a more clinically utilized fashion. The hope would be that we could use this information in clinical trials to identify more intensive regimens or alternative therapies that could improve outcomes.

More recently, there have been newer gene expression profiling tools such as the NanoString assay that can decrease the number of genes involved from thousands down to 20 genes and uses fixed tissue. The common assay known as lymph2Cx has been tested in clinical trials and has good concordance with standard gene expression profiling.

As I mentioned, the main reason to do these studies is to try to identify patients with higher-risk disease who may benefit from more intensive chemotherapy. It has been shown that patients with ABC subtype have an inferior outcome following traditional chemoimmunotherapy, which is rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). There are two other subtypes of DLBCL worth noting that have independent prognostic information beyond the cell of origin. These are lymphoma abnormalities of the MYC oncogene. Specifically, the GCB subtype of lymphomas can commonly have translocations that involve MYC with BCL-2 and/or BCL-6. These have unique names, double-hit or triple-hit lymphomas, and are now recognized by the World Health Organization as a unique entity known as high-grade B-cell lymphoma with translocations involving MYC and BCL-2 and BCL-6. This just highlights the prognostic significance of these genomic abnormalities. Similarly, lymphomas that have high protein expression of MYC, BCL-2, or BCL-6 are double-protein-expression lymphomas. These have also been shown to have a poor prognosis with frontline therapy. [3]

The reason for doing these studies has been to identify patients who may benefit from therapies other than R-CHOP. This has been looked at in a variety of clinical trials, but not yet with success. There has been a randomized phase II trial that combined bortezomib with R-CHOP and a phase III randomized trial, the PHOENIX trial, which added ibrutinib to R-CHOP, and compared to R-CHOP alone, failed to show an improvement in patients, specifically in non-GCB or ABC subtype lymphomas. Thus far, while this information on DLBCL subtype information provides prognostic value, it has yet to really change the way we approach treatment for these patients. More recently, there have been advances. Using next-generation sequencing and whole-exome sequencing, there have been more genomic abnormalities that have been appreciated and have exposed heterogeneity even within the cell of origin.

Q: Are there any other studies that have tried to further classify DLBCL?

Dr. Crombie: There have actually been a few studies published in the last year or two that have further dissected the underlying genomic profiles of DLBCL and identified subgroups beyond cell of origin. Specifically, the authors of these studies have looked at a range of genomic abnormalities, including point mutations, copy number alterations, and structural variants, which all seem to be important in this disease in terms of the classification. As I mentioned, interestingly, these additional studies have revealed heterogeneity among the traditional cell-of-origin classification.
Despite this work, the results of front-line trials targeting the ABC or non-GCB DLBCL subtype by adding new agents to standard RCHOP chemotherapy (so called X-RCHOP combinations, where X stands for added targeted agent) have been disappointing. While there are multiple reasons why these approaches might not have worked, the common problem is that ABC patients in clinical trials do much better than expected based on retrospective database studies. As it turns out, patients with DLBCL with rapidly progressive disease start therapy urgently, frequently in the hospital.[10] These patients have high risk disease but unfortunately are not enrolled in clinical trials due to the complexity of screening testing, including the need for centrally assessed molecular classifier. Patients with a good prognosis are more likely to enter the trial – making measuring of the effect of new agents very difficult, if not impossible. In other words – our clinical trials simply did not capture real world patients.

What does the future hold for COO for the selection of therapy? We now recognize that COO subtypes are molecularly and biologically heterogeneous, as identified by mutational clustering. Indeed, a subset of ABC patients have relatively good outcomes, while subset of GCB patients fare worse than expected for the GCB subtype.[11,12] This new understanding of molecular clusters of DLBCL will likely fuel future trial development. Whatever we do however, we need to make sure that these trials allow for the inclusion of rapidly progressing, sicker patients without any delay. These patients have the most to gain from novel therapies.

FINANCIAL DISCLOSURES: Dr. Nowakowski has consulted for, or been funded by, Bayer, Celgene, Selvita, NanoString, Morphosys, and Seattle Genetics.

For references visit cancernetwork.com/DLBCLI10-19

Dr. Nowakowski is Hematologist, Oncologist, Researcher, and Associate Professor at Mayo Clinic in Rochester, Minnesota.
Mutations and the Importance of Genetic Testing

Advancing towards personalized medicine in breast and ovarian cancers

Recently, ONCOLOGY spoke with primary study author Dr. Allison W. Kurian about a new breast cancer study that analyzed the mutations present in breast tumors, and about emerging targeted therapy options. Dr. Kurian is associate professor of medicine and oncology and health research and policy at the Stanford University Medical Center in California. Her clinical practice focuses on women at high risk for developing breast and gynecologic tumors and treating women who are diagnosed with breast cancer. She is also director of the Stanford Women’s Clinical Cancer Genetics Program.

Q: First, what are the standard genetic tests the vast majority of women who are diagnosed with breast cancer undergo or should undergo? Do these tests assay for both somatic and germline mutations?

Dr. Kurian: This is a great question. I would say the answer is still specific to the kind or stage of breast cancer a woman has. A great number of women now qualify under existing guidelines for testing for inherited genetic mutations. Examples of that would be testing for the BRCA1 and BRCA2 mutations. There is some controversy over whether that should be every single woman with breast cancer or only those who have some personal or family history that would suggest their breast cancer may be linked to an inherited mutation. There are also tests of the tumor that look for somatic mutations. Right now, somatic mutation tests are typically reserved for those women with advanced metastatic disease, but there are some early gene expression tests such as the Oncotype DX® (21-gene test) we often use.

Q: You see women who are, compared to the general population of women, at higher risk for breast and ovarian cancers. How do these women typically find a clinician such as yourself? Do they know they carry a cancer susceptibility mutation because someone in their family has been diagnosed with breast cancer or a gynecologic cancer?

Dr. Kurian: The patients I see tend to be a mix. At the Stanford Women’s Clinical Cancer...
Genetics Program, which is similar to many cancer genetics clinics around the country, we see people because they are referred for their own personal cancer diagnosis. This is often because they had a breast cancer diagnosis at a young age or a breast cancer diagnosis with family history or ovarian cancer. For these patients, we might do a genetic test and find an inherited genetic mutation. If we do, then we might ask them to reach out to their relatives and have them tested. Other times, maybe the relative with cancer has been tested somewhere else and their unaffected relative might ask them to reach out to us for genetic testing and recommendations about how to manage cancer risk.

**Q:** You and your colleagues recently conducted this study survey examining genetic testing among women diagnosed with breast or ovarian cancers.[1] Can you tell us about the study design and what prompted you to do this?

**Dr. Kurian:** Absolutely. The study design is based in the largest and highest-quality population-based cancer registry in the United States, which is the SEER [Surveillance, Epidemiology, and End Results] registry. The SEER registry covers about one-third of the US population in terms of recording (cancer diagnosis), survival, and other outcomes of patients. We were very interested in looking across the whole population, not just people being seen at academic centers like Stanford University but everyone, and understanding what happened in terms of genetic testing. What we were able to do was to look at the large populations of the states of California and Georgia, which together add up to 50 million people. We were able to use the SEER registry from both states that covers the whole population. This means that we did not leave anyone out. We then were able to do a data linkage, which was really exciting and innovative. We worked together with the four major testing laboratories that provide genetic testing to link the genetic data to the cancer registry data. Thus, we were able to learn a great deal about who actually gets tested and what was found.

**Q:** What did your study find that was particularly surprising to you?

**Dr. Kurian:** The study had a number of interesting results. Probably the most striking one was that only less than one-third of patients with ovarian cancer ever got genetic testing.[1] For more than 10 years, there have been guidelines from a number of different societies, from cancer societies to obstetrics and gynecology societies, that say everyone with (the standard kind of) ovarian cancer—high-grade serous ovarian cancer—should get genetic testing. So, to see that it was fewer than 30% was really concerning in terms of under-testing. Now, our analysis was based on data gathered from 2013 to 2014 and this figure may have improved in more recent years. Those years, however, were times when it was very clear that everyone needed to be tested.

**Q:** So about this under-testing, are there potentially obvious reasons for this and is it something that you and your colleagues are looking at further?

**Dr. Kurian:** I think it’s an important question, and I don’t know exactly why there was this under-testing trend. When
The authors of this study have provided us with an important snapshot of the frequency of genetic testing in a population-based cohort of breast and ovarian cancer patients, including a subpopulation analysis in the United States. This study provides important information, helping to build a foundation of the current state of genetic testing in these cancer patients in order for clinicians and geneticists to identify the issues and gaps with regard to genetic testing. The study showed that the frequency of genetic testing is fairly low for both breast and ovarian cancer patients and is even lower for those women without insurance. The work also underscored the racial disparity that exists as the frequency black and Hispanic women who underwent genetic testing was lower compared to the frequency of white women that were tested. This study is a step towards first identifying the populations that are underserved when it comes to genetic testing and second, implementing strategies to improve the frequency of genetic testing.

This study provides important information, helping to build a foundation of the current state of genetic testing in these cancer patients in order for clinicians and geneticists to identify the issues and gaps with regard to genetic testing. Testing in the clinic. While the study focused on data from populations in Georgia and California, future studies should analyze whether testing patterns are similar in other United States geographies, particularly in the southwest. Next, we need to understand why the racial disparities exist and identify approaches that can be implemented to improve genetic testing across the United States for women with breast and ovarian cancers.

Dr. Arun conducts research characterizing risk factors in high-risk women with or without hereditary breast cancer mutations and assessing breast cancer biology in patients with breast cancer who have mutations of the BRCA1 or BRCA2 gene. She also runs clinical treatment trials in patients with BRCA mutations using PARP inhibitors.

**Financial Disclosure:** Dr. Arun has received research funding from Invitae.

**Dr. Arun** is Professor in the Department of Breast Medical Oncology, Division of Cancer Medicine, and Co-Medical Director, Clinical Cancer Genetics Program, University of Texas MD Anderson Cancer Center, Houston, Texas.

We see a difference of disparity by ethnic characteristics, insurance, and socioeconomic status, we think about access barriers in terms of whether some people are getting less effective care or have clinicians who maybe don’t understand that they need to refer them for genetic testing. Or could this be a situation in which patients have other barriers? They may be dealing with a lot other than cancer treatment and doing one more thing like a genetic test is just too much. It was interesting that we didn’t see these problems with breast cancer, only with ovarian cancer. It does suggest a particular area to target. We are actually in the process of applying for funding to do a much more focused study of ovarian cancer patients to try to understand why this might be and how we might fix it.

**Q:** Anything else in general to add on this topic, including any advice for clinicians who see patients with breast and ovarian cancer, and anything else on the specific vulnerable populations that you identified?

**Dr. Kurian:** Ovarian cancer patients need genetic testing, period. This is straightforward and it’s something where again, as we see that there seems to be under-testing in women with less insurance and women of African American ethnicity, there needs to be particular care that those patients are appropriately counseled and tested and referred to specialists and geneticists as needed.

**Q:** Could you talk about the growing therapeutic options specific for breast cancer based on genetic...
mutations that have been uncovered? Are there now novel targets that are being explored in clinical trials or that may be tested in clinical trials soon?

Dr. Kurian: Yes. It’s been an exciting several years in this breast cancer therapeutics space. When I started in the field in 2002, we really didn’t have any targeted therapy related to inherited gene mutations. Over the last several years, we have seen the development of PARP [poly (ADP-ribose) polymerase] inhibitors, which are drugs that can be very effective in treating ovarian cancer in women who have an inherited genetic mutation. These drugs also sometimes work in women who don’t have a genetic mutation, but they seem to be particularly effective if women have an inherited genetic mutation. More recently, PARP inhibitors have also been approved for treatment of breast cancer in women who have an inherited genetic mutation. It’s more relevant than ever before to understand what the genetic testing results are in terms of guiding treatment of cancer.

And there are a number of other clinical trials ongoing also focused on these questions. Some of these clinical trials are combining PARP inhibitors with immunotherapy, which we’re excited to learn more about and seem promising.

Q: Anything else you would like to mention about either therapy or genetic testing for breast cancer patients?

Dr. Kurian: This is an interesting and exciting time to live in, in terms of the practice of medicine and oncology. A lot of the promise of genetics and genomics is just being unlocked. I think there’s great importance both in pursuing the bench science and clinical science side of things in terms of clinical trials and understanding which mutations might be targetable. But there is also a huge need to work on the population sciences and implementation side, which is really thinking about how do we use genetic testing, how do we make sure people get this testing, and how do we make sure that the results are acted on and managed appropriately.

Disclosure: Dr. Kurian has received research funding from Myriad Genetics.

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Diffuse Large B-Cell Lymphoma
Continued from page 405

Q: Finally, what do you see as the evolution of DLBCL subtypes? Are there unanswered questions about the biology of DLBCL that could help clinicians make better therapy decisions for their patients?

Dr. Crombie: There are so many unanswered questions in the field. I think many of the recent studies have highlighted that the genomics are much more complex than we previously thought and that there is significant heterogeneity. But these studies have moved us closer to a better understanding of which patients are highest risk, which patients we should really focus our energy on and develop clinical trials for, which patients don’t need additional therapy, and for which R-CHOP would be an adequate treatment approach. I think that it’s an exciting time in the field and there is a lot to be learned with subsequent trials.

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.

For references visit cancernet.com/breastgen10-19
Immunotherapy in Colorectal Cancer

Mehmet Sitki Copur, MD, FACP

ABSTRACT: Colorectal cancer (CRC) is the third leading cause of cancer deaths, with only 15% of patients surviving 5 years in the metastatic setting. Recent exciting developments in cancer immunotherapy, which involves priming the host’s natural immune defenses to recognize, target, and destroy cancer cells effectively, have brought some glimpse of hope in fighting this deadly disease. Although CRC has been shown to evade immune detection like many other cancers do, immunotherapy has been noted to produce some very impressive results in a select group of patients. Patients with mismatch repair–deficient and microsatellite instability–high type CRC have benefited most from recent immunotherapy approaches, leading to US Food and Drug Administration approval of new immunotherapeutic agents in recurrent refractory metastatic disease. Research continues to explore and hopefully define the role of immunotherapy in CRC as single-agent therapy or in combination with other agents in neoadjuvant, adjuvant, and first-line metastatic setting, and to find the optimal combination and sequencing of this new therapeutic approach. One of the most challenging tasks is to find ways to expand the use of immunotherapy to not only a select group of CRC patients but also to all patients with this disease. This article will provide a practical concise overview of the current landscape of immunotherapy in CRC for the practicing oncologist along with a representative case presentation from our community oncology practice.

Introduction

CRC is the second leading cause of cancer death among men and women and the third most common cancer diagnosis in the United States, with an estimated 143,600 new cases and 51,020 cancer-related deaths to occur in 2019.[1] The majority of patients with metastatic CRC have incurable disease, with a median overall survival of 30 months at best.[2,3] Based on the molecular genetic profile, various subsets of CRC with different predictive and prognostic behavior have been described. Among the most widely recognized and well known to most practicing oncologists are the main subtypes: mismatch repair–deficient or microsatellite instability–high (dMMR–MSI-H) tumors and mismatch repair–proficient or microsatellite instability–low (pMMR–MSI-L) tumors.[4] Microsatellite instability (MSI) occurs as a result of germline mutations in the genes of MLH1, MSH2, MSH6, and PMS2, which are involved in the DNA mismatch repair (MMR) pathway that encode MMR proteins. MSI results from either insertion or deletion of repeat units of DNA base pairs attributed to defects in the DNA MMR system.[5] The MSI subgroup makes up approximately 15% of all comers in CRC, but its prevalence is stage dependent. Whereas up to 15% of stage II/III CRCs are dMMR, only 4% to 5% of stage IV CRCs are dMMR. [6,7] Although two-thirds of the dMMR CRC cases are sporadic and associated with epigenetic modification leading to the inactivation of the MLH1 gene, one-third of dMMR deficiency cases are part of the hereditary nonpolyposis colorectal cancer syndrome, also known as Lynch syndrome.[8] CRC patients with MSI-H tumors exhibit distinct clinical and pathologic features such as younger age, early stage, proximal colon location, and poorly differentiated histology with rich tumor-infiltrating lymphocytes.[9] Immune checkpoint inhibitors have demonstrated impressive activity in patients with CRC and other solid tumors that are dMMR.[10] These dMMR tumors exhibit high levels of frameshift mutations detectable as variability in the
length of short stretches of DNA (microsatellites). This has been called MSI and has been noted to make these tumors more prone to accumulating mutations, which leads to the generation of neoantigens that can be recognized by the immune system. To counteract and avoid immune detection and destruction, tumor cells express cell surface inhibitory checkpoint molecules that downregulate the immune response (e.g., programmed death-1 [PD-1]/PD-1 ligand 1 [PD-L1] and cytotoxic T-lymphocyte–associated antigen-4 [CTLA-4]). Blocking PD-1/PD-L1 and CD80/CTLA-4 interactions has proven to be a very effective immunotherapy approach.

Many critical questions remain regarding the most appropriate use of immunotherapy in CRC. Among these are: role of immunotherapy in neoadjuvant, adjuvant, and first-line metastatic setting; single agent versus most optimal combination with other available cytotoxic, targeted, and immunotherapeutic agents; discovery and development of good prognostic and predictive biomarkers for response; and role of other immunotherapeutic approaches such as vaccines, cellular therapies, and cytokines targeting other immune checkpoint molecules, macrophages, and components of innate immunity.

Current landscape of immunotherapy in colon cancer

Recent discoveries and our better understanding of the complex interactions between cancer cells and the immune system has led to novel and successful immunotherapeutic approaches. Treatment with selective anti-PD-1, anti-PD-L1, and/or anti-CTLA-4 antibodies has shown significant clinical benefits. However, there is still a need for the identification of biomarkers to predict response and optimal use of these therapies in different clinical settings.

A 1-year-old Hispanic woman presented with a 3-month history of abdominal pain and 15-lb weight loss. There was no history of hematemesis, melena, or hematochezia. She was initially treated with antacid and pain medications with no improvement. Further evaluation with a CT scan of chest, abdomen, and pelvis revealed a right-sided colonic mass with associated lymphadenopathy and an enlarged liver with diffuse hepatic metastases in the abdomen (Figure 1) and small bilateral indeterminate pulmonary nodules in the chest. Needle biopsy of the right node of the liver confirmed a diagnosis of adenocarcinoma consistent with colorectal primary cancer. Colorectal gene panel was negative for pathogenic alterations of KRAS, NRAS, or BRAF. Polymerase chain reaction (PCR) testing detected MSI-H. Gene sequence and deletion/duplication analyses of MLH1, MSH2, MSH6, PMS2, and EPCAM revealed a heterozygous p.S461 pathogenic mutation in the PMS2 gene. Family history was notable only for her maternal grandfather, who had had a diagnosis of colon cancer at age 65.

What is the most appropriate next step?
A. Surgical resection of colon mass followed by systemic therapy
B. Systemic chemotherapy plus immunotherapy
C. Systemic chemotherapy followed by immunotherapy
D. Systemic chemotherapy with FOLFOX or FOLFIRI plus cetuximab or panitumumab
E. Systemic immunotherapy with pembrolizumab or nivolumab plus or minus ipilimumab
F. Systemic chemotherapy with the combination regimen of leucovorin, fluorouracil, and oxaliplatin (FOLFOX) or fluorouracil, leucovorin, and irinotecan (FOLFIRI) plus bevacizumab

TURN TO PAGE 406 for the answer and a discussion of this case by experts.
or anti-CTLA-4 monoclonal antibodies have revolutionized our therapeutic approach to several cancer types. While the highest clinical efficacy of immunotherapy has been observed in melanoma and lung cancer, results in CRC have been less than impressive except in the dMMR–MSI-H group.

The clinical heterogeneity of CRC that occurs during its pathogenesis is driven by chromosomal alterations and defective DNA mismatch-repair gene function. Based on both tumor and infiltrating stromal gene expression profiles, a consensus molecular subtype (CMS) classification has been proposed to identify four major groups of colorectal cancer. CMS1 (MSI-like) constitutes approximately 14% of CRC cases and harbors hypermutated tumors with MSI-H features. This group can also exhibit BRAF mutations and display a robust immune infiltration, CMS2 (canonical) constitutes 37% of cases characterized by the activation of the WNT and MYC pathways. CMS3 (metabolic) constitutes approximately 13% of the cases with frequent KRAS mutations and a deregulation of metabolic pathways in cancer cells. Finally, CMS4 (mesenchymal) constitutes approximately 23% of the cases characterized by transforming growth factor (TGF-β) pathway activation, enhanced angiogenesis, stromal activation, and inflammatory infiltration. [11] While CMS1 and CMS4 tumors show intense immune infiltration, CMS2 and CMS3 tumors lack immune activation in their microenvironment. This molecular characterization of CRC has provided some basis for the identification of favorable and unfavorable immune response attributes linked to clinical outcomes. [12]

MSI-H tumors have been identified as the best candidates for immunotherapy treatment, and a number of studies have evaluated the efficacy of anti-PD-L1 and anti-CTLA-4 monoclonal antibodies in this setting. Two phase II trials (KEYNOTE-016 and KEYNOTE-164) and one phase II trial (CheckMate-142) conducted in previously treated MSI-H/dMMR metastatic CRC patients provided objective response rates (ORR) ranging from 28% to 52%, progression-free survival (PFS) rates ranging from 34% to 59%, and overall survival (OS) rates of 72% to 76%. [13–15] CheckMate-142 evaluated nivolumab with or without low-dose ipilimumab in previously treated MSI-H/dMMR metastatic CRC with an ORR of 55% and disease control rate for 12 weeks or longer of 80%. [15] Currently, there are three US Food and Drug Administration (FDA)-approved immunotherapeutic agents (pembrolizumab, nivolumab plus or minus ipilimumab) for metastatic CRC patients with MSI-H/dMMR. [16–18]

Unfortunately, the vast majority of CRC patients, the pMMR/microsatellite stable (MSS) group, does not benefit from immunotherapy. Novel therapeutic approaches are needed to render this group of CRC patients immunogenic and thus offer effective immunotherapies. Hypothetically, immunotherapy might be effective for all CRC types if they were able to be converted to a “CMS1-like” immune phenotype. CMS4 tumors, which show the worst prognosis in terms of overall and relapse-free survival, for example, are characterized by an unfavorable, inflamed immune phenotype revealing high expression of mesenchymal genes, stromal cell infiltration, and an angiogenic microenvironment. Vascular endothelial growth factor-A (VEGF-A), a proangiogenic molecule produced by the tumors, has been shown to have a crucial role in the development of this immunosuppressive microenvironment. [19] Several clinical trials are investigating whether the combination of bevacizumab with either immunotherapy alone or combined with targeted therapies and conventional chemotherapy might show activity in this setting (ie, NCT0287319S, NCT02291289, NCT02876224). CMS4 tumors also show activation of the TGF-β signaling pathway. Targeting the TGF-β pathway either as monotherapy and/or in combination with anti-PD-1 agents has been the subject of some basic science research. [20,21]

The other two molecular types of CRC, CMS2 and CMS3, have been also called “cold” tumors, meaning that they lack immune cell infiltration. In this group, the expression of immunosuppressive genes has been noted to be low, suggesting different mechanisms of immune escape. Novel therapeutic approaches to render CMS2 and CMS3 tumors immunogenic are being explored. Among those are cytokine treatment, cancer vaccination, and passive immunotherapy with adoptive T-cell transfer or monoclonal antibodies targeting tumor-associated antigens. [22]

Critical questions and proposed answers for the practicing community oncologist:

What are the currently approved immunotherapeutic treatment options for colorectal cancer?

Currently, there are three FDA-approved immunotherapeutic treatment options for colorectal cancer. One of these is pembrolizumab, a PD-1 inhibitor, which has shown promising results in the treatment of advanced colorectal cancer. Another option is ipilimumab, a CTLA-4 inhibitor, which has demonstrated effectiveness in melanoma and other tumors. Checkpoint inhibitors, such as nivolumab and durvalumab, are also being evaluated in various tumor types. These treatments target the tumor microenvironment to enhance the immune response against cancer cells. Further research and clinical trials are ongoing to explore the optimal combination and timing of these therapies for improving outcomes in colorectal cancer patients.

ANSWER EXPLAINED: Patient was started on the regimen of FOLFIRI plus bevacizumab for the first-line treatment of her metastatic CRC. After 6 cycles of treatment, restaging CT scans revealed a significant decrease in liver lesions, but several new small (6–9 mm) nodules appeared in bilateral lung fields (Figure 2). Her treatment was changed to single-agent pembrolizumab immunotherapy. After 6 cycles of immunotherapy, restaging scans showed complete disappearance of lung lesions and a further decrease in her liver metastatic disease (Figure 3). To date, she remains on single-agent pembrolizumab with very good tolerance and no evidence of disease progression.
immunotherapeutic agents (pembrolizumab, nivolumab plus or minus ipilimumab) for metastatic CRC patients with MSI-H/dMMR.[16–18]

**What are the biomarkers of immune response in CRC?**

Several ongoing studies are investigating potential targetable pathways involved in the host immune response to CRC. Correlative studies from clinical trials are essential to identify biomarkers that can serve as immune response surrogates. Patients harboring MSI-H/dMMR tumors appear to benefit most from colon cancer immunotherapy.[23] DNA MSI-H defined as instability at more than two loci (or more than 30% of loci if a larger panel of markers is used) results in a high number of DNA replication errors and represents as a predictive biomarker to anti-PD-1 therapy. Utility of PD-L1 expression as a surrogate marker for tumor immunogenicity has been extensively studied. Upregulation of PD-L1 in tumor microenvironment has been found to be associated with an increased effector T-cell infiltration providing higher likelihood of clinical benefit from checkpoint inhibitors in malignancies other than CRC.[24] The immune response to tumor cells can be evaluated by the density and distribution of the tumor-infiltrating lymphocytes, which represents another potential predictive biomarker in CRC. Immunoscore has been developed as a risk stratification tool by quantifying two lymphocyte population densities in the core of the tumor and at the invasive margin.[25] Although immunoscore has been shown to be a better prognostic biomarker than MSI-H status in predicting disease-specific recurrence and survival in CRC, its role in predicting response to immunotherapy agents has not yet been widely accepted.[26]

**What is the role of immunotherapy in MSS/pMMR CRC?**

Analyses of MSS/pMMR metastatic CRC cohorts in the checkpoint inhibitor trials has not shown any clinically meaningful benefit with either single-agent PD-1 or the combination of PD-1 and CTLA-4 immunotherapy.[27] This can be explained by the lower antigenicity due to the presence of fewer neoantigens. Clinical trials are testing strategies to improve tumor antigenicity by increasing tumor antigen and major histocompatibility complex class I molecule expression, and to positively alter the tumor microenvironment by vaccination.[28] Based on preclinical data showing increased T-cell tumor infiltration and PD-L1 activity with MEK inhibition, a phase III clinical trial assessing the combination of cobimetinib and atezolizumab did not provide survival benefit over regorafenib in refractory metastatic MSS/pMMR CRC.[29,30] Several ongoing clinical trials are trying to address the role of immunotherapy in this group of CRC patients (Table).

**When should immunotherapy be utilized in MSI-H/dMMR colon cancer patients?**

For metastatic MSI-H/dMMR CRC patients, currently recommended first-line treatment is still combination chemotherapy plus targeted therapy. Nivolumab with or without low-dose ipilimumab and pembrolizumab is approved on progression following first-line treatment with fluoropyrimidine, oxaliplatin, and irinotecan.[31] Although no trials have directly determined whether patients should receive nivolumab alone or in combination with ipilimumab, an indirect comparison suggested that nivolumab plus low-dose ipilimumab provides...
improved efficacy over nivolumab monotherapy with a favorable risk–benefit profile.[15] Recently, first-line metastatic use of combination immunotherapy (nivolumab 3 mg/kg every 2 weeks plus low-dose ipilimumab 1 mg/kg every 6 weeks) in CRC patients with MSI-H metastatic CRC has been reported with favorable results.[32] This study has enrolled 45 patients. The ORR was 60% (27/45), with 7% complete responses (3/45). The 12-month PFS and OS rates were 77% and 83%, respectively. Grade 3/4 treatment-related adverse events occurred in 16% of patients, with only 7% of patients requiring discontinuation of therapy. Current FDA approval for pembrolizumab, nivolumab, and nivolumab plus ipilimumab for the treatment of MSI-H metastatic CRC patients remains restricted to those who have progressed after first-line therapy. Neoadjuvant treatment with a combination of the immune checkpoint inhibitors nivolumab and ipilimumab achieved major pathologic responses in 7/7 (100%) of early-stage colon cancers with dMMR, according to results reported at ESMO 2018 from the first exploratory phase II trial to investigate this approach.[33] The role of immunotherapy in the adjuvant setting is being evaluated by the ATOMIC trial (Alliance A021502), which is a randomized phase III study of standard chemotherapy (modified FOLFOX-6) alone or in combination with atezolizumab as adjuvant treatment for stage III colon cancer patients with tumors that are deficient DNA MMR with MSL. NCT02912559.

When should immunotherapy be discontinued in responding patients, and what is the outcome of patients who discontinue treatment? Although outcomes associated with the discontinuation of checkpoint inhibitors have not been rigorously evaluated, subgroup analyses suggest that checkpoint inhibitor therapy may produce long-lasting clinical benefit despite limited treatment duration. Eighteen patients from KEYNOTE-016 who discontinued pembrolizumab after 2 years because of complete remission (n = 11) or intolerance to therapy (n = 7) showed no evidence of recurrence or progression after median times off therapy for 8.3 and 7.6 months, respectively. Sixteen patients from CheckMate-142 with MSI-H/dMMR CRC who discontinued nivolumab plus low-dose ipilimumab because of treatment-related side effects had a disease control rate of 81%, with a median duration of response that was not reached. [34,35] Currently, there are no clear data to define exact treatment duration with checkpoint inhibitors. In most cases, treatments are given until true progression or toxicity occurs.

What is the role of immunotherapy in combination with other available therapies? Combinations of immune checkpoint inhibitors with chemotherapy, radiation therapy, and targeted therapies (including other immunotherapies) in MSI-H/dMMR metastatic CRC are under rigorous investigation. In a phase Ib/II trial investigating pembrolizumab plus cetuximab in RAS wild-type metastatic CRC, 7 of 9 patients achieved stable disease and treatment was well tolerated.[36] Atezolizumab plus bevacizumab has also been studied in an attempt to augment the antitumor immune response in MSI-H/dMMR CRC.[37] In this phase Ib trial of 10 previously treated patients with MSI-H/dMMR metastatic CRC, atezolizumab plus bevacizumab produced an ORR of 40% and disease control rate of 90%. Nivolumab plus other immunotherapies, such as the anti-lymphocyte-activation gene 3, relatlimab, and daratumumab, and an anti-CD38 cytolytic monoclonal antibody are being investigated in CheckMate-142.[38]

Conclusion

Immunotherapy of cancer is a novel and effective therapeutic strategy. Treatment with selective anti-PD-1, anti-PD-L1, and/or anti-CTLA-4 monoclonal antibodies has brought revolutionary results in MSI-H/dMMR CRC patients. As immune checkpoint inhibitors are integrated into the CRC treatment landscape, their use as single-agent therapy or in combination therapy will evolve and be better defined. Currently, there remain more questions than answers including the timing of treatment initiation, optimal sequencing and optimal duration of treatments and accurate evaluation of response, and management of adverse events. The most difficult challenge of all, however, is to identify those patients with specific tumor and tumor-infiltrating stromal molecular and functional characteristics that could be effectively treated with immunotherapy among the heterogeneous spectrum of CRC patients with MSS/pMMR CRC.

For references visit cancernetwork.com/CQ-immColorec

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The year has not quite come to an end yet, but as predicted by many experts in the field, 2019 has offered up many advances in immunotherapy. These advances shed light on such important aspects as biomarkers, better targeted therapies, chemotherapy outcomes, and resistance. Summarized herein are several high-profile conference presentations that highlight key advances in the field.

**From the Mystic trial**

Researchers explored the relationship between STK11, KEAP1, and ARID1A mutations and chemotherapy outcomes/prognostic factors in a follow-up to the phase III MYSTIC trial. Results were presented at the International Association for the Study of Lung Cancer (IASLC) 2019 World Conference on Lung Cancer (WCLC).[1]

In phase III MYSTIC trial patients with metastatic non-small-cell lung cancer (NSCLC) without epidermal growth-factor receptor and anaplastic lymphoma kinase mutations, investigators compared durvalumab monotherapy and durvalumab–tremelimumab with chemotherapy versus standard-of-care platinum-based chemotherapy as first-line treatment.[2,3] A subset of patients with high tumor mutational burden (TMB) was examined in the current follow-up. High tumor mutational burden was defined as more than 20 mutations/megabase.[1] Of note, although the MYSTIC trial did not reach its primary endpoint in terms of overall survival (OS), the hazard ratio of combination therapy was 0.85 (98.77% CI, 0.611–1.173; P = .202), which suggested that further exploration of patient subsets was warranted.[2,3]

In the 943 patients from the study population that could be evaluated, the frequency of STK11, KEAP1, and ARID1A mutations was 16%, 18%, and 12%, respectively. In the general population, after p53 and KRAS mutations, STK11 and KEAP1 are the most common lung cancer mutations.[1]

In his presentation, primary author Naiyer A. Rizvi, MD, director of thoracic oncology for the division of hematology/oncology at Columbia University Medical Center in New York, stated: “ARID1A patients are about 10% of the population and seem to do particularly well with durvalumab–tremelimumab. The key finding is the response rate of patients with ARID1A mutations in the durvalumab–tremelimumab arm being pretty impressive as well as overall survival in this patient population. The STK11-KEAP1 mutations also influence outcomes and need to be factored into our analysis of TMB and other outcomes of lung cancer.”[1]

**New hope for advanced urothelial cancer**

For patients with urothelial cancer who progress after receiving platinum/checkpoint inhibitors, few treatment options exist. Enfortumab vedotin (EV) could be effective in these patients, according to preliminary results from the EV-201 trial presented at ASCO 2019.[4]

The phase II results closely replicate the results from phase I according to primary author Daniel P. Petrylak, MD, professor of medicine and urology at Yale Cancer Center in New Haven, Connecticut. This therapy may be instrumental for patients who don’t benefit from checkpoint inhibitors.[5]

In this open-label, single-arm, phase II study, patients were given 1.25 mg/kg EV on days 1, 8, and 15 of each 28-day cycle, with the primary outcome being objective response rate (ORR). Secondary outcomes were progression-free survival (PFS), overall survival (OS), duration of response, and safety/tolerability. Patients with locally advanced or metastatic urothelial cancer (squamous differentiation or mixed cell types allowed) were split into two cohorts. Cohort 1 included participants with prior checkpoint inhibitor treatment and platinum-containing chemotherapy, and cohort 2 included patients who only received checkpoint inhibitor therapy.[4]

At the conference, results from cohort 1 (N = 128; 70% men; median age, 69 years; median of 2 prior systemic therapies) were presented. Petrylak et al found that about 44% of patients experienced tumor shrinkage or no tumor growth,
Utility of TMB

Tumor mutational burden is a measurement of mutations carried by tumor cells and is a predictive biomarker being studied to evaluate its association with response to immunotherapy. TMB, in concert with PD-L1 expression, has been demonstrated to be a useful biomarker across some cancer types. For some time, researchers have wondered about the value of tumor mutational burden (TMB) as a predictive marker for response to immunotherapy. In disappointing news, TMB has been found to not be related to the efficacy of pembrolizumab plus chemotherapy or placebo plus chemotherapy in patients with metastatic non-small cell lung cancer (NSCLC).

During a presentation at IASLC 2019 WCLC, first author Marina C. Garassino, of the Fondazione IRCCS Istituto Nazionale dei Tumori in Milan, stated the following: “Our data suggest that tissue TMB may not help select patients who would have better outcomes with the combination of pembrolizumab plus pemetrexed and a platinum given as first-line therapy for metastatic nonsquamous NSCLC. Pembrolizumab plus chemotherapy had a similar overall survival benefit in the TMB-high and TMB-low subgroups.”[6]

In the trial, 616 patients were randomized 2:1 to receive either pembrolizumab and chemotherapy or placebo with chemotherapy. TMB was determined by whole-exome sequencing of tumor cells and is a predictive biomarker being studied to evaluate its association with response to immunotherapy. TMB, in concert with PD-L1 expression, has been demonstrated to be a useful biomarker across some cancer types. For some time, researchers have wondered about the value of tumor mutational burden (TMB) as a predictive marker for response to immunotherapy. In disappointing news, TMB has been found to not be related to the efficacy of pembrolizumab plus chemotherapy or placebo plus chemotherapy in patients with metastatic non-small cell lung cancer (NSCLC).

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In the trial, 616 patients were randomized 2:1 to receive either pembrolizumab and chemotherapy or placebo with chemotherapy. TMB was determined by whole-exome sequencing of tumor cells and matched normal DNA. The clinical utility of TMB on outcomes was assessed using prespecified TMB cut points of 175 and 150 Mut/MB. To measure the clinical importance of TMB, prespecified TMB thresholds were established.

For either chemotherapy alternative, TMB was not associated with OS, ORR, or PFS in patients who could be evaluated. Notably, baseline characteristics in the study population were similar to the general population.[6]

At the conference, Corey J. Langer, MD, director of thoracic oncology at the University of Pennsylvania Abramson Cancer Center, presented another similar study examining the relationship between TMB and pembrolizumab.[7]

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“I think it’s still an investigational marker,” he said. “From my own perspective as a clinical researcher, the approach to TMB can be divided into two groups: the TMB cultists and the TMB skeptics. I would group myself in the latter. Although I still think it has a potential role, we haven’t figured it out. It would not be used, at least not yet, in therapeutic decision making.”[7]

Dr. Langer also opened the door to further considerations regarding TMB. For instance, he wondered whether patients with high TMB and programmed death ligand-1 expression would perform well with different combinations of immunotherapy and chemotherapy agents. He also wondered whether blood samples would more accurately mirror TMB levels as compared with single tissue samples, which were used in the study.

Surmounting anti-PD1 resistance

In patients who had progressed with melanoma after previous anti-programmed death 1 (PD-1) treatment, the experimental histone deacetylase (HDAC) inhibitor entinostat plus anti-PD-1 therapeutic pembrolizumab showed early efficacy per results of an open-label, single-arm, phase Ib/2 trial presented at the American Association for Cancer Research (AACR) Annual Meeting 2019.[8]

“A number of studies, including this trial, are endeavoring to identify key immunotherapy combinations to overcome resistance to checkpoint blockade immunotherapy,” stated Ryan Sullivan, MD, an assistant professor of hematology and oncology at Massachusetts General Hospital Cancer Center in Boston. Patients received 5 mg orally of entinostat weekly plus 200 mg intravenously of pembrolizumab every 3 weeks in this single-臂 trial, with the primary outcome being ORR. The median duration of prior anti-PD-1 treatment was 4.9 months. Partial response was evidenced in 9 of 53 patients, with one patient experiencing complete response. The ORR in the study was 19%.[8]

“Our results suggest that this combination may be an active regimen for patients who never responded to or progressed during treatment with PD-1 inhibitors,” said Dr. Sullivan. “A key next step will be to identify a biomarker to better determine which patients will respond to this treatment.”[8]
Personality Disorders in Patients with Cancer
Daniel C. McFarland, DO, Jody Morita, MD, and Yesne Alici, MD

ABSTRACT: Personality disorders exist on a spectrum in the general population and therefore may coexist in patients who have cancer. Patients with these disorders exhibit character rigidity resulting from enduring patterns of inner experience and behavior and may experience some level of interpersonal conflict among medical staff caring for them. These conditions become exacerbated under stressful cancer-related situations and may lead to adverse consequences and outcomes. This review highlights the conceptual and diagnostic issues of personality disorders for practicing oncologists and provides recommendations for recognizing and managing cancer patients with difficult personality traits or personality disorders.

Introduction
The inner experience of patients with personality disorders tends to be chaotic, fearful, scary, and/or intense and these feelings become transmitted and transposed onto their caretakers or anyone near them. Patients with personality disorders tend to invoke strong feelings in their clinicians and are often talked about informally outside of bedside rounds. These patients are recognized by staff for their atypical behavioral and communication styles and can cause conflict among providers. Relational interactions are difficult for patients with personality disorders, almost by definition; the complexity of cancer care (e.g., specific staff roles, interchanging medical care systems) heightens these difficulties, which are also felt by oncology staff.

Patients with severe personality traits and/or personality disorders are more frequently seen in medical/surgical clinics than in the psychiatrist’s or therapist’s office, despite long standing patterns of interpersonal dysfunction. They could benefit from psychiatric or psychological intervention if the patient were amenable to treatment. The reason for this is in itself diagnostic. Even with high levels of social impairment, personality disorders are “ego-syntonic” and therefore the patient does not see his or her way of living, interacting, and communicating with others as problematic. Patients with other major categories of psychiatric illness (e.g., major depressive disorder, bipolar disorder, schizophrenia) are distressed by their symptoms which are seen as “other,” not part of what the patient considers to be his or her core self. “Other” psychiatric disorders are “ego-dystonic” or experienced as foreign or disturbing to the person experiencing them. Also, they have higher levels of impairment and inability to function in routine daily life. Patients with personality disorders display dysfunctional patterns of communication and behavior; they function much less well in the midst of stressful life-changing circumstances. They usually do not seek help until they are gravely ill or have suffered multiple personal losses. However, there are always signs of impaired functioning such as dysfunctional relationships, odd communication styles, unusual demands or threats, or excessive emotion over tasks that cause even a slight amount of discomfort. Limited recognition of pervasive dysfunction tends to persist or is not usually appreciated until later in life. They are more likely to seek out medical rather than psychiatric care to remedy physical complaints and ailments, for example.

What Is a Personality Disorder? What Is Its Origin?
The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) provides general definitions and direction
that apply to each of the 10 specific personality disorder types. In general, a personality disorder is an enduring pattern of inner experience and behavior that deviates markedly from the expectations of the individual’s culture, is pervasive and inflexible, has an onset in adolescence or early adulthood, is stable over time, and leads to distress or impairment.[1] Personality traits are also enduring and pervasive in terms of motivation, emotion, interpersonal style, attitudes, and behaviors, but they are not necessarily maladaptive and may not cause distress or impairment.[2] The DSM-5 provides diagnostic criteria for 10 distinct personality disorders (see below). While these diagnostic categories are certainly useful and recognizable from a clinical perspective, they do not complete the entire picture of these disorders. Mental health clinicians often note either overlap or hybrid descriptions or apparent personality disorders that do not clearly meet any one particular subtype criteria. As noted above, the inner experience and behaviors must be enduring throughout many life circumstances or context and have begun by adolescence or early adulthood. This is particularly important because many other psychological/mental conditions, especially when a person is under stress for one reason or another, can mimic behaviors attributable to personality disorders. Identifying a disorder helps clinicians direct their care in a more appropriate way. But caution must be used to protect against overdiagnosis. For this reason, mental health clinicians will often document a “rule out” x,y, or z personality disorder. It is always crucial to critically assess the acute situation in which the patients are evaluated and think of alternative diagnoses. The diagnosis of personality disorders requires comprehensive and longitudinal assessments of behavior patterns that must have manifested prior to age 18.

Character rigidity is the key characteristic of personality disorders resulting in communication and behavioral styles that are not flexible under the changing or evolving circumstances inherent to the cancer trajectory. Typically, patients with personality disorders lack the coping reserve to be adaptable, which is clearly necessary to transition between social and environmental contexts and tends to be more pronounced under stressful situations such as a cancer diagnosis. Interestingly, personality disorder generation to generation but their etiology is not altogether clear. Genetics clearly plays a role but also influences the nurturing style of the early childhood environment. Differentiating between genetics and nurturing is difficult in this context. Severe personality traits or personality disorders may even be influenced epigenetically by the home environment as well.[3]

What Are the Different Types of Personality Disorders?
The DSM-5 classifies personality disorders into three categories or clusters of disorders: A) odd or eccentric; B) dramatic, emotional, or erratic; and C) anxious or fearful. (Table 1)

**Cluster A.** Cluster A includes paranoid, schizoid, and schizotypal personality disorders. They are clustered together based on behaviors that are odd or eccentric in comparison to societal norms. The hallmark of these personality styles is the experience of pervasive social discomfort. [6] Therefore, interpersonal closeness is either of no interest or experienced as highly unpleasant and can lead to avoidance, odd, or eccentric behaviors. These patients typically want to be left alone; they may or may not desire social contact to some extent.[7]

**Cluster B.** Cluster B includes antisocial, borderline, histrionic, and narcissistic personality disorders. This cluster is based on struggling to relate to others or with relationship structures, which can be particularly problematic in the medical setting where many patients adopt a passive role.[8] Patients in Cluster B are typically uncomfortable with high levels of interpersonal stress, decision-making, and shifting relationships (i.e., with medical staff).[8] Interpersonal ambiguity or strain on relationship definition is particularly difficult for these patients.[7]

**Cluster C.** Cluster C includes avoidant...
This paper offers a clear review of personality disorders for the oncologist, with helpful suggestions for their management. Clinicians may also benefit from considering a few additional points. First, just as diagnosable personality disorders imply the need for specific approaches to management, personality styles, which are even more common, similarly benefit from approaches tailored to their needs. These styles often become evident, and can interfere with care, in a very ill cancer patient. Kahana and Bibring’s 1965 paper Personality Types in Medical Management is a classic resource, which considers personality attitudes that do not necessarily fall under a disorder from the Diagnostic Statistical Manual of Mental Disorders Fifth Edition (DSM-5).[1] One example from this paper is the long-suffering, self-sacrificing (masochistic) patient who may escalate complaints when reassurances are given but responds well to validation of suffering. Second, personality disordered patients often cause difficulty by engendering strong emotional reactions in their caregivers, which are important to recognize and take into account since they can influence care. James Groves’ 1978 paper The Hateful Patient highlights some of the ways this can present problems in their care[2]. Third, disruptive behavior, often but not always caused by personality disordered oncology patients, benefits from a clear process of differential diagnosis, teamwork and clarification of expectations and limits. John Peteet et. al’s 2011 “Possibly Impossible Patients” paper provides several practical principles and goals for responding to disruptive behavior[3]. Finally, the prudent clinician may recall the fundamental attribution error, the tendency to over-emphasize internal factors in judging others’ behaviors. A comprehensive evaluation should consider psychosocial factors as well as personality changes secondary to disease- or treatment-related ones.

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Roxanne Sholevar, MD, Carrie Wu, MD, and John Peteet, MD

Personality Factors in All Patients

Personality, Personality Traits, and Cancer

Personality is a relational style based on environment and genetics that is gradually established during childhood and adolescence. It starts to become fixed in one’s 20’s and only changes minimally after age of 30 years old.[10] These patterns of relating to others and the world at large are mostly adaptive and relate to our innate temperament, imitative patterns, and repetitive reinforcement regarding what has worked in the past. For the most part, adults are diagnosed with cancer with their personality and personality traits firmly in place.

The intersection of cancer, adaptation, coping, and personality style has long fascinated researchers. At one time, having difficulty in expressing emotions and an attitude or tendency towards helplessness/hopelessness (the so-called Type C personality) was thought to be a cancer-prone personality.[11] This idea of a cancer-prone personality type has been debunked in longitudinal studies. [12] However, there is a rich literature of distinct coping styles during stressful situations. For example, Lazarus and Folkman presented the “transactional model of stress” where a given situation requires both a cognitive appraisal about the situation and the person’s relation to the situation.[13] Many of these types of models have been applied to dealing with cancer-related stress.[14] Other coping styles have been investigated such as “fighting spirit”, where the patient views cancer as a challenge with optimism to overcome the adversity; ultimately, consequences of a “fighting spirit” on cancer-related outcomes remains undefined and should not be considered as a prognostic factor for cancer-related survival.[15-17]

Three basic personality traits have mainly been researched in relation to cancer:
neuroticism, extraversion, and conscientiousness. Neuroticism is essentially a state of nervousness that exists on a spectrum from safe to anxious. Extraversion concerns an interest in social company from minimal (introverted) to maximal (extraverted). And conscientiousness (personal reliability) is a personality construct that varies from being responsible and efficient to being irresponsible and lacking efficiency.[10,18] Similar to Hippocrates’ original idea of personality based on the varied construction of four basic personality types composed of varied body fluids, these three personality constructs exist on a spectrum and everyone has essentially a unique contrast that remains relatively stable over time. Optimism may also be considered, especially in its relation to cancer and as a trait in “positive psychology,” but it has also been thought of as the inverse of neuroticism.[19] High optimism is generally thought of as protective in stressful situations.

### TABLE 1

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Dominant Features</th>
<th>Typical Interactions With Staff</th>
<th>Helpful Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cluster A Paranoid</td>
<td>• Has difficulty understanding other's actions</td>
<td>Patients may make angry accusations and withdraw from staff making staff feel misunderstood and wrongly accused.</td>
<td>Take extra time to explain and clarify problems and procedures. Expect to provide repetition and reassurance. Assess patients’ understanding.</td>
</tr>
<tr>
<td></td>
<td>• Exhibits distrust and suspiciousness</td>
<td></td>
<td></td>
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<td></td>
<td>• Interprets other’s motives as malevolent</td>
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<tr>
<td>Cluster A Schizoid and Schizotypal</td>
<td>• Social detachment</td>
<td>Patient perceived as odd or even frightening by staff who thus misinterpret the patient’s intent and needs and do not perceive intense anxiety and suffering.</td>
<td>Recognize diminished needs for interpersonal connection and lesser skills in relating to others. Explain restricted range to staff and provide reassurance regarding unusual behaviors, especially “unfriendliness.” Encourage simple, straightforward social interactions without humor, irony, or sarcasm. Beware of interpersonal “over-stimulation.”</td>
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<tr>
<td></td>
<td>• Restricted range of emotional expression</td>
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<td></td>
<td>• Masks shame and feelings of inadequacy</td>
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<tr>
<td></td>
<td>• Acute discomfort in close relationships</td>
<td></td>
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<tr>
<td></td>
<td>• Cognitive or perceptual distortions</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>• Eccentricities of behavior</td>
<td></td>
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<tr>
<td>Cluster B Antisocial</td>
<td>Disregard for rights of others (which are also frequently violated)</td>
<td>Staff splits between feeling special and rejected. Staff splits. Staff can feel seduced, deceived, loved, and manipulated. Patient responds to confrontation with glib explanations of outrageous behavior or sham contrition.</td>
<td>Anticipate, educate, and address splitting. Encourage staff to discuss various impressions and to share information with one another. Reinforce what is to be done and who will do it. Address needs for consistent and coherent responses to complaints, demands, and threats.</td>
</tr>
<tr>
<td>Cluster B Borderline</td>
<td>• Unstable relationships, self-image, and affects</td>
<td>Patient is panicky and needy, stimulating staff fantasies of specialness and rescuing the patient (e.g., from other staff). Staff reactions range from deep attachment to hatred and aggressive fantasies.</td>
<td>Clarify dysfunctional help-seeking style and disentangle unrealistic expectations without blame. Be alert to bargaining, seduction, and manipulation. Reassure patient and facilitate staff alignment with role and task clarity. Help staff appreciate and discuss their own emotional responses, especially anger, neediness, and low self-worth.</td>
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<tr>
<td></td>
<td>• Marked impulsivity</td>
<td></td>
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<td></td>
<td>• Intense sensitivity to threats of rejection or abandonment</td>
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<tr>
<td>Cluster B Histrionic</td>
<td>• Excessive emotionality and attention seeking</td>
<td>Staff repelled by dramatic attention seeking, but may experience sexual attraction and arousal, splitting</td>
<td>Similar to borderline.</td>
</tr>
<tr>
<td>Cluster B Narcissistic</td>
<td>• Grandiosity</td>
<td></td>
<td></td>
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<td></td>
<td>• Need for admiration</td>
<td>Anxiously outbursts, pitiful apologies, dramatic withdrawal. Staff feel special or worthless. Patient found to be “demanding and unreasonable” or “misunderstood and special.”</td>
<td>Staff awareness and reassurance. Try to provide consistency but also ensure expectations, limits, and boundaries.</td>
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<tr>
<td></td>
<td>• Lack of empathy</td>
<td></td>
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<tr>
<td>Cluster C Avoidant</td>
<td>• Social inhibition</td>
<td>Patients seem fearful or uninterested, staff feel clumsy, intrusive, or unjustly accused of same.</td>
<td>Explain patient vulnerability and aversions to staff. Attend to dependency needs to the extent that they do not compromise staff or disrupt patient care.</td>
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<tr>
<td></td>
<td>• Feelings of inadequacy</td>
<td></td>
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<td>• Hypersensitivity to negative evaluation</td>
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<tr>
<td>Cluster C Dependent</td>
<td>• Submissive</td>
<td>Patients are needy, demanding, childlike, and vulnerable. Staff feel protective or repelled by excessive demands for care and attention</td>
<td>Describe and explain problems and procedures. Give patient options and clear role in decision-making as tolerated. Return locus of control to patient whenever possible.</td>
</tr>
<tr>
<td></td>
<td>• Clinging behavior from excessive need to be taken care of</td>
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<tr>
<td></td>
<td>• Terrible fear of being alone</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>• Helpless, guilty, and indecisive</td>
<td></td>
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<tr>
<td>Cluster C Obsessive-Compulsive</td>
<td>• Preoccupation with orderliness</td>
<td>Patient may seem like the ideal patient, or staff may feel their performance is being monitored and harshly judged.</td>
<td>Encourage staff discussion of their own sensitivities, dependency needs or meticulousness.</td>
</tr>
<tr>
<td></td>
<td>• Perfectionism</td>
<td></td>
<td></td>
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<td></td>
<td>• Control</td>
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</table>

There are several ways in which personality may intersect with cancer. Since personality is life-long and pervasive, its features, consequences, and implications endure and are manifest by specific patterns of behavior, choices, environment, stress, and internal hormonal dysregulation. The central nervous system, where personality originates, has a strong influence on biological and cellular systems over long periods of time. This stands in contrast to acute changes one may encounter throughout life. Therefore, personality may influence cancer development and progression through 1) perpetuation of unhealthy lifestyle that is personality driven; 2) negative affect (depressive or anxious symptoms, anger) or poor coping; and 3) being an etiological factor for somatic diseases or mental disorders that predispose to cancer.[20]

Epidemiological studies of personality and cancer development and/or progression show a few associations with a positive association but the majority shows no significant association leading researchers to conclude that there is no significant association between personality and increased risk of cancer.[17,21,22]

What Happens When a Patient With a Personality Disorder Develops Cancer?

According to the American Cancer Society, men have a 39.66% risk of developing cancer in their lifetimes, while women have a 37.65% chance.[23] At the same time, a national epidemiologic study of 43,093 patients found an overall prevalence of 14.79% of adult Americans with at least one personality disorder. Obsessive-compulsive (7.88%), paranoid (4.41%), antisocial (3.63%), schizoid (3.13%), avoidant (2.36%), histrionic (1.84%), and dependent (0.49%) were the most common types of personality disorders.[24] Other community epidemiological studies have shown that approximately 10% of the general population has a personality disorder.[25] Limited data exist on the prevalence of personality traits, but up to 20% of the general population may have severe personality traits that cause significant impairment not meeting a diagnostic specification.[20,26]

Surprisingly, the overlap between cancer and personality disorders remains relatively unexplored. While it is difficult to generalize “normal” reactions to life-threatening cancer-related medical issues, oncology clinicians observe patterns of reactions to life-threatening news and develop a sense for who is reacting “too much or too little”, which may be indicative of a personality- or other mood-related issue.

It should be noted that the vast majority of uncooperative patients do not have a personality disorder. Personality disorders are pervasive patterns that require understanding a patient’s behavior in multiple contexts over many years. In fact, personality disorders cannot be diagnosed under the age of 18.

Nonetheless, a cancer diagnosis followed by treatments and numerous life changes requires patients to not only adapt but to thrive in order to face all the unique challenges. Adaptability, flexibility, and resourcefulness are needed to meet the multitude of cancer-related challenges. These characteristics are the exact opposite of the character rigidity of personality disorders. In fact, some personality disorders, such as narcissistic or obsessive-compulsive personality disorders, can be very adaptive for particular work environments. However, even patients with adaptive personality disorders who have been successful in their work-life endeavors find that those same attitudes and behaviors don’t necessarily select for success as a cancer patient.

Personality traits and disorders exist on a spectrum. While patients with severe personality disorders represent a minority of patients that the oncologist will see, they will inevitably require a considerable amount of time and patience due to their extreme difficulty adjusting to the new environment of being treated for cancer.[2]

Major psychiatric issues (e.g., major depressive episode, generalized anxiety disorder) tend to go unnoticed in the cancer context as patients and doctors are paying attention to other more life-threatening matters. While screening for psychiatric disorder in the cancer setting is helpful diagnostically, it is not always done and can still miss more varied or subtle presentations. There is considerable overlap between mood and personality disorders, especially in the cancer setting.[27,28] A personality disorder may provide the context in which a mood or other disorder presents itself. [29] For example, patients with schizoid or schizotypal personality disorder are more vulnerable to psychosis; borderline and narcissistic patients are prone to depression.[30] Cluster C personalities are prone to anxiety disorders perhaps through distortion of social perception and alienating interpersonal styles.[31] In addition, patients with long-standing psychiatric disorders may develop behaviors that look like personality disorders but may not be pervasive and may not have started before early adulthood.[32] Distorted perceptions isolate patients leaving them without social buffers against adverse life events. Solitary coping is less effective and reinforces aberrant patterns of thinking, feeling, and relating.

At the same time, other disorders may be precursors to a personality disorder if it is long standing. Chronic mood, anxiety, or substance abuse disorders may restrict social interactions and may obscure opportunities to learn social coping strategies. This restricted repertoire of interpersonal interactions constitutes the character rigidity that defines personality disorders.

The cancer experience is a series of acute...
and chronic stressors that can alienate patients with personality disorders and severe personality traits. A longitudinal study found that neuroticism is associated with distinctly worse quality-of-life following localized breast cancer treatment.[33] In a similar population, poor quality of life after treatment was more strongly predicted from pre-morbid psychological characteristics (e.g., depression and personality factors) than from actual cancer-related variables (e.g., treatment types and cancer severity).[34] Among testicular cancer survivors, neuroticism was associated with somatic and mental morbidities.[35]

How Does a Personality Disorder or Personality Trait Change and Challenge Oncologic Management?

The majority of intervention data has focused on cancer control and prevention and how personality disorders influence outcomes. In general, research into the specific management of patients with personality disorders and cancer is lacking. Table 1 highlights various suggestions specific to each type of personality disorder. The primary issue is to acknowledge feelings and emotions raised among staff and to avoid patient blame. It is also helpful to remember that these behaviors have likely been successful in another environment in which the patient has found him or herself, particularly early in life and indicate a severe deficiency of interpersonal skills.

Aside from managing the emotions of the treating team, setting appropriate boundaries and expectations is very important. For the suspicious, incredulous patient, it is crucial to make sure that they understand the information clearly and can repeat it back to you. For the patient who is overly intrusive (e.g., with agreeableness or even seduction), stating and maintaining boundaries helps them establish a working relationship that can be negotiated since many patients with personality disorders tend to sabotage their relationships. Patients who are fearful, anxious, or avoidant should be approached with respect, concern, and space to feel in control of the doctor-patient relationship. Physicians often rely on the inherent power dynamic to move forward with important medical issues that need to be attended to. The typical passive role of the patriarchal medicine paradigm can be very uncomfortable for some patients with personality disorders. Therefore, considered attention should be placed on shared decision making and even discussing how the patient would like the relationship to work. Although these are not typical conversations in the oncologic medical setting, they can be invaluable in terms of preserving doctor-patient relationship integrity.

It is critical to consider a formal mood or thought disorder diagnosis as well when unusual behaviors or thought patterns are encountered. There should be a low threshold to seek help from mental health professional colleagues. Screening programs can be helpful in determining other mood components but usually a skilled interview is also needed to assess patients for both mood and psychotic disorders. If the patient has family or a significant other who is involved in the patient’s care, alignment is very important so that the patient feels everyone understands each other and opportunities for splitting are minimized.

Conclusion

Patients with personality disorder and personality traits will test our limitations of interpersonal skills as physicians. In general, they are relying on the treating doctors to provide organization, structure, and a blueprint for acceptable behavior in order to move forward with their medical care. Although their oncologic management may be more involved, more time-consuming, and may frequently require interdisciplinary care, addressing these personality issues in a humane way is an integral part of their overall comprehensive care. It is no less important than their actual oncologic management.

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All human cells maintain a redox balance between reactive oxygen species (ROS) and antioxidants, such as NQO1, to resist oxidative stress.\(^1,2\) The optimal redox balance differs between cells and determines their specific “redox signature,” which can have downstream effects on potent oncogenic signaling pathways, including STAT3.\(^1,2,3\)

Research suggests that a subset of cancer cells, including some cancer stem cells, possess a distinct redox signature that may make them susceptible to approaches that generate cytotoxic levels of ROS.\(^3,4\) These cells signal to other cells in the tumor microenvironment and promote the phosphorylation of STAT3. The presence of phosphorylated STAT3 in a tumor may indicate this redox signature and favorability to ROS-generating intervention.\(^3\)

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