CARMELO J. BLANQUICETT, MD, PHD, FACP, ON

The Critical Role of Assessment

‘This cannot fall to the wayside’
Start early with ERLEADA®
For your patients with metastatic prostate cancer who will be starting ADT or have recently initiated ADT*.

INDICATION
ERLEADA® (apalutamide) is an androgen receptor inhibitor indicated for the treatment of patients with:
• Metastatic castration-sensitive prostate cancer (mCSPC)
• Non-metastatic castration-resistant prostate cancer (nmCRPC)

IMPORTANT SAFETY INFORMATION
WARNINGs AND PRECAUTIONs
Ischemic Cardiovascular Events—In a randomized study (SPARTAN) of patients with nmCRPC, 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 6 months of randomization 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 nmCRPC, 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.

Rash—In a randomized study (SPARTAN), rash occurred in 16% of patients treated with ERLEADA® compared with 9% of patients treated with placebo. Rash was 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, arthralgia, rash, decreased appetite, fall, weight decreased, hypertension, hot flush, diarrhea, and fracture.

Laboratory Abnormalities—All Grades (Grade 3-4)
• Hematology—In the TITAN study, white 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® 17% (0.9%), placebo 12% (2%). In the SPARTAN study: hypercholesterolemia ERLEADA® 76% (0.1%), placebo 46% (0%). Hyperglycemia ERLEADA® 70% (2%), placebo 59% (1%). Hyperuricemia ERLEADA® 67% (2%), placebo 51% (1%). Weak acidosis 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 coining >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 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% and 28% of patients, respectively. Of the patients who had dose interruption, 59% experienced recurrence of rash upon re-introduction of ERLEADA®.


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

NEW INDICATION
ERLEADA® + ADT reduced the risk of death by 33% vs placebo + ADT†

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

In the TITAN study:

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

Hypothyroidism—in 2 randomized studies, hypothyroidism was reported for 8% of patients treated with ERLEADA® and 2% of patients treated with placebo. Concomitant administration of ERLEADA® with medications that are substrates of 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. Medications will prevent seizures with ERLEADA®. Medications with 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. [see Drug Interactions (7.5)].

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

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=1652). 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 orchectomy. 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.†

Visit erleadalhcp.com
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></td>
<td>All Grades</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Adverse reaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>39</td>
<td>1</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>12</td>
<td>0.1</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fall</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>Fracture</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight decreased</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>25</td>
<td>14</td>
</tr>
<tr>
<td>Hot flush</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>18</td>
<td>0</td>
</tr>
</tbody>
</table>

1 Includes fatigue and asthenia
2 Includes rash, rash maculo-papular, rash generalized, urticaria, rash pruritic, rash macular, conjunctivitis, erythema multiforme, rash hyperemia, skin exfoliation, genital rash, rash erythematous, stomatitis, drug eruption, mucocutaneous, rash pustular, blister, papule, pemphigoid, 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, perianal 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</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>70</td>
<td>0.4</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>47</td>
<td>0.3</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>41</td>
<td>2</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ERLEADA</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>76</td>
<td>0.1</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>70</td>
<td>2</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>67</td>
<td>2</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>32</td>
<td>2</td>
</tr>
</tbody>
</table>

1 Does not reflect fasting values

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 76 days from onset of rash. Rash was commonly managed with oral antihistamines, topical corticosteroids, and 19% of patients received systemic corticosteroids. Discontinuation or dose interruption occurred in 14% of patients, 11% of patients, and 10% of patients, respectively. Of the patients who had dose interruption, 99% experienced recurrence of rash upon reintroduction of ERLEADA.

In the combined data of two randomized, placebo-controlled clinical studies, hypothyroidism was reported for 8% of patients treated with ERLEADA and 2% of patients treated with placebo based on assessments of thyroid-stimulating hormone (TSH) every 4 months. Elevated TSH occurred in 25% 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 or 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

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/DATP1B1 substrate). Concomitant use of ERLEADA with medications that are substrates of P-gp, BCRP, or DATP1B1 can result in lower exposure of these medications. Substitution for these medications is recommended when possible or evaluate for loss of activity if medication is continued. Concomitant administration of ERLEADA with medications that are substrates of UDP-glucuronosyl transferase (UGT) can result in decreased exposure. Use caution if substrates of UGT must be co-administered with ERLEADA and evaluate for loss of activity [see Clinical Pharmacology (12.3) in full Prescribing Information].

P-gp, BCRP or DATP1B1 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). At steady-state, apalutamide reduced the plasma exposure to fexofenadine (a P-gp substrate) and rosuvastatin (a BCRP/DATP1B1 substrate). Concomitant use of ERLEADA with medications that are substrates of P-gp, BCRP, or DATP1B1 can result in lower exposure of these medications. Use caution if substrates of P-gp, BCRP, or DATP1B1 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 breastfed child, or the effect on milk production.
Brief Summary of Prescribing Information for ERLEADA® (apalutamide)

ERLEADA® (apalutamide) tablets, for oral use

See package insert for Full Prescribing Information

INDICATIONS AND USAGE
ERLEADA is indicated for the treatment of patients with:
• 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-sensitive 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.

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 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 8% 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. Falls occurred in patients receiving ERLEADA with increased frequency in the elderly [See Use in Specific Populations]. 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. Advise patients of the risk of developing a seizure while receiving ERLEADA, and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others.

In two randomized studies (SPARTAN and TITAN), five patients (0.4%) treated with ERLEADA and one patient treated with placebo (0.1%) experienced a seizure. Patients with a history of seizure, predisposing factors for seizure, or receiving drugs known to decrease the seizure threshold or to induce seizure 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 [See Clinical Pharmacology (12.1) in full Prescribing Information]. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 12 months after the last dose of ERLEADA [see Use in Specific Populations].

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.

ADVERSE REACTIONS Ocurring in ≥10% on the ERLEADA Arm Compared to Placebo (Between Arm Difference ≥5% All Grades in TITAN (mCSPC))

Table 2: Laboratory Abnormalities Occurring in ≥15% of ERLEADA-Treated Patients and at a Higher Incidence than Placebo (Between Arm Difference ≥5% All Grades) in TITAN (mCSPC)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades</th>
<th>Grade 3-4</th>
<th>All Grades</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood cell decreased</td>
<td>27 0.4 19 0.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>17 3 12 2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Includes fatigue and anemia
2 Includes rash, maculo-papular, rash generalized, urticaria, rash pruritic, rash macular, conjunctivitis, erythema multiforme, rash papular, 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 1% on placebo), and hypothyroidism (4% versus 1% on placebo).

Table 1: System/Organ Class Adverse Reaction Occurring in ≥10% of ERLEADA-Treated Patients

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>All Grades</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue1,2</td>
<td>26 3 25 2</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>17 0.4 15 0.9</td>
<td></td>
</tr>
<tr>
<td>Arthralgia3</td>
<td>28 6 9 0.6</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>11 &lt;1 5 &lt;1</td>
<td></td>
</tr>
<tr>
<td>Rash2</td>
<td>23 0 16 0</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>18 8 16 9</td>
<td></td>
</tr>
</tbody>
</table>

1 Includes fatigue and anemia
2 Includes rash, maculo-papular, rash generalized, urticaria, rash pruritic, rash macular, conjunctivitis, erythema multiforme, rash papular, 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

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, hypertension, 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), cardiac-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 hypertension. 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.
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 38% 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].
REVIEW ARTICLE: Cover
The Role of the Comprehensive Geriatric Assessment in the Evaluation of the Older Cancer Patient
Carmelo J. Blanquicett, MD, PhD, Theodore M. Johnson II, MD, MPH, Christopher R. Flowers, MD, MS, Jonathon B. Cohen, MD, MS
PERSPECTIVE: Erika Ramsdale, MD
Emory oncologists address an often neglected but critical aspect of the treatment decision making process in the oncology setting.

LUNG CANCER: Continuing Medical Education
Current and Emerging Immunotherapies in SCLC: Promise and Challenges
Stephen Y. Liu, MD, faculty

LUNG CANCER: Medical Conference Review
World Conference on Lung Cancer 2019
Jennifer Leavitt, MS, with Joanna Pangilinan, PharmD, BCOP

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THE EDITORS ARE PLEASED TO ANNOUNCE
the availability of our new parent company's continuing education activities.

We’ve picked this one especially for our ONCOLOGY readers. Go to: https://bit.ly/2tRAkNz
COMMUNITY ONCOLOGIST ADVISORY BOARD  The Community Oncologist Advisory Board plays a vital role in helping ONCOLOGY fulfill its mission. They peer-review articles to ensure that they are clinically relevant and applicable to the realities of day-to-day oncology practice. Community oncologists who are interested in joining the Advisory Board are welcome to contact Jennifer Leavitt at jleavitt@mmhgroup.com.
Dear Reader,

No one recognizes more profoundly than oncologists do how incredibly personal cancer treatment is. Therapies that succeed in one patient, may be totally ineffective for another. Today, genomic and biomarker testing are making it exponentially more possible to implement treatment strategies that take the individual patient's biology into consideration.

Amidst so many groundbreaking diagnostic and prognostic advances, sometimes the much less innovative, but equally critical basics are neglected.

In their review article on “The Role of the Comprehensive Geriatric Assessment in the Evaluation of the Older Cancer Patient,” Drs. Blanquicett, Johnson, Flowers, and Cohen, explore the importance of assessment in the largest demographic of cancer patients—the geriatric community. The authors point out that, in fact, the majority of cancer diagnoses and morbidity occurs in patients age 65 and older, yet this group is persistently understated and underrepresented in clinical trials.

For 20 years now, these assessments have been part of the standard evaluation for the geriatric cancer patient, but they are time-consuming and often end up on the back burner in favor of more urgent clinical procedures. The evidence does suggest that “incorporating such an evaluation could be useful for potentially determining the patient’s chemotherapy tolerability or treatment completion, toxicity and survival, as age alone has been shown to poorly predict treatment failure, and performance status assessments commonly used in oncology practice may lack predictability.” The authors go on to evaluate and describe various tools and their uses in various settings.

In the accompanying perspective, Erika Ramsdale, MD, laments the fact that, despite strong evidence supporting implementation, less than 25% of the community oncologist population in the United States report using GA for their older patients.

Elsewhere in the issue, we present a clinical quandary on malignancy of the esophagus; offer an overview of alpelisib, review open clinical trials in prostate cancer, and recap breast cancer research presented at the recent ESMO Congress, as well as presentations at the World Lung Cancer Conference.

We also look at the CLL14 Trial, on a fixed-duration chemotherapy-free regimen for frail patients with treatment-naïve CLL.

In our CME feature, Stephen Liu, MD, leads the activity in challenges and promises in current and emerging immunotherapies for SCLC.

Finally, we look at the toll that oncology takes on its practitioners, as Mehmet Sitki, Copur, MD, FACP, our Editor at Large, reviews the research on oncologist burnout and how to avoid or temper it.

- Mike Hennessy, Sr.
Chairman and Founder of ONC’s parent company, MJH Life Sciences
The US Food and Drug Administration (FDA) recently approved alpelisib (BYL719) plus fulvestrant for the treatment of metastatic or otherwise advanced breast cancer. Details of the drug alpelisib and its clinical approval are discussed herein.[1]

**Background**

Most breast cancers (>70%) are human epidermal growth factor receptor 2 (HER2)–negative and hormone-receptor (HR)–positive. Of patients living with HR-positive advanced breast cancer, approximately 40% harbor PIK3CA mutations, which hyperactivate the alpha isoform (p110α) of the phosphatidylinositol 3-kinase (PI3K) pathway.

Alpelisib is an oral α-specific PI3K inhibitor that selectively inhibits p110α to nearly 50 times stronger compared with other isoforms of the small molecule. Alpelisib has shown efficacy in targeting PIK3CA-mutated cancer based on preclinical models. When alpelisib is combined with fulvestrant, it exhibits a synergistic effect in PIK3CA-mutated, estrogen-receptor (ER)–positive xenograft models.

Specifically, alpelisib combined with fulvestrant led to a complete or partial response in 29% of patients with PIK3CA-altered, ER-positive advanced breast cancer, according to results of a phase I b trial.[2] These effects were evident when compared with complete or partial responses in patients without PIK3CA-mutated tumors.

**FDA approval**

On May 24, 2019, the FDA approved alpelisib plus fulvestrant for postmenopausal women, and men, with metastatic or otherwise advanced breast cancer that is PIK3CA-altered, HR-positive, and HER2-negative.

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**SOLAR-1 trial**

In this global, randomized, placebo-controlled trial, 572 patients (341 patients with confirmed PIK3CA mutations)
were assigned to one of two cohorts based on PIK3CA-mutation status. In each group, patients were randomized to receive either 1) oral alpelisib (300 mg/d) plus fulvestrant (300 mg IM on day 1 and day15 of cycle 1 and on day 1 of subsequent 28-day cycles) or 2) placebo plus fulvestrant. Patients in each cohort were stratified per status of liver or lung metastases, as well as prior cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor treatment.[3]

At a median follow-up of 20 months in patients with PIK3CA-mutated tumors, the progression-free survival was 11.0 months (95% CI, 7.5–14.5) in the alpelisib–fulvestrant group compared with that of 5.7 months (95% CI, 3.7–7.4) in the placebo–fulvestrant group (hazard ratio, 0.65; 95% CI, 0.50–0.85; P < .001). The hazard ratio was 0.85 (95% CI, 0.58–1.25) in those without PIK3CA-mutated cancer.

Other findings included an overall response rate of 26.6% in PIK3CA-mutated cancer patients receiving alpelisib plus fulvestrant compared with that of 12.8% in those taking placebo plus fulvestrant. These values were 35.7% and 16.2%, respectively, in patients with measurable disease.

“Alpelisib has activity in patients with PIK3CA-mutated, HR-positive, HER2-negative advanced breast cancer that has progressed during or after treatment with an aromatase inhibitor,” wrote the authors. “Therefore, the integration of genomic testing for PIK3CA mutation into routine clinical practice may be useful in the selection of therapy; validated diagnostic testing procedures are not yet available.”[3]

Previous research on PI3K inhibitors has demonstrated that in patients with PIK3CA-mutated breast cancer, there was longer progression-free survival that was significant but not clinically impactful. These previous studies, however, involved the pan-PI3K inhibitor buparlisib and the β-sparing PI3K inhibitor taselisib, both of which have a narrower therapeutic index, thus resulting in off-target and discontinued treatments.

“Specific inhibition of PI3Kα may represent improved biologic targeting, a finding supported by the observed incidence of hyperglycemia of grade 3 or 4 (10.8% with taselisib vs 36.6% with alpelisib),” wrote the authors.[3]

The SOLAR-1 trial had a safety profile comparable with other trials involving alpelisib and fulvestrant. The most frequent grade 3 or 4 treatment-related adverse events were hyperglycemia (36.6% in alpelisib–fulvestrant group vs 0.7% in placebo–fulvestrant group) and rash (9.9% vs 0.3%, respectively). Furthermore, 25.0% of those taking alpelisib discontinued treatment compared with 4.2% of those taking placebo.

In total, 6.3% of patients stopped the trial secondary to hyperglycemia, which is an on-target effect of alpelisib. Hyperglycemia is yoked to α-specific PI3K inhibition; therefore, the researchers closely monitored safety to decrease participant attrition and realize maximum clinical benefit. They managed adverse events by modifying doses and providing responsive medical intervention as needed.[3]

**Future directions**

Standard of care for patients with HR-positive, HER2-negative advanced breast cancer is endocrine therapy plus or minus CDK4/6 inhibitors. In the future, more patients will likely receive the combination of CDK4/6 inhibitors, including ribociclib, palbociclib, and abemaciclib, and endocrine therapy for the treatment of HR-positive, HER2-negative advanced breast cancer. Nevertheless, acquired resistance to endocrine therapy is an issue. To test the efficacy of alpelisib in patients who have progressed during or after CDK4/6 inhibitor treatment, the BYLieve trial is currently enrolling patients.[4]

Certain tumors that are less sensitive to alpelisib could harbor increased concentrations of retinoblastoma protein, according to the results of preclinical studies. In these patients, a combination of PI3Kα and CDK4/6 inhibitors surmounted intrinsic and adaptive resistance in PIK3CA-mutated xenografts.[3]

**Other applications**

Alpelisib could be used in a wide range of solid tumors, and other indications are beginning to be explored. For example, results from a phase Ib study published in *Lancet Oncology* lend preliminary support to the rationale underlying the combination of poly (ADP-ribose) polymerase (PARP) inhibitors along with PI3K inhibitors in the treatment of platinum-resistant BRCA-wild type epithelial ovarian cancer. According to the authors, this combination could sensitize homologous recombination repair (HR)-proficient epithelial ovarian cancers to PARP inhibitors, thus representing a new mechanism of action.[5]

In this trial, the 33% overall response rate of combined olaparib and alpelisib was much higher than monotherapy with either olaparib (4%–5%) or alpelisib (<5%). Of the 28 patients with epithelial ovarian cancer, 50% exhibited stable disease and 36% attained a partial response. “Our study has shown that the combination of alpelisib and olaparib exhibits synergistic activity in BRCA wild-type, platinum-resistant ovarian cancer.”

Continued on page 438
The ESMO Congress was held in Barcelona from September 27 to October 1, 2019. The conference recognized excellence in translational research and focused on clinically important findings and multidisciplinary topics. Following are highlights of breast cancer advances.

**Neoadjuvant treatment for triple-negative breast cancer**

In patients with early triple-negative breast cancer (TNBC), neoadjuvant pembrolizumab with chemotherapy followed by adjuvant pembrolizumab led to a higher pathologic complete response (pCR) rate than did neoadjuvant chemotherapy plus placebo.

Lead study author Peter Schmid, of the Centre for Experimental Cancer Medicine, Barts Cancer Institute-Queen Mary University of London, commented, “Now this is important, because large analyses have demonstrated that patients who achieve a pCR have a fantastic outlook and the recurrence risk is very low. Ninety to 95% of patients will not see any recurrence in that situation. However, patients who do not experience a PCR, we find residual tumor at the surgery. Even if we remove that residual tumor, unfortunately they have a relatively high risk of recurrence. Often around 40% to 50% in the first 3 to 5 years.”[2]

In the study, 784 patients with untreated, metastatic TNBC were randomized to receive pembrolizumab (200 mg every 3 weeks) and 390 were randomized to receive placebo. Both arms were treated with neoadjuvant chemotherapy before definitive surgery and adjuvant pembrolizumab.

In total, 602 patients could be assessed after a median follow-up of 15.5 months. In those receiving the pembrolizumab-chemotherapy regimen, the pCR rate was 64.8% compared with that of 51.2% for placebo plus chemotherapy. Of note, pCR was defined as ypT0/Tis ypN0.

A beneficial trend in event-free survival was also observed in those receiving neoadjuvant pembrolizumab arm compared with those in the placebo arm (hazard ratio [HR] 0.63; 95% CI, 0.43-0.93). On subgroup analysis, pCR was increased regardless of PD-L1 status.

The rate of grade 3 or more treatment-related adverse events was 78.0% in those in the pembrolizumab arm compared with that of those in the placebo arm. Moreover, mortality rates were 0.4% vs. 0.3% in these arms, respectively.[1,2,3]

**HER2+ Advanced Breast Cancer and PD-L1 inhibitors**

In patients with HER2+ advanced breast cancer who progressed following treatment with trastuzumab and a taxane, the programmed death ligand 1 (PD-L1)
Results presented from the phase 1/II MEDIOLA trial supported the combination treatment of olaparib and durvalumab in the treatment of patients with breast cancer. The MEDIOLA trial assessed the efficacy and safety of olaparib and durvalumab in patients with germline BRCA-mutated metastatic breast cancer.

Inhibitor atezolizumab plus trastuzumab emtansine (T-DM1) outperformed placebo plus T-DM1 in terms of overall survival (OS), according to the results of the phase 2 KATE2 trial.

Lead author Leisha Emens, of UPMC Hillman Cancer Center, Pittsburgh, stated, “Currently, there is a large effort to develop effective immunotherapy combinations that can enhance the activity of single agent PD-1 or PDL-1 blockade. HER2-positive breast cancer is unique in that there are a number of HER2-targeted agents that could potentially be combined with immune checkpoint blockade. The main ones include trastuzumab and trastuzumab emtansine, an antibody-drug conjugate. Both of those have, as a backbone, the trastuzumab antibody which in and of itself has immune-modulating activity. The antibody drug conjugate also has a chemotherapeutic agent conjugated directly to the antibody and that could also potentially have immune-modulating activity.”

She continued, “So, the rationale underlying KATE2, which is a phase II randomized trial that explored the clinical activity of adding atezolizumab to TDM1, is that combining these 2 agents may be additive or even synergistic relative to the clinical activity of the single agents alone.”[4]

In the current trial, patients were assigned 2:1 to receive either atezolizumab 1200 mg or placebo, with both cohorts receiving T-DM1 3.6 mg/kg intravenously every 3 weeks. Patients with PD-L1+ subtypes were determined via immune cell (IC) staining and included IC0 versus IC1/2/3 (<1% vs ≥1%, respectively).

In the atezolizumab plus T-DM1 arm, the median follow-up was 19.5 months compared with that of 18.2 months in the placebo arm. Although median overall survival was not attained, there were 52 measures of overall survival reported. One-year survival was similar in all patients, per the intention-to-treat population; whereas in PD-L1+ patients, 1-year OS was longer in the atezolizumab plus T-DM1 cohort. Compared with known safety profiles of each individual drug, the combined treatments had similar profiles. Pyrexia, however, was more common in those receiving atezolizumab plus T-DM1.

“Given the small number of OS events, the short follow-up and lack of statistical power, further study is necessary,” concluded the authors.[5]

Olaparib and durvalumab in breast cancer

Results presented from the phase 1/II MEDIOLA trial supported the combination treatment of olaparib and durvalumab in the treatment of patients with breast cancer.

The MEDIOLA trial assessed the efficacy and safety of olaparib and durvalumab in patients with breast cancer. The MEDIOLA trial assessed the efficacy and safety of olaparib and durvalumab in patients with breast cancer. Olaparib and durvalumab in breast cancer

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More specifically, in patients with hormone receptor (HR)-positive disease, mPFS was 9.9 months. The mPFS was 4.9 months in patients with triple-negative breast cancer.

“Thedata suggest thats with fewer prior lines of chemotherapy (0/1) had higher ORR, longer mDoR, mPFS and mOS than those with 2 prior lines,” concluded the authors. “The chemo-free combination was well-tolerated, with safety consistent with the individual agent profiles. Confirmation of these results in early-line patients is warranted.”[6]

Abemaciclib and fulvestrant in breast cancer

In hormone-receptor (HR)-positive HER2-negative patients with advanced breast cancer resistant to endocrine therapy, adding the CD4/6 inhibitor abemaciclib to fulvestrant extended OS compared with fulvestrant and placebo, per the results of the MONARCH 2 trial.

In total, 669 patients were randomly...
Alpelisib is Changing the Clinical Landscape
Continued from page 435

Alpelisib is a PI3K inhibitor with a specific targeting of the α-subunit of PI3K, which is activated in a variety of tumors, thereby expanding potential use of PARP inhibitors beyond the setting of HRR deficiency, for which they currently have approval from the European Medicines Agency and US Food and Drug Administration,” wrote the authors.

They continued, “Our results and the mechanistic rationale behind PARP and PI3K inhibitor combinations might be applicable not only to BRCA wild-type, platinum-resistant ovarian cancers but also to other solid tumours with or without PI3K pathway alterations, including BRCA wild-type breast cancer, prostate, colorectal, and endometrial cancers.”[5]

Finally, results of a phase 1 trial indicated that 350 mg/d alpelisib monotherapy exhibited preliminary efficacy in Japanese patients with advanced solid breast cancer (TNBC). Ann Oncol. 2019;30(suppl 5):abstr 233TP.

FIVE KEY REFERENCES


For full reference list, visit cancernetwork.com/ESMO11.19

FOUR KEY REFERENCES


For full reference list, visit cancernetwork.com/alpelisib11.19
Continuing Medical Education

Current and Emerging Immunotherapies in SCLC: Promise and Challenges

Learning Objectives

Upon successful completion of this activity, you should be better prepared to:

• Describe the benefit of adding immunotherapy to first line chemotherapy for SCLC.
• Discuss the safety of first line chemo-immunotherapy combination therapy in SCLC.
• Analyze the efficacy of immunotherapy in patients with previously treated SCLC.

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Instructor

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Small cell lung cancer (SCLC) is a highly aggressive neuroendocrine tumor characterized by rapid growth and early metastases. The clinical onset of SCLC is often associated with heavy symptomatic burden and rapid decline of overall health.1 Chemotherapy and radiotherapy still represent the mainstay of SCLC treatment, and an initial high sensitivity to such treatments is often observed.2,3 However, recurrence occurs very early in most cases, leading to a dismal prognosis and poor overall survival (OS).1

In this limited therapeutic scenario, the rationale for immune checkpoint inhibitors (ICIs) emerged based on the epidemiological, biological, and clinical features of SCLC. SCLC has a strong association with smoking status, and exposure to cigarette smoking is a predictive factor for responsiveness to ICIs in NSCLC.4 SCLC harbors a high number of nonsynonymous somatic mutations (high tumor mutational burden [TMB]).5,6 Additionally, the capacity of SCLC to elicit immune response is also suggested by the presence of autoimmune paraneoplastic syndromes.7 Tumor-enhanced immunity and neurologic paraneoplastic syndromes have been associated with better prognosis.8,9 On the other hand, specific clinical features of SCLC may limit the usefulness and benefit of ICIs. SCLC is a rapidly progressive disease, requiring rapid tumor shrinkage with chemotherapy. Moreover, most patients with SCLC are symptomatic and require steroids; this is particularly true in the case of superior vena cava syndrome and brain metastases.10,11 Chronic steroid use is a known limitation for ICI treatment.12

Considering the potential synergy between chemotherapy and immunotherapy, and the often pressing need to deliver chemotherapy, first-line trials have focused on the combined approach.13,14 IMpower133, a phase III, double-blind, placebo-controlled randomized trial, evaluated the efficacy and safety of the PD-L1 inhibitor atezolizumab when added to carboplatin and etoposide as first-line treatment for patients with extensive-disease SCLC (ED-SCLC). The addition of atezolizumab improved both PFS and OS, with a hazard ratio for death of 0.70, meeting both clinical and statistical significance. There was not a significant difference in safety or tolerability with the addition of atezolizumab to chemotherapy. Based on the results of the IMpower133 clinical trial, atezolizumab was approved by the FDA in March 2019 for the initial treatment of patients with ED-SCLC.15

This was followed by another positive trial. The phase III CASPIAN trial tested durvalumab with and without tremelimumab in combination with platinum-based chemotherapy in untreated ED-SCLC. While results of durvalumab with and without tremelimumab arm are still pending, analysis of the durvalumab-plus-chemotherapy arm compared with chemotherapy alone demonstrated a significant improvement in overall survival, with a HR for death of 0.73. The survival benefit was not accompanied by a significant increase in toxicity. Based on these results, the FDA has granted an orphan drug designation to durvalumab for the treatment of patients with SCLC.16,17 Promising results were observed beyond the first line in the CheckMate 032, KEYNOTE-28, and KEYNOTE-158 clinical studies. CheckMate 032 evaluated immunotherapy for patients with SCLC who had failed a first-line platinum-based chemotherapy.18 Responses were seen with nivolumab alone and in combination with the CTLA-4 inhibitor ipilimumab. While the response rate was modest, responses were very durable and landmark survival analyses were impressive. Nivolumab was granted accelerated approval for patients with metastatic SCLC with progression after platinum-based chemotherapy and at least 1 other line of therapy. The safety profile was manageable, with fewer treatment-related toxic effects compared with previous trials of topotecan and amrubicin.19 KEYNOTE-028, a phase Ib trial, tested the activity and safety of pembrolizumab in 24 patients with ED-SCLC selected for PD-L1 expression (tumor proportion score ≥1%) who had failed at least 1 line of standard therapy.20 Overall response rate (ORR) and duration of response (DOR) were 33.3% and 19.4 months, respectively; only 8 patients experienced grade ≥3 immune-related adverse events (AEs). KEYNOTE-158 was a larger phase II trial of pembrolizumab in 107 pretreated patients with advanced SCLC with no PD-L1 selection,21,22 and it showed an ORR of 18.7%. A pooled analysis of these 2 trials noted a response rate of 16%, with 61% of responses lasting at least 18 months. In patients treated in the third-line setting, the ORR was 19.3% and median DOR was not reached.23 Based on these data, the FDA granted an accelerated approval to pembrolizumab for patients with advanced SCLC with disease progression on or after platinum-based chemotherapy.
and at least 1 other prior line of therapy.

In the search for predictive biomarkers of response to ICIs in SCLC, several trials have included correlative studies to find potential predictive markers of response. A retrospective study evaluated tumor mutational burden (defined as total number of nonsynonymous mutations) of 120 patients with SCLC of all stages and the association with PD-L1 expression on both tumor and immune cells.24 Tumor mutational burden had no particular relationship with tumor expression of PD-L1, whereas investigators observed a positive correlation with PD-L1 expression on immune infiltrate (P = .04). Gadgel et al have studied PD-L1 expression of cells confined in the tumor stroma of patients receiving pembrolizumab as a maintenance treatment after first-line chemotherapy.25 The stromal interface was considered PD-L1 positive if PD-L1 membrane-stained cells surrounding the tumor nests were identified with low-power magnification. Patients with PD-L1 expression at the stromal interface had longer median PFS and median OS than patients with no expression (6.5 vs 1.3 months and 12.8 vs 7.6 months, respectively). Exploratory analysis performed in the SCLC cohort of KEYNOTE-158 has shown the potential of the PD-L1 combined score, measuring PD-L1 expression on tumor and immune cells.21 This PD-L1 score was able to define a subset of pretreated patients with ED-SCLC who achieved a better ORR (35.7% vs 6.0%), 1-year PFS (28.5% vs 8.2%), and 1-year OS (53.1% vs 30.7%) while on pembrolizumab.

With several novel therapeutic options entering the treatment landscape, as well as different immunotherapy approaches currently being investigated in SCLC, the standard of care for SCLC will continue to evolve. Some of the challenges that healthcare providers may face include determining the most optimal approach (sequencing/combination) and personalizing treatment based on predictive biomarkers as they become available.

In the expert interview below, Stephen Liu, MD, associate professor of medicine and director of thoracic oncology at Georgetown University in Washington, DC, provides his insights into the current and emerging role of ICIs in SCLC.

Q: What is the rationale for combining immunotherapy with other therapies in SCLC? What data do we have, so far, supporting any such combinations?

Dr Liu: Combining cytotoxic chemotherapy and immunotherapy in SCLC was explored for several reasons. There can be a synergy between this combination: Chemotherapy can promote antigen release to antigen-presenting cells like dendritic cells. Certain types of chemotherapy can also have a favorable impact on immunosuppressive cells in the microenvironment, like regulatory T cells and myeloid-derived suppressor cells. Also, given the aggressive natural history of this disease, it would have been very difficult to withhold first-line chemotherapy in SCLC. In the absence of a reliable predictive marker, approaches combining the initially effective cytotoxic chemotherapy with immunotherapy in hopes of prolonging long-term survival were explored.

The first study that explored this approach was IMpower133. This was a well-powered, global, placebo-controlled, double-blind, randomized phase III trial of chemotherapy plus the PD-L1 inhibitor atezolizumab or placebo. Enrolled patients had untreated ED-SCLC with intact organ function and a good performance status. All patients received 4 cycles of standard carboplatin plus etoposide and were randomized 1:1 to receive concurrent atezolizumab at a flat dose of 200 mg or placebo followed by maintenance with atezolizumab or placebo until progression or loss of benefit. The study had 2 key primary endpoints, PFS and OS. This study was positive, meeting both of its primary endpoints. Importantly, the rate of severe AEs was comparable between the 2 arms. Patients received a median of 4 doses of carboplatin and 12 doses of etoposide or 4 complete cycles of chemotherapy in both arms, showing that the addition of atezolizumab improved PFS and OS without compromising the ability to complete 4 cycles of chemotherapy. This regimen of carboplatin, etoposide, and atezolizumab was approved in March 2019 and is currently listed in the National Comprehensive Cancer Network guidelines as the preferred approach.

Outcomes were updated at the European Society for Medical Oncology 2019 Congress; a 22.9-month follow-up reported an improvement in 18-month survival rate, from 21% to 34%, as well as a 13% improvement at 18 months, showing that the survival benefit persists over time.
The CASPIAN trial was reported in September 2019 and is also a positive trial. We saw results comparing chemotherapy alone with chemotherapy with durvalumab. The addition of durvalumab improved OS, which was the primary endpoint. We saw an improvement in median OS from 10.3 months to 13.0 months.16,17 There were no concerning safety signals noted in the trial. Looking at the efficacy of durvalumab plus chemotherapy, the safety and efficacy endpoints are very similar to those in IMpower133, showing that when you add a PD-L1 inhibitor to chemotherapy, we consistently see an improvement in OS with a favorable safety profile. These 2 trials are the first in several decades to show an improvement in OS for ED-SCLC.

Q: What is the rationale of administration ICI as a maintenance or consolidation treatment?

Dr Liu: The use of a maintenance immunotherapy approach is very appealing when you look at the survival curves from IMpower133 and CASPIAN. The survival curves do not separate until after approximately 6 months, suggesting that most of the benefit could be related to the maintenance portion of therapy. However, we have to bear in mind the results from CheckMate 451.26 This was a very large randomized phase III trial that included almost 1000 patients. These patients had SCLC and had completed first-line chemotherapy, without progression of their cancer. Patients were randomized to 1 of 3 arms: nivolumab alone, the PD-1 inhibitor; nivolumab plus ipilimumab, a CTLA-4 inhibitor; or placebo. Unfortunately, CheckMate 451 was a negative trial. The use of maintenance nivolumab and ipilimumab after chemotherapy did not improve survival compared with placebo. This strategy was disappointing and the only strategy to extend survival in this setting remains first-line concurrent use of immunotherapy with chemotherapy.

Q: What options exist for patients with SCLC who experience a recurrence after first-line treatment or who failed a first-line platinum-based chemotherapy? What is the role of immunotherapy for these patients?

Dr Liu: For patients who have not received immunotherapy in the first-line setting, there is activity with these agents in the salvage setting. Most of the early data come from CheckMate 032. This is a multicohort phase I/II study exploring several different dosing strategies. Patients received either nivolumab alone or in combination with ipilimumab. In the first analysis of 216 patients, the response rate to nivolumab monotherapy was 10%. The combination of nivolumab and ipilimumab offered higher response rates, between 19% and 23%, but that combination had a higher rate of grade 3 to 4 AEs. Importantly, responses were durable, and the landmark survival rates were quite impressive, with a 2-year OS rate of 26% with the combination of nivolumab and ipilimumab for patients with previously treated SCLC. This led to a cohort of patients who were randomized to receive nivolumab, or nivolumab with ipilimumab, which showed response rates similar to those of the nonrandomized cohort. Within CheckMate 032, an analysis was performed on patients who had received third-line nivolumab monotherapy. The response rate to nivolumab monotherapy was 12%, with a very long duration of response approaching 18 months. The landmark survival rates were also impressive, with an 18-month survival rate of 20% in the third-line setting. The quality of these responses coupled with the unmet need in the third-line setting led to the FDA accelerated approval of nivolumab as monotherapy in the third-line setting.18 Pembrolizumab, another PD-1 inhibitor, has also been explored in this setting in KEYNOTE-028, which was a multicohort phase IB study of patients with PD-L1-positive SCLC. The response rate in this cohort was 33%, with a low median PFS of 1.9 months but a fairly high 12-month PFS rate of 24%.20 A larger follow-up study was KEYNOTE-158. This single-arm phase II study included 107 patients; no PD-L1 selection was used in this trial. The primary endpoint was response rate, and the response rate reported was approximately 19%, which included several complete responses and 73% of responses lasting more than 1 year.22 A pooled analysis of KEYNOTE-028 and KEYNOTE-158 was reported at the American Association for Cancer Research meeting in 2019. In this analysis of 131 patients, the response rate was noted to be 16%, but the responses were quite durable. And the 1-year survival rate was a very impressive 34%. Looking at patients who had received third-line pembrolizumab monotherapy, the response rate was 19%, but nearly all those responses lasted at least 6 months, with 56% of those responses lasting more than 18 months. Based on the quality of the responses, pembrolizumab was granted FDA accelerated approval in June 2019 as third-line monotherapy.23 Although these third-line approvals are important for patients who had not received prior immunotherapy, there is a high attrition rate in SCLC, with a small minority of patients well enough to receive any third-line therapy. This led to exploration of immunotherapy in the earlier setting. CheckMate 331 was a randomized phase III trial for patients who had received prior platinum doublet chemotherapy, and it explored second-line nivolumab versus second-line topotecan or amrubicin. This study unfortunately was negative. Nivolumab failed to improve survival compared with topotecan or amrubicin. PFS favored the chemotherapy arm, with a hazard ratio of 1.41.
Q: What are some of the emerging combination strategies and mechanisms of action of drugs being studied for new combination strategies in SCLC?

Dr Liu: Our current immunotherapy strategies have used inhibitors of PD-1, PD-L1, and/or CTLA-4. Although these have shown promising activity, these are only some of the many checkpoints involved in regulating an immune response. There has been considerable interest in agents targeting the DNA damage response pathway. Molecules targeting mediators such as PARP, ATM, and ATR have shown promise both as monotherapy and in combination with checkpoint inhibitors. An interesting target in SCLC is DLL3. This protein presents primarily on SCLC cells and is not expressed in adult normal cells. These are the characteristics of a promising therapeutic target. Rovalpituzumab tesirine is an antibody–drug conjugate that targets DLL3-positive cells. This agent showed promising activity, with fairly high response rates in refractory SCLC. Unfortunately, toxicity has proved to be a considerable concern, and the more recent trials have failed to improve long-term outcome. This target itself still holds promise, and other agents targeting DLL3 under active investigation including a bispecific T-cell engager antibody and chimeric antigen receptor T-cell strategies. In addition, radiotherapy is likely to play a role in the management of SCLC. These cells are very radiosensitive, and the connection between radiotherapy or radiation treatment and immunotherapy has been explored in many other cancers. The introduction of consolidated thoracic radiation, or targeted stereotyped radiosurgery combined with immunotherapy, is an exciting area of research, with many trials already under way. Another interesting molecule explored in SCLC is trilaciclib. This molecule targets CDK4/6 in SCLC. It is primarily being explored as part of a myelo-preservation strategy because SCLC tumor cells lack retinoblastoma in the vast majority of cases. They replicate independently of CDK4/6, which is different from hematologic progenitor cells. Trilaciclib can protect these progenitor cells from being destroyed by chemotherapy, lessening the hematologic toxicity of chemotherapy in SCLC. Another theoretical advantage of this agent would be preservation of cells important for an antitumor immune-mediated response. There may be some advantage to using this agent in combination with immunotherapy during cytotoxic treatment.

Q: What are the most common AEs associated with immunotherapy in patients with SCLC? In which patients do we see the most severe toxicities?

Dr Liu: The most common AEs associated with chemotherapy in the IMpower133 and CASPIAN trials were hematologic in nature. Although the rate of grade 3 AEs was relatively high, these were primarily hematologic in nature, reversible and attributed to the backbone chemotherapy. Immune-related AEs were fairly uncommon in both of these trials. Immunotherapy in a salvage setting has comparable immune-related toxicity. Patients with an underlying autoimmune disorder were largely excluded from these trials, with a concern that the immune-related AE rate would be higher in these patients. Other trials in other cancers have confirmed that the rate of AEs is higher in patients with underlying autoimmune disease, although this is not necessarily a contraindication. In SCLC, many patients will also have coexisting paraneoplastic syndromes. Significant paraneoplastic syndromes were an exclusion factor for many of these trials. However, current clinical practice suggests that these agents are safe in patients with an underlying endocrine paraneoplastic syndrome. Their safety in patients with an underlying antibody-mediated neurologic paraneoplastic syndrome has yet to be elucidated. When combining ICIs with radiation therapy, there have been concerns about safety, primarily pulmonary toxicity with concurrent thoracic radiotherapy. Although this is still an area of investigation, results of recent studies do not show a significantly higher rate of pneumonitis when checkpoint inhibitors are given concurrently with radiotherapy to the chest. Consolidation thoracic radiotherapy was not part of the IMpower133 or CASPIAN trials and is worthy of further study.

Q: Several trials have included correlative studies to find potential predictive biomarkers of response. What are the roles played by PD-L1 expression and TMB in predicting response to treatment?

Dr Liu: It is clear from immunotherapy studies that the long-term benefit of checkpoint inhibitors is derived from a subpopulation of patients with SCLC. Identification of the subset is critical to advancing the field. A common predictive marker for immunotherapy is PD-L1 expression. This was explored in several studies. In KEYNOTE-158, PD-L1 expression was determined using the combined score looking at expression of PD-L1 on tumor cells or on surrounding immune cells. The response rate in PD-L1-positive tumors was 36% compared with only 6% in PD-L1-negative tumors. However, this is in contrast with the results of PD-1 expression in CheckMate 032. In this study, responses were more frequent in the PD-L1-negative cohort, with a response rate of 14% to nivolumab in the PD-L1-negative group versus 9% in the positive group. In IMpower133 and CASPIAN, PD-L1 was assayed and did not hold predictive power and was not a viable predictive biomarker in determining benefit from either atezolizumab or durvalumab. TMB has also been ex-
plored as a possible predictive marker. In CheckMate 032, when samples were available, they were subject to whole exome sequencing. The TMB-evaluated population was about 53% in this study, and responses were more common in the PD-L1-high group. With nivolumab monotherapy, the response rate was 5% in TMB low compared with 21% in PD-L1 high. With a combination of nivolumab and ipilimumab, the response rate was 22% in PD-L1 low and 46% in PD-L1 high. Blood-based TMB was then explored in IMpower133 based on blood collected at study entry. Whether a cutoff of 10 or 16 mutations per megabase was used and whether patients fell above or below those cutoffs, there was no predictive power to this assay, as all patients derived benefit from atezolizumab.

In the current landscape, PD-L1 or TMB does not hold predictive power in determining who can derive benefit from immunotherapy for SCLC.

**Q. What does the future hold for checkpoint inhibitors, specifically regarding treatment of patients with SCLC and patient selection? Do you think we’re on the verge of dropping the standard chemotherapies and giving patients just immunotherapy, or is that far in the future?**

**Dr Liu:** It is clear that the checkpoint inhibitors have activity in SCLC and can provide impressive and durable responses, extending long-term survival. It is also clear that this benefit is limited to a subset of patients. For the field to move forward, this subset needs to be identified so that those patients can be sure to receive that therapy and so we can better understand why that benefit is not derived in all patients. This will involve intense use of biomarkers in SCLC, which has consistently been a challenge through the years.

Genomic sequencing of SCLC has not yielded therapeudic targets, but recent work has identified several unique subsets of SCLC. Although still under investigation, there are several unique subsets of SCLC defined by differential expression of several key transcription factors. These subsets may respond differently to unique therapeutic strategies, including immunotherapy.

By understanding these unique subsets and how they best respond to therapy, we can design more rational trials that can help deliver the proper therapy to the proper subsets of patients.

Although some patients may be more likely to respond to immunotherapy, we are not quite ready to eliminate chemotherapy for SCLC. The natural history of this disease is a short one. Given the aggressive nature of SCLC, withholding chemotherapy may lead to a rapid decline in patients’ clinical status, forfeiting any opportunity to benefit from that initial chemotherapy. Until a more reliable predictive marker can be identified, chemotherapy will remain at least part of our initial therapy for SCLC. The goal would be to deliver the most effective treatment to patients when a powerful predictive marker is identified. Our hope is to be able to remove the toxic chemotherapy for a subset of patients.

**FIVE KEY REFERENCES**


From September 7-10, 2019, the International Association for the Study of Lung Cancer (IASLC) hosted the 2019 World Conference on Lung Cancer (WCLC) in Barcelona, touted as the biggest gathering of lung cancer researchers and clinicians worldwide. Below are five notable abstracts from the conference.

 Concerning Lack of Public Knowledge About Lung Cancer Clinical Trials
A study performed by Lung Cancer Europe (LuCE) to garner insights into clinical trials from a patient perspective found that 50% of Europeans surveyed did not know what cancer clinical trials were and 22% were unaware that cancer clinical trials existed.[1]

“We shared our online survey with lung cancer advocates and patients with lung cancer,” stated lead author AM Baird, on behalf of LuCE in an IASLC press release.[2]

LuCE advocates for the interests of lung cancer patients in Europe and is dedicated to education as well as addressing disparities in detection, diagnosis, and treatment. In this study, researchers interviewed 15 stakeholders in the medical community and surveyed 262 lung cancer patients from 15 European countries.[1]

Only 11% of patients surveyed had participated in a clinical trial, with more than 50% reporting it to be a positive experience. Moreover, 89% found trial information on the Internet, but only 10% reported that they could routinely find the information they required.[1]

“This is critical, as the more information patients obtained, the more willing they were to participate in clinical trials,” wrote the authors in the study abstract. “Overall 80% wanted to find out more about clinical trials, and 75% believed that it would be beneficial for patients to work together with researchers in the clinical trial development process.”[1]

The authors continued, “Key areas identified by this research included difficulties in cross-border access, language barriers, lack of accurate accessible information, lack of awareness by patients and clinicians, and disparities in access across Europe.”[1]

European Lung Cancer Screening

Model Bests United States Model
Globally, PLCoM2012 is the best validated and most popular lung cancer risk prediction model; it calls for CT screening in patients with a 6-year lung cancer risk of ≥ 1.5%. Although this model has demonstrated efficacy, it runs counter to recommendations of the United States Preventive Services Task Force (USPSTF) and the Centers for Medicare and Medicaid Services which recommend screening in those with 30 or more pack-years, those who smoked within the past 15 years, and patients age 55 to around 80 years.[3]

“Our analysis of ILST (International Lung Screening Trial) data indicates that classification accuracy of lung cancer screening outcomes supports the PL-
KEYNOTE-021: Tumor Mutational Burden With or Without Pembrolizumab

According to the results of an exploratory study in first-line treatment for metastatic non-squamous non-small cell lung cancer (NSCLC), tumor mutational burden (TMB) was not related to the efficacy of pembrolizumab plus carboplatin and pemetrexed or carboplatin and pemetrexed alone. TMB was not related to PD-L1 expression.[5]

“KEYNOTE-021 cohort C was the first study to show antitumor activity for pembrolizumab plus platinum-based chemotherapy in previously untreated advanced nonsquamous NSCLC; the combination significantly improved efficacy vs platinum-based chemotherapy alone in cohort G. We explored the relationship between TMB and outcomes in KEYNOTE-021 cohorts C and G,” wrote authors, led by Corey Langer, MD, Abramson Cancer Center, University of Pennsylvania.[5]

Patients in Cohort C were given pembrolizumab plus carboplatin and pemetrexed. Whereas, patients in cohort G were randomly assigned 1:1 to receive either pembrolizumab plus carboplatin and pemetrexed or the chemotherapy component alone. Langer et al. used whole-exome sequencing of tumors, as well as matched normal DNA, to assess TMB.[6]

Data on TMB were available for 70 patients, with initial patient characteristics similar among both cohorts. As a continuous variable, TMB was not related to progression-free survival, overall response rate (ORR), or overall survival (OS) in either arm of the study. Notably, ORR was high in both the TMB low and high subgroups. In the pembrolizumab with chemotherapy arm, the ORR was 60.8% (95% confidence interval [CI], 38.5-80.3) in the 23 patients with high TMB (TMB ≥175) and 71.4% (95% CI, 47.8-88.7) in the 21 patients with low TMB (TMB <175). No association between TMB and tissue polypeptide-specific antigen was observed (r=0.12, P = .34).[5]

“The study was not powered to detect a difference in mortality, however there was a non-significant trend suggesting fewer deaths in the intervention arm compared to the control.”

Autoantibody Test Followed by CT Decreases Diagnosis of Late-Stage Lung Cancer and May Reduce Mortality

The novel EarlyCDT-Lung Test plus CT imaging in a Scottish cohort of patients at risk for lung cancer led to a decrease in the diagnosis of late-stage lung cancer and could drop mortality secondary to the disease.[7]

“Many studies indicate that using accurate risk prediction models is superior for selecting individuals for screening, but these findings are based on retrospective analyses. The ILST was implemented to prospectively identify which approach is superior,” wrote the authors.[3]

Overall, 110 of 5013 patients screened had lung cancer, with 99% of cancers discovered per PLCOM2012 criteria compared with 77% per USPSTF criteria. Furthermore, 21.8% of cancers were discovered solely per PLCOM2012 whereas only 0.9% was discovered solely using USPSTF guidelines.[4]

“Our analysis of ILST data indicates that classification accuracy of lung cancer screening outcomes supports the PLCOM2012 criteria over the USPSTF criteria,” concluded Dr Lam.[4]
What Are the Most Common Esophageal Metastases?

A rare occurrence, cancer in the esophagus requires an individualized treatment plan.

Lara M. Bolaños, MD, Francisco Javier Castro-Alonso, MD, Braulio Martínez-Benitez, MD, MSc, and María T. Bourlon, MD, MSc

A 63-year-old man presented with a 3-month history of significant weight loss, dysphagia, and odynophagia. His past medical history was relevant for a radical cystectomy for a stage II muscle-invasive urothelial bladder cancer 10 years ago. He had an hepatic, pulmonary, and lymph-node systemic recurrence 8 years ago, with complete response to 6 cycles of gemcitabine/carboplatin, and has been in continuous surveillance ever since.

His physical examination and laboratory tests were unremarkable. An esophagram revealed distal esophageal stenosis with proximal dilation. A CT scan showed a concentric thickening in the middle and distal esophagus. Positron emission tomography and F-18-fluorodeoxyglucose (18F-FDG) integrated with CT (18F-FDG PET/CT) displayed hypermetabolism in the middle and distal third of the esophagus, with no evidence of other sites of metastatic disease (Figure 1).

An upper gastrointestinal endoscopy was performed and revealed a complex ulcerated stenosis at 35 cm from the upper incisors. Biopsies were taken. The pathology examination revealed metastatic high-grade urothelial carcinoma: CK7-positive, CK20-negative, GATA3-positive, p63-positive, and uroplakin-positive (Figure 2). Morphologic appearance and immunohistochemistry were highly similar to that of the primary tumor and the previous systemic recurrence.

What is the primary tumor that most commonly metastasizes to the esophagus?

A. Breast Cancer
B. Lung Cancer
C. Kidney Cancer
D. Urothelial Cancer

Turn to page 462 for the answer and a discussion of this case by experts.
Discussion

Esophageal metastases are a rare phenomenon. According to autopsy registries of any kind of neoplasm, incidence ranges from 0.3% to 6.1% of all metastases, most of them asymptomatic.[1,2] Esophageal involvement may be caused by three principal mechanisms: direct extension, mediastinal lymph node metastases with subsequent esophageal infiltration, and hematogenous dissemination. Direct extension from adjacent organs is by far the most common manifestation (up to 45.2% of cases), followed by infiltration from mediastinal lymphatic metastases (35.5% of cases). True distant hematogenous metastases are the rarest mechanism, accounting for 19.3% of cases.[3] Direct extension from a contiguous organ can be recognized most of the time by the obvious primary tumor. This does not hold true for the other two mechanisms, and therefore most clinical series admix them.[3]

The first case of esophageal metastasis (from the prostate) was published by Gross and Freedman in 1942.[4] After that, a wide array of malignant tumors with metastases to the esophagus were reported, including lung, breast, ovarian, kidney, gastrointestinal, lymphoma, testicular, tongue, bone, liver, uterine, and skin.[2,3] According to the largest retrospective autopsy case series, the most common cause of esophageal metastases is lung cancer, followed by breast and gastric neoplasms (45.5%, 12.5%, and 11.6% of all esophageal metastases, respectively).[2] This study and other case series are summarized in the Table. Thus, option B is correct, but histologic differences need to be addressed. Up to 15% of adenocarcinomas metastasize to the esophagus and the corresponding percentages for small-cell lung cancer and squamous cell carcinoma are 9.8% and 8.1%, respectively.[2]

Urothelial carcinoma is the 10th most common malignant neoplasia worldwide.[5] About 10% to 20% of those patients have the aggressive muscle-invasive disease, which gives them higher risk of lymphatic and systemic dissemination.[6,7] Even with curative treatments like radical cystectomy, up to 16% and 50% will have locoregional and distant recurrences, respectively.[8–10] The most common sites of distant metastases from urothelial carcinoma are nonregional lymph nodes (90%), liver (47%), lung (45%), and bone (32%); other sites might include peritoneum, pleura, kidney, adrenal gland, and intestine.[11] To the best of our knowledge, this is the first case report of esophageal metastasis ever reported.

Esophageal metastases are a diagnostic challenge, because in most cases clinical presentation is indistinguishable from primary esophageal cancers. No difference in the severity or duration of symptoms correlates to primary versus secondary neo-

**FIGURE 2** Esophageal Biopsy. (A) Hematoxylin and eosin 20x: Malignant high-grade epithelial neoplasm with solid and glandular patterns. (B) GATA3 nuclear expression in neoplastic cells; normal epithelium nuclei have no GATA3 expression. (C) Diffuse and intense p63 expression in normal epithelium; focal nuclear p63 expression in neoplastic cells.

**Key Points**

- Esophageal metastases are a rare phenomenon, ranging from 0.3% to 6.1% of all metastases.
- The most common cause of esophageal metastases is lung cancer, followed by breast and gastric neoplasms.
- In esophageal stenosis with normal mucosa, metastasis must be considered as a differential diagnosis, especially if the patient has a previous history of cancer.
- There is no standard treatment for esophageal metastases; a case-by-case selection for aggressive treatment must be considered.

**CORRECT ANSWER:** B. Lung cancer is the primary tumor that most often causes secondary infiltration to the esophagus.

Continued from page 461
plasms. Radiographic studies might be useful to detect primary adjacent tumors, but these are not that useful to discriminate metastasis from primary neoplasms. Esophagrams can display esophageal stenosis with normal mucosa, and CT scans may show concentric thickening of the esophageal wall, with or without an associated extrinsic mass.

Upper gastric endoscopy is the most useful test in this setting. A normal epithelium is seen in 68% of esophageal stenosis due to the submucosal nature of most metastases. In any esophageal stenosis with normal mucosa, metastasis must be contemplated as a differential diagnosis, especially in patients with a history of cancer. Endoscopic ultrasound might also help to determine the layer where a tumor comes from and also to achieve histopathologic diagnosis, as many traditional endoscopy biopsies might only show normal epithelium overlying to the tumor.

Treatment of esophageal metastases depends on several factors, such as origin, symptom severity, and presence of metastases to other organs. In most patients, treatment consists of chemotherapy with or without radiotherapy. Although chemosensitive, most metastatic urothelial carcinomas remain an incurable disease. Without systemic treatment, most patients die of progressive disease within 6 months.

The cornerstone of treatment for urothelial cancer is platinum-based chemotherapy, achieving an objective response rate of 50% to 60% and complete responses in 10% to 20% of patients. In most cases, responses are transitory and few patients achieve long-term survival.

Local control with esophagectomy has provided excellent palliation in several case reports of esophageal metastases, with primary tumors coming from breast, lung, and malignant melanoma. Metastectomy in urothelial carcinoma and its impact in survival is controversial. Single-site metachronous tumors have achieved prolonged survival in case reports, however, so an aggressive surgical approach must be taken into consideration. Palliation with endoscopic dilation and stents might be an alternative, given that many patients have maintained oral intake with those procedures in recent reports of esophageal metastases.

Prognosis of esophageal metastases is uncertain, ranging from a few months to several years. A case-by-case detailed analysis must be done in every patient to select the best treatment options.

### TABLE Case Series and Autopsies Reports on Esophageal Metastases

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**FAST FACTS about Esophageal Cancer**

- Esophageal cancer is the 7th most common cancer worldwide.
- When esophageal cancer occurs, it starts in the inner layers of the esophagus and grows outward.
- Other cancers metastasizing to the esophagus is a rare occurrence, but symptoms are often similar to those in primary esophageal cancer.
- Cancer affecting the esophagus can sometimes narrow the esophagus which may make it difficult to swallow or eat properly.
- Other signs and symptoms of esophageal cancer or cancer metastasized to the esophagus include heartburn, unexplained weight loss, hiccups, or a lasting cough.
- An esophagectomy, surgery to move all or part of the esophagus, is a common treatment for esophageal cancer.
- While recovering from surgery, patients with cancer in the esophageal may not be able to eat by mouth and need a feeding tube to meet their nutritional needs.
- Barrett esophagus is a pre-cancerous condition in which the cells at the lower part of the esophagus have been replaced by abnormal cells due to damage by stomach acid from reflux. People with Barret esophagus are at higher risk for esophageal cancer.
- There are approximately 17,000 new esophageal cancer diagnoses each year in the USA.
- Esophageal cancer is 3-4 times more common in men than women.
the proper treatment and attain quality of life.

**Outcome of This Case**

The patient was started on chemotherapy with gemcitabine and carboplatin, given the adequate clinical response he had had to this combination previously and the fact that he could sustain adequate oral intake despite his symptoms. Currently, he has received 2 cycles of chemotherapy with adequate tolerance. A control CT scan to ascertain response is pending.

**FINANCIAL DISCLOSURE:** The other authors have no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

Dr. María Bourlon has served as a speaker and a member of the advisory board for Bristol-Myers Squibb. She has been a speaker, advisor, and/or travel grant recipient for BMS, Janssen, Ipsen, MSD, and Asofarma. She has been a speaker, advisor, and/or member of the advisory board for Bristol-Myers Squibb. She has been a speaker and a member of the advisory board for AstraZeneca, MSD, and Asofarma.

**5 KEY REFERENCES**


**For full reference list, visit cancernetwork.com/XCQ-esophMets**

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**Mutations Associated with Response to Immunotherapy: MYSTIC Trial**

In patients with metastatic NSCLC, investigators assessed the relationship between STK11, KEAP1, and ARID1A mutations and response to immunotherapy.[9,10]

“The STK11 and KEAP1 mutations … influence outcomes and need to be factored into our analysis of TMB and other outcomes of lung cancer,” said presenter Naiyer A. Rizvi, MD, Director of Thoracic Oncology, Division of Hematology/Oncology, Columbia University Medical Center, New York. “STK11 and KEAP1 are sort of bad actors in terms of lung cancer outcomes [as supported by current knowledge].”[11]

The phase III MYSTIC trial compared durvalumab monotherapy or durvalumab/tremelimumab vs chemotherapy as first-line treatment in patients with epidermal growth-factor receptor and anaplastic lymphoma kinase wild-type locally advanced or metastatic NSCLC. During further analysis, a subset of patients with high TMB were identified via plasma assay using a 20 mutation/megabase threshold.

Participants harboring STK11 or KEAP1 mutations had lower median OS in all experimental groups. In those with ARID1A mutations who received durvalumab/tremelimumab, the investigators saw survival benefits.[9,10]

**FIVE KEY REFERENCES**


**For full reference list, visit cancernetwork.com/WLungConf2019**
Burnout in Oncology

Mehmet Sitki Copur, MD, FACP

ABSTRACT: Burnout is defined as an occupational-related syndrome characterized by physical and emotional exhaustion, cynicism/depersonalization, and low sense of professional accomplishment. Multiple oncology-specific risk factors are associated with an increased susceptibility for the development of burnout. On a daily basis, oncologists are faced with life and death decisions and grieving much more frequently than are physicians in other specialties. Continuous exposure to fatal illnesses with limited success in curing them, exceedingly long work hours with more administrative time demands, limited autonomy over daily responsibilities, endless electronic documentation requirements, and a shifting medical landscape seem to be making oncologists more vulnerable to suffering from burnout. Evidence suggests that burnout can impact quality of care in a variety of ways and have potentially profound personal implications. In this review, the definition, prevalence, causes, and management of oncologist burnout are analyzed. Steps oncologists can take to promote personal well-being and professional satisfaction are also explored.

Introduction

Oncology is largely viewed as an inherently challenging specialty due to its nature of dealing with daily life and death circumstances. Exposure to long hours of direct patient care for desperately ill patients, counseling their families, endless electronic documentation requirements, continual loss of autonomy over daily responsibilities, and a constantly changing medical environment set the stage for what is called a “burnout syndrome” for most practicing oncologists. Feeling inadequately equipped to deal with the emotional reactions of patients and their families can be a further source of stress among oncologists whose daily work may also force them to face their own mortality, as well as that of their family and friends.

Burnout was first described by psychologist Herbert Freudenberger in the 1970s as a condition that occurs when work coupled with additional life pressures exceeds the ability to cope, resulting in physical and mental distress.[1] In the 1980s came the 22-item Maslach Burnout Inventory (MBI)-Human Services Survey, which became the most widely used and validated assessment tool for self-reported symptoms of burnout.[2] The MBI consists of three distinct components: emotional exhaustion, depersonalization, and personal accomplishment/experience of ineffectiveness. These components, however, are usually part of a continuum that may include overlapping symptoms of cardiovascular, gastrointestinal, musculoskeletal, cognitive, and affective origin. The Copenhagen Burnout Inventory, which was introduced in the early 2000s, gauges burnout at three scales: personal burnout, work-related burnout, and client-related burnout.[3] Finally in May 2019, the World Health Organization added burnout to the 11th revision of the International Classification of Diseases (ICD-11), characterizing it as a syndrome of three dimensions: feelings of energy depletion or exhaustion, increased mental distance from one’s job and feelings of cynicism or negativism about one’s job, and reduced professional efficacy.[4]

Energy depletion or exhaustion is described as a complete lack of energy frequently resulting in a debilitating feeling of dread for what the day ahead will bring. Basic tasks and, sadly, even things that would normally provide joy turn into chores. Trouble sleeping to the point of insomnia, inability to rest and recharge, and difficulty to concentrate and focus eventually lead to panic attacks, chest pain, breathing difficulties, migraines, and stomach pains. Increased mental distance from one’s job and feelings of cynicism or negativism about one’s job, and reduced professional efficacy.

Steps oncologists can take to promote personal well-being and professional satisfaction are also explored.
manifest as going through the motions, making it to the office, and somehow still getting the job done in an almost robotic manner. There is no zest, no pleasure, and therefore, no optimum performance. Ordinary tasks take longer, and things that were once easy now seem overwhelming.

Burnout is not a diagnosis listed in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition, but it is classified by ICD-11 as a phenomenon under problems associated with employment and has been recognized as a diagnosable condition (diagnostic code QD85) resulting from chronic workplace stress about exhaustion, cynicism, and reduced efficacy. Notably, it is highlighted to be an occupational phenomenon rather than a medical condition. An occupational phenomenon is defined as factors influencing health status or contact with health services, which includes reasons individuals look for health services. It is not classified as an illness or health condition.

The hallmark features of burnout are similar to the criteria for endogenous depression; however, ICD-11 specifically excludes mood disorders from the definition of burnout. Although burnout is classified and conceptualized as a workplace-related disorder, this assertion may not be entirely true. Burnout may look similar to depression and other psychiatric disorders, in that it is multifactorial and complex. Symptoms of emotional exhaustion and depersonalization can originate from not only direct workplace stress but also stress at home, such as having difficulties in marriage, having to care for an older parent, or a long commute to work, and more. Many of the factors that contribute to depression also contribute to burnout. Sufficiently long vacations can help differentiate depression from burnout, but burnout relief post vacation has been shown to be short lived. Psychiatrists who support physicians affected by burnout are left to consider the possibility of differential diagnoses or comorbidities because burnout and depression may have overlapping symptoms and clinical features. The stigma of mental illness and its treatment may allow burnout to become a catchall term for emotional distress and thus less stigmatized. Importantly, erroneously labeling a physician’s distress as burnout may prevent or delay appropriate treatment of depression and sometimes a life-threatening mental disorder.

As burnout is poorly defined, one may expect considerable variation in the reported prevalence of burnout to exist due to significant differences in the way it has been defined, diagnosed, and assessed. Depending on the definition chosen, the prevalence of burnout identified can vary significantly. This complexity arises because the classic triad of burnout symptoms can manifest to differing degrees in each individual. Most of the reported data come from survey studies. A national survey among US oncologists found a 45% burnout prevalence, while other studies reported 20% to 70% burnout rate globally. A systematic review and meta-analysis of 4,876 participants from 17 studies reported a 32% rate of burnout, which possibly gives the best estimate on oncologist burnout.

Causes and Risk Factors
Similar to its definition and prevalence, leading causes and risk factors of burnout come from observational, cross-sectional, and survey-type studies. The three most commonly stated causative factors include clinical and nonclinical work burden, electronic medical record (EMR) implementation, and loss of autonomy. Causes and risk factors can be summarized into demographic, workplace, and work/life balance categories. Among demographic factors, younger age, living alone, lack of access to support services, and being an early career oncologist have been found to be related to burnout. Workplace-related factors refer to not only increased work hours but also increased administrative workload and reduced meaningful professional activity such as research and educational time. The significant loss of physician independence, excessive time spent on regulatory and clerical work, and stressful professional experiences in delivering bad news to cancer patients have been connected to workplace-related burnout among oncologists. Impaired work/life balance occurs...
when quality time away from work such as vacation time, time for hobbies, and time for family becomes increasingly inadequate. [23,24] Every additional after-hours time at home spent on work-related tasks such as accessing work-related emails and EMRs has been associated with higher rates of burnout.[25]

**Managing Burnout in Oncology**

As oncologists, we deal with life and death and grieving much more frequently than other specialties. With continuous exposure to lethal illnesses and limited success in curing them, oncologists may seem to be particularly vulnerable to stress and burnout. Challenges of staying ahead of the extensive new discoveries in cancer science and trying to assimilate enormous quantities of new research on new drugs and molecular therapies, augmented by demands posed by EMRs and compliance, regulation, and payment issues, oncologists may very quickly reach a breaking point. Despite speculation that oncologists may be at greater risk for burnout than physicians in other disciplines, however, there have been very few well-designed studies examining distress rates among oncologists relative to other specialties. [26] A preliminary analysis from a national study conducted in collaboration with the American Medical Association of 7,000 US physicians did not find evidence to support the supposition that oncologists are at higher risk for burnout (unpublished data). Medical oncologists (n = 87) had a lower rate of burnout than other internal medicine physicians (n = 1,328), with a burnout rate of 37.9% vs 48.8%, respectively (P = .05). Medical oncologists were also more likely to state they would choose the same specialty if they could redo their career choice compared with other internal medicine physicians, at 81.4% vs 61.9%, respectively (P < .001).[27]

On the brighter side, practicing oncologists caring for cancer patients have the most rewarding profession. Cancer research is intellectually more than stimulating. Witnessing revolutionary discoveries in molecular biology and seeing them translated into clinical practice, ie, “bench to bedside” happening more frequently than in any other specialty, is extremely gratifying. Being part of cancer science discoveries and having the opportunity to implement these advances into clinical practice by taking part in standard care and/or participating in clinical trials, oncologists have the unique advantage of professional satisfaction more than those in other specialties of medicine. Being part of the efforts leading to improved patient outcomes in prevention, diagnosis, treatment, palliative care, and quality of life of cancer patients provides tremendous opportunity for meaning and purpose in the professional lives of oncologists. They can derive high levels of satisfaction from their professional status and associated collegial respect, as well as from the intellectual stimulation that their role provides. [22]

As oncologists, we evaluate and diagnose complex problems, devise and administer individualized treatment strategies, and provide critical support to patients and their families who face life-threatening illnesses. We can identify values and determine how to align our work activities with the areas we find most meaningful. Our relationships with patients, along with the intellectual stimulation that our specialty provides, establish the foundation for professional meaning for many of us. Every day, we directly and indirectly affect hundreds of people’s lives. Although in most other medical specialties beneficence and altruism overlap, in oncology, we have the advantage and capability of being more altruistic than beneficent in our daily practice. In fact, neurobiologists have found that when engaged in an altruistic act, the pleasure centers of the brain become active. [28]

Given the high prevalence of physician distress and the potential repercussions for quality of care, however, hospitals, practice groups, national societies, and healthcare organizations must have a responsibility and obligation in coming up with solutions to help reduce

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**We can identify values and determine how to align our work activities with the areas we find most meaningful.**

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ONCOLOGY recently spoke with Dr. Sandip Patel about a potential novel therapeutic approach to treating patients with neuroendocrine tumors. Dr. Patel is an associate professor of medicine at the University of California San Diego School of Medicine in La Jolla, California. He is also a medical oncologist who specializes in cancer immunotherapy and early-phase immunotherapy clinical trials for patients with various cancer types.

Q: First, how frequently are neuroendocrine tumors diagnosed? What do we know about the biology of these types of tumors?

DR. PATEL: Neuroendocrine cancers are a rare, heterogeneous group of tumors that range from low-grade, more indolent tumors to high-grade carcinomas that can be very aggressive. In the United States, the incidence rate of neuroendocrine tumors is approximately 5 cases per 100,000. Since they can manifest in almost any part of the body, clinical trials in this arena have historically been complicated by the varying biologies and sites of origin in which these cancers develop.

Q: Is there an existing standard of care for treating neuroendocrine tumors, or is therapy individualized based on the organ or tissue in which they arise?

DR. PATEL: Broadly speaking, various treatments are used to manage neuroendocrine cancers based on the grade of the tumor and, potentially, the site of origin. For example, pancreatic neuroendocrine tumors are often treated with more targeted approaches, such as agents like sunitinib—an oral, multi-targeted tyrosine kinase inhibitor of vascular endothelial growth factor receptor 1 (VEGFR-1), vascular endothelial growth factor receptor 2 (VEGFR-2), fms-like tyrosine kinase 3 (FLT3), KIT, platelet-derived growth factor receptor β (PDGFRβ), and platelet-derived growth factor receptor β (PDGFRβ)—and everolimus, an oral inhibitor of mammalian target of rapamycin (mTOR).

Neuroendocrine cancers that arise in other organs have different therapy options depending on the grade of the tumor. High-grade tumors are often treated with cytotoxic chemotherapy, while low-grade tumors are often treated with somatostatin analogs.
as well as radio-conjugated somatostatin analogs. So, broadly speaking, the heterogeneity of the tumor type is reflected in the variety of treatment options available for these cancers.

Q: Is there evidence that these tumors respond to immunotherapy?

DR. PATEL: Based on the limited clinical trial data that we have, neuroendocrine cancers do not have a robust response rate to immune checkpoint blockade antibodies. These are agents that activate the immune system via the programmed death 1 (PD-1) and cytotoxic T lymphocyte–associated protein 4 (CTLA-4) pathways. Historically, the response rates to these therapies have been less than 5%.

Q: You are one of the principle investigators of the SWOG 1609 (S1609) trial, also called DART [Dual Anti-CTLA-4 and Anti-PD-1 blockade in Rare Tumors],[1] a study funded by the National Cancer Institute. Can you tell us more about the rationale behind this trial and the study design?

DR. PATEL: S1609 is investigating a dual checkpoint blockade approach that combines ipilimumab, an anti–CTLA-4 antibody, with nivolumab, an anti–PD-1 immunotherapy antibody, across a variety of cancer types in which these agents have not previously been studied. Neuroendocrine tumors are one such tumor type for which limited efficacy data for these immune checkpoint blockade antibodies exist.

I presented the latest data from this trial at the American Association for Cancer Research (AACR) Annual Meeting in April 2019. The most significant finding was that a subset of patients with neuroendocrine tumors, those with high-grade carcinoma, seem to benefit most from dual immunotherapy, with a response rate approaching 44%. Many of those responses, at least initially, appear to be long-lasting and continuous.[1]

Q: What about the toxicity of this immunotherapy combination? How did patients react to this combination therapy?

DR. PATEL: With immune checkpoint blockade antibody treatment, we often see unique immunologic-based toxicities, called immune-related adverse events (IRAEs). In S1609, we utilized a lower dose of ipilimumab than that conventionally utilized to treat patients with metastatic melanoma. Specifically, 1 mg/kg ipilimumab was administered every 6 weeks in combination with nivolumab at a fixed dose every 2 weeks. No fatal IRAEs occurred in this cohort, and there was no evidence of pneumonitis. In addition, the rate of high-grade colitis—one of the most concerning side effects seen with this combination therapy—was 6%. So, overall, the toxicity profile is manageable. Patients, particularly those who continue to respond to therapy, can continue to derive benefit without increasing their toxicity burden.

Q: What is the status of this cohort? How long are the patients being treated and followed up, and when will the next update be?

DR. PATEL: Currently, patients in the neuroendocrine cohort of S1609 continue to receive treatment as long as they derive clinical benefit, do not experience major toxicity, and wish to continue on this study. We scan the study participants every few months, so we plan to update the data at least annually. In particular, we’re interested in investigating the patients with high-grade neuroendocrine carcinoma, given that this is the cohort in which we saw responses.

Q: What have you and your colleagues learned about treating neuroendocrine tumors with immunotherapy? Based on S1609 and other studies, what do we now know about combination treatment with an anti–PD1 and anti–CTLA4 immune checkpoint antibody, and what’s next?

DR. PATEL: To date, neuroendocrine carcinoma clinical trials have faced the same issues that clinical trials for rare cancers and particularly immunotherapy have encountered. Historically, these studies were not done because of the heterogeneity, either related to their tumors or to the neuroendocrine cancer, which is a subset of a rare tumor that has heterogeneity itself. The potential that high-grade neuroendocrine carcinoma has, however, is that it is uniquely sensitive to immune checkpoint blockade, regardless of the organ in which the cancer develops. This may present a development strategy for us to help treat these patients more broadly, regardless of where the cancer begins.

Looking forward, I think that beyond just identifying patients with high-grade neuroendocrine tumors who may respond to this therapy, we will need to find ways to select patients whose responses to therapy are durable enough to warrant the toxicities associated with this treatment.

At the AACR 2019 Annual Meeting, you also presented data from this trial on the cohort of patients with nonpancreatic neuroendocrine tumors. Can you tell us about your findings and what the efficacy results show so far?

DR. PATEL: The cohort data presented at AACR included patients with both low-grade and high-grade nonpancreatic neuroendocrine cancers who were treated with immune checkpoint blockade. We found a 44% overall response rate among patients with high-grade carcinoma compared with a 8% response rate in patients with low- to intermediate-grade tumors.[1] Based on these findings, we are currently planning a new cohort study as part of S1609 that is dedicated to patients with high-grade neuroendocrine carcinoma to evaluate this effect further.
The management of patients with high-grade neuroendocrine tumors (NETs) remains challenging despite the significant objective responses seen with frontline therapy of platinum-based chemotherapy and etoposide combinations. Historically, there has been a paucity of clinical investigation of patients with neuroendocrine tumors partly because of the low incidence of this tumor type. It is therefore very encouraging that there may be another option for those patients based on the preliminary results from the DART study. The objective response rate of 44% and the durable responses seen in the DART study are intriguing because to date such a response rate has not been seen beyond the response rates using etoposide and platinum combination therapy in treatment naïve patients. However, we need more mature data from the DART study, and particularly overall survival data. Additionally, one cannot be certain at this time whether a dual blockade of PD-1 or PD-L1 inhibition combined with inhibition of CTLA-4 is necessarily better in terms of efficacy and safe compared to the use of a PD-1 or PD-L1 inhibitor alone. In a disease such as high-grade NET it may also be interesting to see whether the addition of immunotherapy to the frontline cytotoxic therapy will produce a better outcome compared to cytotoxic therapy alone. Another attractive option would be to use immunotherapy as a maintenance treatment following the conclusion of initial successful induction chemotherapy. The use of the DART regimen in the frontline setting without chemotherapy will not be an option because of the objective response rate of 44% that is inferior to what we get with the currently used combination therapy. In patients with high grade NET who often are symptomatic there is a need to achieve a timely and effective cytoreduction.

Results of the DART study also support what we know about the microenvironment in high-grade NETs which is that the microenvironment is very different compared to that in well-differentiated neuroendocrine tumors and that the microenvironment within NETs is more conducive to a response to immunotherapy. These data also are consistent with the benefits of immune checkpoint inhibitors in patients with small cell lung cancer, a biologically related disease. It would be interesting to see whether immunotherapy is also beneficial for grade 3 well differentiated NETs, although my guess is that it is not going to be as effective as in patients poorly differentiated NETs. There is a need to support future studies in this disease realizing the rarity of high-grade NETs. Any opportunity for a national trial, especially a prospective, randomized one, must be strongly supported by the oncology community. Research on how best to select patients for such therapy is also needed.

**FINANCIAL DISCLOSURE:** Dr. Philip has received research funding, and/or speaker or consultant fees from AAA, Merck, and BMS.

**Dr. Philip** is leader of the Multidisciplinary Team for Gastrointestinal Oncology at the Barbara Ann Karmanos Cancer Institute, and Professor at Wayne State University School of Medicine, Detroit, Michigan.
cancers, but also patients with other cancer types, once we can figure out the pertinent biomarker that helps drive the response to immunotherapy.

Q: Is there anything else you’d like to add about the uniqueness of treating patients with neuroendocrine cancers?

DR. PATEL: Another reason it has been difficult to conduct studies of rare tumors, including neuroendocrine tumors, is because they often cut across histologies or specialties or even subspecialties within oncology. So, the idea that patients with high-grade neuroendocrine carcinoma appear to benefit from combination immunotherapy, regardless of where the cancer initially developed, is interesting. It provides us with the opportunity to understand the biology and how to best treat these patients, potentially with a biomarker-selected strategy; this may be as simple as factoring in the grade of the tumor, but is likely more nuanced and related to actual immunobiology.

We are particularly interested in sharing this part of the translational analysis. The knowledge we gain may aid in guiding the discovery of new biomarkers and in finding patients with other cancer types who may benefit. Further, it will help us select for patients with neuroendocrine carcinoma who will benefit from this combination therapy, above and beyond just selecting patients based on the grade of their tumors.

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Burnout in Oncology

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physician burnout. This will require various individual strategies as well as concerted efforts across national, organizational, and departmental levels for change. Professional bodies such as the American Society of Clinical Oncology, the European Society for Medical Oncology, and the Society of Gynecologic Oncology have already taken important steps to promote cultural change through the introduction of sessions addressing burnout at international congresses and the provision of policy recommendations. We oncologists, just like our cancer patients, are strong, resilient, and capable of handling the very demanding aspects of our profession. Still, what is most needed are concerted efforts to address characteristics in the organizational culture and environment that contribute to distress and burnout. These include nonclinical work burden; EMR burden; compliance, regulation, and payment issues; loss of autonomy; productiv-
Introduction

The majority of cancer diagnoses and morbidity occurs in patients age 65 and older.[1] Elderly patients remain under-represented in cancer clinical trials and undertreated clinically for cancer, despite evidence that they experience similar chemotherapy efficacy to younger adults.[2–5] This may be related to the perception of increased risk for toxicity that can occur in some older adults. While there may be concern that elderly patients experience increased toxicities with treatment, this is likely not the case for all patients. The aging population is growing, and designing appropriate clinical trials that are more inclusive, in addition to recommending trials to elderly patients who might be eligible, continues to be an emerging need.

In the context of cancer treatment, older adults have several disadvantages when compared to their younger cohorts. They are more likely to have baseline comorbidities, they take more medications, and they may not tolerate chemotherapy as well as younger patients. These factors can complicate their treatment and render cancer therapy decisions in older patients, particularly challenging.[6]

Presently, most oncologists rely on global assessment measures such as Karnofsky Performance Status (KPS) or the Eastern Cooperative Oncology Group Performance Status (ECOG PS) tool to determine a patient’s performance status, and subsequently, their eligibility for chemotherapy or clinical trial participation. The thought is that individuals who are too frail to benefit would be affected by undesirable side effects and should not be enrolled. However, these tools may not be sufficient when assessing the older adult’s potential to undergo chemotherapy.

The comprehensive geriatric assess-
The CGA involves the assessment of an individual’s functional status; comorbidities, including fall risk; cognition; psychosocial state; social support; nutritional status; and it also includes a medication review.

A CGA includes a review of the patient’s medications at each visit, as polypharmacy can be a problem among the elderly.

Functional status assessments such as KPS can miss elderly patients with cancer who might be rated as functionally normal by that measure but have deficits identified on a CGA, and such deficits could affect treatment tolerance and patient outcomes. [8] Geriatric assessments, in a prospective study, were found to predict overall survival (OS) better than KPS, in elderly cancer patients. [7] Others present evidence on how the CGA can detect issues not reflected in ECOG assessments and how impairments in geriatric domains have predictive value for mortality and chemotherapy completion in older patients with cancer. [10]

The incorporation of a CGA in the evaluation and care of the senior adult with cancer acknowledges and may address some of the common, age-associated conditions occurring in the elderly.

Addressing geriatric syndromes or impairments identified in a CGA could have a positive impact on outcomes such as chemotherapy completion, morbidity or mortality, as well as on the frequency of emergency department visits and hospitalization rates among elderly cancer patients. [11] This review will describe the increasing role of the use of a CGA and its pertinent variables in the evaluation of the older adult with cancer.

**Comprehensive Geriatric Assessment and Select Geriatric Assessment Tools in the Oncology Practice**

Geriatric assessments have now been recommended in the evaluation of an older adult considering cancer therapy. [12,13] and the evidence is mounting with respect to the utility of the CGA in oncology practice. [14–16] Unfortunately, the incorporation of the CGA in the oncology practice remains infrequent. [17]

While the need for a more in-depth evaluation of an older person with cancer was identified over 20 years ago, [18,19] completion of a CGA is time-consuming and may not be feasible in the standard care of patients, resulting in its infrequent implementation. Initially, the use of a CGA in the care of the elderly cancer patient originated from extrapolating its ability to predict morbidity and mortality in the general geriatric population. [20] Older adults often suffer from common health conditions that have multifactorial causes, referred to as geriatric syndromes. Cognitive impairment, delirium, incontinence, malnutrition, falls, gait disorders, pressure ulcers, sleep disorders, sensory deficits, fatigue, and dizziness frequently ail the older adult. Geriatric syndromes can be identified by a CGA. [21] This evaluation can identify impairments across several domains that may contribute to the vulnerability and adverse outcomes of older individuals. [20,22]

Incorporating such an evaluation into the oncology practice could be useful in determining who might tolerate chemotherapy, who would be susceptible to toxicity, or what factors, if addressed, could increase the likelihood of completing treatment, as age itself has been shown to poorly predict treatment failure. [23,24] Because a CGA is a multi-component evaluation, it would not appear to be practical in a busy oncology practice. An abbreviation or modification of a CGA is an approach that can be adopted to make the assessment feasible in routine cancer practice.
Geriatric assessment (GA) is now recommended by for all older adults receiving chemotherapy, in a clinical practice guideline released by the American Society of Clinical Oncology (ASCO). As the accompanying review article discusses, GA can detect vulnerabilities not identified by a routine oncology assessment, and it outperforms common tools such as the Eastern Cooperative Oncology Group (ECOG) and Karnofsky performance status in predicting outcomes including survival and chemotherapy toxicity.

The Comprehensive Geriatric Assessment (CGA) is not always needed; a shorter GA with selected elements can provide valuable information for many older patients, as outlined in the ASCO guideline. Despite strong evidence supporting implementation, less than 25% of community oncologists in the United States report using GA for their older patients.

In my interviews with oncologists across the country about implementation of GA, time and resource limitations were frequently cited as barriers. However, surprisingly, oncologists more frequently cited a lack of buy-in as a barrier: they either did not believe that GA could add information to their assessment of a patient’s functioning, or they felt unsure about how to interpret and act on GA information. Given the dearth of geriatricians nationwide, it is important that we investigate how best to disseminate and implement GA and GA-driven interventions within oncology clinics.

One potential implementation could emerge from information technologies such as the electronic medical record (EMR). Most GA elements are patient-reported, and older adults are growing increasingly comfortable with digital technologies. We are investigating the use of EMR-integrated GA in our oncology clinics. The patients can complete the instruments in their own homes, via a web-based portal, or in the waiting room on a tablet computer, with data fed to the EMR. The EMR could further be leveraged to score instruments, view longitudinal changes, provide individualized recommendations, and/or link to automated order sets. If implemented thoughtfully, an EMR-integrated GA could offload busy oncologists and provide information support and data analysis.

This, in turn, will support treatment decision-making and beneficial outcomes for older adults with cancer.

**FIVE KEY REFERENCES**


**Geriatric Assessment: How can we increase implementation?**

Erika Ramsdale, MD

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Care. Ingram et al. and Hurria et al. were among the first to describe the feasibility of incorporating a GA in the evaluation of a cancer patient.[25,26] In their study, Hurria and others suggest that a GA can reasonably be incorporated into the busy oncology practice, with the majority of the assessment being self-administered. A mean time of 27 minutes (range: 8-45 minutes) to completion of the assessment was reported by that group.[26] Others have also determined that performing a brief GA in the community oncology setting is a feasible task.[27] Specific attributes or elements that comprise the CGA may confer greater utility than others, and select, more relevant domains can also be incorporated into screening tools that would be briefer than a CGA. Consequently, these tools could be quickly administered in an outpatient setting.[15] Similar tools have also been suggested to be feasible in the inpatient setting,[28] as well as in a variety of settings.[29] There are specific domains within a GA that have been shown to be predictive of chemotherapy toxicity when examined...
by Hurria [16,30] and others[31] and ultimately, resulted in the development of toxicity predictor tools such as the Cancer and Aging Research Group (CARG) toxicity tool[16] and the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score.[31] In particular, the CARG chemotherapy toxicity score is a validated tool that predicts the likelihood of chemotherapy toxicity and incorporates cancer and treatment-specific variables in addition to domains from the CGA, such as history of falls and difficulties with medication management.[16] Whereas the CRASH score includes several CGA risk factors such as IADL dependence and impaired cognition. In addition, these tools have also been shown to be superior to assessments commonly used in oncology practice that determine eligibility for chemotherapy (e.g. ECOG, KPS).[30]

A modified CGA tool demonstrated superiority as compared with the oncologist’s clinical judgment in identifying frailty. Kirkhus et al. revealed that frailty assessed by a modified GA—where patients were defined as frail if they met one of the following criteria: dependencies in ADLs, significant comorbidity, polypharmacy, physical function, or having one or more geriatric syndrome—was independently prognostic for survival, compared with oncologists’ subjective classification. Agreement between the modified CGA and the oncologist’s assessment was reported as fair, using kappa statistics (kappa value 0.30 [95% CI, 0.19; 0.41]), and only the modified tool’s determination of frailty was independently prognostic for survival.[32] An abridged CGA, in a prospective study, was also found to be a better predictor of OS compared to KPS, and in fact, the assessment tool was the only one that resulted in predictive of mortality of elderly patients.[7] Further, KPS assessments can potentially miss older cancer patients who might be rated as functionally normal by that measure but have deficits identified by a GA; these deficits could affect treatment tolerance and patient outcomes.[8] This is possibly related to the fact that KPS does not include a cognition assessment that may impact treatment adherence nor a nutritional assessment or social support inquiry which may influence tolerance and therapy completion.

Another notable aspect is the suggestion that older patients can be assigned lower performance status scores compared to their younger cohorts, even when measured physical activity may not differ between the two groups.[33,34] This highlights the potential of adopting a CGA to evaluate an older cancer patient and also suggests its superiority to commonly employed assessments of performance status (e.g. KPS).

Subsequent tools have emerged that involve an abbreviated CGA to assess geriatric cancer patients. Martinez-Tapia et al. evaluated the G8 and modified-G8 screening tools (tools that elicit items on nutrition, mobility, falls, polypharmacy, cognition) in a European study and revealed that abnormal scores were strong and consistent predictors of OS, regardless of metastatic status or tumor site.[33] The G8 score tool was validated in the ONCODAGE French prospective study that included adults ≥ 70 years with several solid malignancies and a minority (7.8%) of lymphoma patients.[35]

**Diversity of Settings and Malignancies Using CGA Tools or Its Variables in Older Patients with Cancer**

Several additional studies have illustrated the value of using a variation of the CGA or elements within a CGA in the geriatric oncology setting and in various cancer types and stages. In one of the landmark studies where the majority of patients had solid malignancies (81%), the abbreviated assessment was largely self-administered.[26] While subsequent earlier studies of CGAs in the context of cancer were initially performed in predominantly-solid malignancies, applications in hematologic malignancies have been progressively increasing over time and have demonstrated the utility of these tools,[11,24,26,28,36-51] as shown in the Table.

**Solid Malignancies**

Among the individual variables within a CGA that have resulted in abridged tools, slow gait speed has been shown to be an independent predictor of early death in older cancer patients with predominantly (98%) solid malignancies.[52] In patients ≥ 65 years (median age of 73), who had primarily lung, breast or colorectal cancer, a brief GA prior to chemotherapy was associated with completion of chemotherapy by 67.6% of the participants.[43] Visual and hearing impairments are additional variables that were found to have prognostic value among older oncology patients,[7] as was cognitive impairment, which was found to predict survival at the initiation of treatment (hazard ratio [HR] = 6.13; 95% confidence interval [CI] = 2.07-18.09; P = .001).[44] Paillaud et al. in a prospective study found a link between metastasis and malnutrition evaluated by an MNA in those with non-digestive malignancies (adjusted odds ratio [ORa] = 25.25; 95% CI, 5.97-106.8).[45]
A randomized study of metastatic colorectal carcinoma elderly patients demonstrated the MMSE (OR, 3.84) and impaired instrumental activities of daily living (IADLs (OR, 4.67) to be predictive of severe toxicity, with the MMSE (OR, 4.56) and Geriatric Depression Scale (OR, 5.52) being predictive of unexpected hospitalizations, suggesting cognitive function, independence impairment and depression to be important factors that should be considered when choosing a chemotherapy regimen in older adults.[11] In a separate study, a mini CGA performed by gastroenterologists was shown to be useful in adapting the anticancer treatments of elderly patients with digestive cancers.[46]

Schulkes and his group examined evidence from 18 studies and in their review, highlight how the CGA can detect issues not reflected in ECOG assessments and how impairments in geriatric domains such as physical capacity, nutritional status, cognition and IADL impairment have predictive value for mortality and chemotherapy completion in lung cancer patients.[10]

A CGA was also useful in predicting tolerance of treatment, mortality[47] and 3-year survival in geriatric patients with breast cancer.[53] Interestingly, Okonji and others evaluated CGAs in 326 women ≥ 70 years with breast cancer and found under-treatment in this group. Nearly 50% of fit women with high risk disease did not receive adjuvant chemotherapy.[54] This may allude to a hesitancy of oncologists to treat advanced-age patients, partly due to current, imperfect methods that are commonly used to assess these patients prior to chemotherapy initiation (e.g. KPS, ECOG). In the metastatic breast cancer setting, van de Water et al. maintain that a geriatric oncology approach might improve survival in elderly patients because 3-year mortality was 13% lower than for those receiving a standard approach.[55]

Among the patients who are deemed candidates for treatment, a CGA may facilitate the identification of those who are at risk for therapy discontinuation. When elderly patients with prostate cancer were assessed for frailty by CGA, a statistically-significant relationship between frailty assessed by CGA and early docetaxel discontinuation was found. [56].

A prospective study of older (median age of 76 years) patients with advanced ovarian cancer in which CGAs were used, showed domains such as depression (P = .003) and polypharmacy (P = .043) to be independent predictors of toxicity and OS.[48]

Studies incorporating GAs in the evaluation of patients with hematologic malignancies have followed those performed in patients with solid malignancies (Table). A recent analysis maintains that pretreatment CGAs accurately predict survival and treatment related toxicities in geriatric patients with diffuse large B cell lymphoma (DLBCL) who received anthracycline-based therapy, and treating them with anthracycline-containing regimens was associated with a three-year OS rate of 63% vs 44% for anthracycline-free regimens.[57] Ribi et al. also evaluated a “cancer specific” GA and quality of life in older patients with aggressive B cell lymphomas receiving rituximab-bendamustine-velidomide (R-BL) and determined that pre-treatment impaired functional status was an important factor of clinical outcomes, as 53% of patients who died had pre-treatment impaired functional status (vs. 0%, P = .003).[40] Additionally, a retrospective analysis suggested that certain factors affected survival in non-Hodgkin lymphoma (NHL). Comorbidity scores ≥ 6, doxorubicin exclusion, and cognitive impairment were strongly associated with survival in NHL.[49] It is of interest that besides having predictive value, application of the CGA to the hematologic malignancy setting could be used to adjust a treatment regimen, possibly impacting outcomes. This was exemplified by Spina et al., who suggest that the use of a CGA can be used to adjust chemoinmunotherapy, with potentially better cure rates in fit and unfit patients. In their study of 100 DLBCL patients, 81% of patients had a complete response and mild toxicity was seen in only 17%.[50] Individual elements within a CGA...
have been studied in hematologic malignancies and may also have predictive potential. The timed-up-and-go test (a measure of gait speed) was found to be strongly associated with poor survival in a German study of 75 patients with chronic lymphocytic leukemia (CLL). Median OS was found to be 53.8 months in those with speeds less than or equal to 10 seconds vs 18.2 months for those with twice the gait speed.[51] Hand grip strength is yet another variable that has been correlated with frailty in geriatric hematology patients. Velghe et al. proposed using grip strength as a screening tool after having revealed it to be associated with a concurrent abnormal CGA (P = .058 and .009 for women and men, respectively).[41] Park and others determined that an MNA comprised of a short form assessment was predictive of tolerability to multi-agent chemotherapy involving CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or “CHOP-like” regimens in elderly patients with aggressive NHL;[42] whereas Aaldriks et al. showed that both an inferior MNA and a mini cognitive screen (MMSE) were predictive of chemotherapy discontinuation (P = .001 and 0.04, respectively) with an inferior MNA presenting an increased mortality risk (HR = 2.19) after initiation of chemotherapy in patients with predominantly hematologic malignancies.[37]

Upon conducting a search in PubMed and Medline in November 2017, using the medical subject headings (MeSH) terms geriatric assessment AND oncology OR cancer, with limits of the search restricted to the human species, collectively, the majority of the studies suggest utility of a CGA in the assessment of an elderly cancer patient. There were, however, a few instances where a CGA did not have benefit, in terms of predictive value. Osborne et al. found that a CGA did not predict acute radiotherapy toxicity in men ≥ 70 years with localized prostate cancer.[58] It is possible that because the mechanisms for radiotoxicity are different from those involving chemotherapy or targeted therapy, a CGA may not identify patients at risk of radiotoxicity. This point highlights how the specificity of a particular treatment could affect results, and it illustrates the consideration that a CGA may have a role in certain regimens but less relevance in others. Guion-Dusserre and others, for example, did not find geriatric parameters within a CGA to be linked to OS in older patients with pancreatic or colorectal cancer who were treated with FOLFIRINOX (leucovorin, fluorouracil, irinotecan, oxaliplatin).[59] In one study

<table>
<thead>
<tr>
<th>Domains Assessed</th>
<th>Malignancy</th>
<th>N</th>
<th>Study Type</th>
<th>Key Findings</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional status, comorbidities, psychological, social support, nutrition, cognition</td>
<td>Predominantly solid (81%)</td>
<td>43</td>
<td>Feasibility</td>
<td>A brief CGA could be completed by the majority of patients without assistance.</td>
<td>[26]</td>
</tr>
<tr>
<td>Cognition, psychological, functional status, comorbidities</td>
<td>Hematologic (AML)</td>
<td>54</td>
<td>Feasibility</td>
<td>Inpatient, bedside GA was feasible and added to standard oncology assessment.</td>
<td>[28]</td>
</tr>
<tr>
<td>Cognition, psychological, functional status, comorbidities, nutrition, medications, social support, hemoglobin, serum creatinine</td>
<td>Solid (Digestive)</td>
<td>21</td>
<td>Pilot Study</td>
<td>A mini GA could help gastroenterologists adapt cancer treatment.</td>
<td>[46]</td>
</tr>
<tr>
<td>Cognition, psychological, functional status, comorbidities, nutrition, medications, quality of life</td>
<td>Solid</td>
<td>65</td>
<td>Feasibility</td>
<td>A CGA was feasible and could detect multiple unsuspected health problems.</td>
<td>[36]</td>
</tr>
<tr>
<td>Functional status, comorbidities, psychological, nutrition</td>
<td>Solid</td>
<td>110</td>
<td>Prospective study</td>
<td>Predictivity of CGA was found to be weak in predicting the occurrence of adverse events during chemotherapy.</td>
<td>[24]</td>
</tr>
<tr>
<td>Socio-demographic, comorbidities, functional status, psychosocial</td>
<td>Solid (Breast)</td>
<td>660</td>
<td>Survival</td>
<td>Cancer-specific GA predicted 5- and 10-year all-cause survival in older women.</td>
<td>[38]</td>
</tr>
<tr>
<td>Functional status, nutrition, psychological, medications, falls, cognition, comorbidities</td>
<td>Solid</td>
<td>375</td>
<td>Prospective study to identify CGA components associated with changes in planned cancer treatment</td>
<td>Functional status and malnutrition were independently associated with changes in planned cancer treatment.</td>
<td>[39]</td>
</tr>
<tr>
<td>Domains Assessed</td>
<td>Malignancy</td>
<td>N</td>
<td>Study Type</td>
<td>Key Findings</td>
<td>References</td>
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</tr>
<tr>
<td>Cognition, socio-demographics</td>
<td>Solid</td>
<td>357</td>
<td>Prospective</td>
<td>Survival was significantly influenced by cognitive impairment.</td>
<td>[44]</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Solid</td>
<td>643</td>
<td>Prospective cohort</td>
<td>Geriatric syndromes (cognitive impairment, depressed mood and fall risk) were independent risk factors for malnutrition. Metastatic status was significantly associated with malnutrition in non-digestive tumors than digestive tumors.</td>
<td>[45]</td>
</tr>
<tr>
<td>Cognition, functional status, psychological</td>
<td>Solid (colorectal)</td>
<td>123</td>
<td>Randomized study</td>
<td>MMSE, IADLS and GDS were significant predictive factors for grade 3-4 toxicity and unexpected hospitalization.</td>
<td>[11]</td>
</tr>
<tr>
<td>Comorbidities, psychological, functional status</td>
<td>Solid (breast)</td>
<td>660</td>
<td>Longitudinal study</td>
<td>GA domains are associated with poor treatment tolerance and predict mortality at 7 years of follow-up, independent of age and disease stage.</td>
<td>[47]</td>
</tr>
<tr>
<td>Comorbidities, medications, cognition, nutrition, functional status</td>
<td>Solid (ovarian)</td>
<td>83</td>
<td>Prospective study</td>
<td>CGA could predict severe toxicity and overall survival of elderly patients with advanced ovarian carcinoma.</td>
<td>[48]</td>
</tr>
<tr>
<td>Functional status, comorbidities, psychosocial, nutrition, cognition</td>
<td>Hematologic (DLBCL)</td>
<td>57</td>
<td>Prospective, multi-center</td>
<td>Pre-treatment impaired functional status impacts clinical outcomes in patients receiving rituximab-bendamustine- lenalidomide.</td>
<td>[40]</td>
</tr>
<tr>
<td>Functional status, psychological, cognition, nutrition, comorbidities</td>
<td>Hematologic (NHL)</td>
<td>93</td>
<td>Retrospective</td>
<td>Comorbidity and cognition was found to be a significant prognostic factor in NHL.</td>
<td>[49]</td>
</tr>
<tr>
<td>Functional status, cognition, psychological</td>
<td>Hematologic (DLBCL)</td>
<td>100</td>
<td>Prospective</td>
<td>The use of a CGA-tailored treatment resulted in lower rates of treatment-related mortality, manageable toxicity, and better outcomes in older patients, even among patients 80 years and older.</td>
<td>[50]</td>
</tr>
<tr>
<td>Gait speed</td>
<td>Hematologic (CLL)</td>
<td>75</td>
<td>Multi-center, randomized</td>
<td>Under performance in the Timed up and go test or dementia detection test was strongly associated with poor survival</td>
<td>[51]</td>
</tr>
<tr>
<td>Hand grip strength</td>
<td>Hematologic</td>
<td>59</td>
<td>Single center, cohort</td>
<td>Hand grip strength could be a promising screening tool to identify patients with abnormal CGA.</td>
<td>[41]</td>
</tr>
<tr>
<td>Nutrition, cognition, psychological</td>
<td>Hematologic (NHL)</td>
<td>70</td>
<td>Prospective</td>
<td>A mini nutritional assessment predicted tolerability to combination chemotherapy and overall survival in elderly patients with NHL.</td>
<td>[42]</td>
</tr>
<tr>
<td>Nutrition, cognition</td>
<td>Solid and hematologic</td>
<td>202</td>
<td>Prospective</td>
<td>Inferior nutrition assessment and MMSE scores increased the probability that patients would not complete chemotherapy.</td>
<td>[37]</td>
</tr>
</tbody>
</table>

AML = acute myeloid leukemia; CGA = comprehensive geriatric assessment; CLL = chronic lymphocytic leukemia; DLBCL = diffuse large B-cell lymphoma; GA = geriatric assessment; GDS = geriatric depression scale; IADLS = instrumental activities of daily living; MMSE = mini-mental state examination; NHL = non-Hodgkin lymphoma.
of 494 patients with advanced non-small cell lung cancer, results suggested that treatment allocation based on a CGA did not improve treatment failure free survival or OS, but did slightly reduce treatment toxicity.[60]

Although diverse and in multiple cancer types, these studies have not typically involved the gold-standard study design: the randomized clinical trial. The first multicenter, randomized clinical trial (NCT02025062) using a CGA in elderly patients with head and neck cancer is currently in the recruitment phase.[61] More importantly, whether managing the deficits detected on screening results in a meaningful impact, remains inconclusive, as illustrated by a French study in which dietary counseling was provided to at-risk patients who had been identified on a nutritional screen, but such counseling had no significant effect on mortality, toxicity or chemotherapy outcomes. [63] (this reference is a falls-risk reference instead of the Bourdel et al. study, listed as #62 in this version)

### Intervention after Identifying Abnormal Screenings on CGA or CGA Tools

Although CGA screens followed by management interventions have not been evaluated at length in randomized studies in geriatric oncology patients, several studies in the non-cancer setting report a benefit of incorporating CGA-prompted management and may also represent benefit in the oncology setting.[22,63–65] Geriatric assessment management interventions are employed by geriatricians to support or reverse any identified impairments. Similarly, impairments detected in the evaluation of an older cancer patient who is about to start chemotherapy can be addressed. Magnuson et al. recently conducted a randomized pilot study comparing GA with management interventions versus usual care in patients with stage III/IV solid tumor malignancies, and in that study, it was discovered that the incidence of grade 3-5 chemotherapy toxicity did not differ between the two groups. Prevalence of dose reduction, dose delays, hospitalization, and early treatment discontinuation also was not different between groups; however, the recommendations made to the primary oncologist by geriatricians had a low implementation rate.[66] It is possible that if execution of recommendations had been greater or if barriers to implementations had been identified, intervention could have led to improved outcomes. Notable is the fact that the sample size of that pilot study was modest (N = 71) and thus, differences may have not been detected with that sample size or in a pilot study design. Further, the two study arms were not balanced, given that the intervention arm had higher rates of IADL impairment and greater frequency of high-risk CARG toxicity scores, possibly minimizing the benefit of intervention. That study proved to be a feasible one, however, and recommendations for referrals that were more easily attainable (e.g. social work consults, nutrition consults) were implemented at a higher frequency compared to more “geriatric-specific” recommendations.

In a different study of CGA evaluation with intervention for reducing toxicity in older patients with advanced cancer, Kalsi et al. observed benefit from intervention with respect to chemotherapy tolerance, albeit in a non-randomized trial design. The authors revealed that the geriatrician-led CGA interventions were associated with improved chemotherapy tolerance and that patients were more likely to complete treatment (odds ratio, 4.14) with lower toxicity rates observed (43.8%) vs the non-intervention group (52.9%).[67] Although intuitive, whether intervening after detecting deficits identified in a CGA or CGA-abbreviated tools could impact outcomes in the oncology setting, remains unclear. No significant effect on OS was found when intervention was performed in the non-cancer population in a trial of 1388 patients, although intervention appeared to reduce functional decline and improve mental health without added costs.[68] As discussed, in the context of cancer, a study in which dietary counseling of elderly patients with cancer was offered had no effect on mortality or chemotherapy outcomes (e.g. progression, remission),[62] pointing to the need to further evaluate the effect of CGA-prompted interventions in oncology settings.

### Future Research

The elderly remain under-represented in cancer clinical trials. The need for inclusion of older patients in clinical studies and determining their treatment eligibility is a recurrent theme that is being highlighted more and more frequently. Many, such as Hurria, Extermann, Balducci, Power, Lichtman and others, emphasize the urgent need to include older patients in
It also remains to be determined more definitively whether there are cancer types or specific treatment regimens in which CGAs would confer the largest benefit.

clinical trials and to employ the CGA in the oncology setting to better understand its use in identifying patients who would likely derive benefits.\[1,15,16,20,69\] Ideally, trials that involve management of deficits identified on screening could help answer the question as to whether interventions have a significant impact on cancer outcomes. As mentioned, a randomized trial involving patients with head and neck cancer with intervention strategies is in progress (NCT02025062). Similarly, a trial that evaluates the feasibility of a midlevel practitioner to develop and implement GA-management interventions is also under way (NCT02517034). The current evidence predominantly supports the benefit of incorporating CGAs or abbreviated tools in the evaluation of the elderly cancer patient; this task appears to be feasible in the routine oncology setting.

It also remains to be determined more definitively whether there are cancer types or specific treatment regimens in which CGAs would confer the largest benefit. Bamias et al. suggest that a CGA might be useful to select patients with advanced urothelial carcinoma unfit for cisplatin who may be likely to benefit from first-line gemcitabine/carboplatin combinations [70], for example. More importantly, it remains to be determined whether identifying deficits on a CGA screen is consequential and intervening and addressing such deficits would alter outcomes of older cancer patients.\[50,51\] A CGA is comprised of multiple elements, across several domains and identifying the individual elements within a CGA that could have the greatest predictive value in the right setting or whether intervening on that single element is of benefit could prove to be challenging.

**Conclusions**

The CGA is being considered with greater frequency in the geriatric oncology setting since it was first proposed for this scenario. The CGA is now often implemented as a brief screening tool or cancer-specific GA tool whose limited domains can quickly be employed to assess the older cancer patient who is about to undergo a standard or experimental treatment regimen. Further research including randomized trials and interventional trials are needed to better identify the more cancer-relevant domains within a CGA and to clarify the cancer types and specific chemotherapy regimens in which oncology-themed CGA tools would confer the greatest utility.

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**FIVE KEY REFERENCES**


For a full list of references, visit: cancernetwork.com/Geri-Assess2019
The treatment landscape for chronic lymphocytic leukemia (CLL) has dramatically changed in the past decade. Ibrutinib, a once-daily oral Bruton tyrosine kinase (BTK) inhibitor, has proved to significantly improve outcomes for patients with CLL. The phase 3 RESONATE trial, which compared the single-agent ibrutinib to the anti-CD20 antibody ofatumumab in 391 high-risk, multiply relapsed/refractory patients with CLL (rrCLL) led to the approval of ibrutinib in the United States and Europe.[1] In the frontline setting, the RESONATE-2 study compared ibrutinib to chlorambucil in 269 patients age 65 years or older. Ibrutinib consistently demonstrated significant improvements in survival outcomes for patients in all subgroups, including those considered at high risk.[2–4] The extended follow-up of the RESONATE-2 trial indicated a 5-year progression-free survival (PFS) of 70% versus 12%, favoring the ibrutinib arm.[4]

Given the outstanding results of the RESONATE-2 trial, more recent trials have investigated ibrutinib-based combinations in the frontline setting. The Alliance Data and Safety Monitoring Board evaluated the efficacy of ibrutinib, either alone or in combination with rituximab, compared to chemo-immuno-therapy with bendamustine plus rituximab (BR) in 547 patients age 65 years or older with untreated CLL. Their results indicated superior PFS in patients randomized to ibrutinib-based arms compared to BR. There was no significant difference between ibrutinib and ibrutinib plus rituximab with regard to PFS.[5] In a similar fashion for the younger patient population, the Eastern Cooperative Oncology Group (ECOG)-American College of Radiology Imaging Network (ACRIN) Cancer Research Group (E1912) compared treatment with ibrutinib–rituximab to chemoimmuno-therapy with fludara-bine, cyclophosphamide, and rituximab (FCR) in 529 patients age 70 years or younger with treatment-naive CLL. The ECOG-ACRIN study of the ibrutinib–rituximab regimen resulted in improved outcomes for the younger patient population.

Chronic lymphocytic leukemia is clonal aberration associated with the build-up of number of circulating lymphocytes. It is associated with marked lymphocytosis and presence of smear cells.
PFS compared to FCR.[6] Based on the robust data from these two landmark trials, the field of CLL has undergone a paradigm shift, abandoning traditional chemoimmunotherapy options for novel targeted agents.

Outside clinical trials, the majority of patients with CLL are older than age 70 years and have multiple coexisting medical conditions. Such patients require effective treatment options with acceptable side-effect profiles. The CLL11 trial established chlorambucil–obinutuzumab as a standard of care in this frail patient population.[7] Venetoclax, an inhibitor of B-cell lymphoma 2 (BCL2) protein, was initially approved for patients with rrCLL harboring chromosome 17p deletion (deletion 17p) and later approved in combination with rituximab based on results of the phase 3 MURANO trial.[8,9]

The phase 3 CLL14 trial investigated the efficacy of the fixed-duration venetoclax–obinutuzumab combination compared to the previously established regimen of chlorambucil–obinutuzumab in patients with untreated CLL and coexisting conditions.[10] In total, 432 patients from 21 countries with a Cumulative Illness Rating Scale (CIRS) score of greater than 6 (range, 0–56, with higher scores indicative of diminished organ function) or a calculated creatinine clearance (CrCl) of less than 70 mL/min were randomly assigned to receive venetoclax–obinutuzumab or chlorambucil–obinutuzumab. Treatment duration in both groups consisted of 12 28-day cycles, and no crossover was allowed. The primary endpoint was PFS. Key secondary endpoints included minimal residual disease (MRD) negativity (with a cutoff of 10−4 [< 1 cell in 10,000 leukocytes]) in peripheral blood and bone marrow, overall and complete response rates, and overall survival. In terms of patient characteristics, the median age was 72 years; median CIRS score was 8; and median CrCl was 66 mL/min. In total, 14% of patients had TP53 deletion and/or mutation and 60% had unmutated immunoglobulin heavy chain variable region (IGHV) genes. With regard to the risk of tumor lysis syndrome, 13%, 64%, and 22% of patients in the venetoclax–obinutuzumab group were at low, medium, and high risk, respectively. A total of 78% of the patients in the venetoclax–obinutuzumab group and 75% in the chlorambucil–obinutuzumab group received the planned 12 treatment cycles. At a median follow-up of 28 months, 30 (14%) primary endpoint events (disease progression or death) were observed in the venetoclax–obinutuzumab group compared to 77 (36%) in the chlorambucil–obinutuzumab group (hazard ratio, 0.35; 95% CI, 0.23–0.53; P < .001). The 2-year PFS for the venetoclax–obinutuzumab group was significantly higher compared to the chlorambucil–obinutuzumab group: 88% (95% CI, 84–93) compared with 64% (95% CI, 57–71%). This benefit also included the patients with TP53 deletion/mutation in addition to patients with unmutated IGHV.

Three months following treatment completion, a higher number of patients in the venetoclax–obinutuzumab group had achieved MRD negativity in peripheral blood (76% vs 35%, P < .001) and in bone marrow (57% vs 17%, P < .001). The median overall survival was not reached in either group. The differences in grade 3 or 4 neutropenia, infections, and all-cause mortality were not statistically significant between the two arms.[10] Tumor lysis syndrome was reported in three patients in the venetoclax–obinutuzumab group (all cases occurred during treatment with obinutuzumab and before initiation of venetoclax) and in five patients in the chlorambucil–obinutuzumab group. None of these events met the Howard criteria for clinical tumor lysis syndrome. Adverse events leading to treatment discontinuation occurred in 16% of patients in the venetoclax–obinutuzumab group and 15% of patients in the chlorambucil–obinutuzumab group. The superiority in PFS benefit favoring the venetoclax–obinutuzumab group coupled with an acceptable toxicity profile resulted in the approval of venetoclax–obinutuzumab in patients with untreated CLL and multiple comorbidities by the US Food and Drug Administration in May 2019.

Although ibrutinib has been established as a reliable and convenient orally administered agent in the frontline setting for patients with treatment-naïve CLL, the indefinite course of therapy can pose a challenge. In a real-world
the activity and safety of venetoclax in patients with rCLL whose disease progressed during or after discontinuation of ibrutinib therapy. An interim analysis of this trial indicated that venetoclax has durable clinical activity and favorable tolerability in this patient population, with an overall response rate of 65% (95% CI, 53–74). Similar studies, however, supporting the activity and safety of ibrutinib following venetoclax failure are not yet available.

With the growing armamentarium of treatment options in the frontline setting for patients with CLL, clinical research should focus on time-limited combination therapies with a favorable toxicity profile that provide patients with durable remissions. It is also critical to delineate optimal therapies in the second line and beyond to maximize clinical benefit from advances in the field. In an effort to address these unmet needs, the Alliance and ECOG groups are currently conducting two important phase 3 clinical trials, each targeting a separate age group. These trials are designed to investigate the efficacy and safety of adding venetoclax to the currently established regimen of obinutuzumab–ibrutinib in older patients with chronic lymphoid leukemia. Presented at the 2019 European Hematology Association Annual Congress; June 13–16, 2019; Amsterdam, the Netherlands: abstract S107.

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Prostate cancer is the most common malignancy and second leading cause of cancer death among males in the United States. Based on the data to date, it is likely that by the end of 2019, as many as 300,000 new cases of prostate cancer will have been diagnosed in the United States, with a potential 62,000 deaths[1]. The incidence of prostate cancer rises with age. Risk factors include family history, African American heritage, and a diet high in fat.

The most prevalent prostate malignancies are adenocarcinomas. Treatment options include active surveillance; surgical and radiation therapy; hormonal treatment with androgen deprivation at the pituitary/hypothalamus, prostate cells, testes, and adrenal gland levels; chemotherapy; and immunotherapy.[2]

A number of important clinical trials are underway and recruiting participants:

- Outcomes of Focal Therapies for Prostate Cancer. ClinicalTrials.gov Identifier: NCT03492424. Weill Cornell Medicine, New York, New York.
- Imaging Studies to Check the Local Response of Prostate Cancer to Radiation Therapy. ClinicalTrials.gov Identifier: NCT01834001. National Institutes of Health Clinical Center, Bethesda, Maryland.
- PD-L1 Inhibition as Checkpoint Immunotherapy for Neuroendocrine Phenotype Prostate Cancer (PICK-NET). ClinicalTrials.gov Identifier: NCT03179a10. Duke University Medical Center, Durham, North Carolina.
- Nivolumab in Patients With High-Risk Biochemically Recurrent Prostate Cancer. ClinicalTrials.gov Identifier: NCT03637843. Beth Israel Deaconess Medical Center, Boston, Massachusetts, 2 U.S. locations.
- Effect of Androgen Deprivation Therapy on Cardiovascular Function in Prostate Cancer. ClinicalTrials.gov Identifier: NCT03275118. Kansas State University, Clinical Integrative Physiology Laboratory, Manhattan, Kansas.
- Trial of Curcumin to Prevent Progression of Low-risk Prostate Cancer Under Active Surveillance. ClinicalTrials.gov Identifier: NCT03790766. UT Southwestern Medical Center, Dallas, Texas.
- BrUOG 337: Olaparib Prior to Radical Prostatectomy For Patients With Locally Advanced Prostate Cancer and Defects in DNA Repair Genes (337). ClinicalTrials.gov Identifier: NCT03432897. Lifespan Cancer Institute: The Miriam and Rhode Island Hospitals, Providence, Rhode Island.
- Prostate Cancer Intensive, Non-Cross Reactive Therapy (PRINT) for Castration Resistant Prostate Cancer (CRPC). ClinicalTrials.gov Identifier: NCT02903160. Mount Sinai Beth Israel, New York, New York, 3 U.S. locations.
- Study of VERU-944 to Ameliorate Hot Flashes in Men With Advanced Prostate Cancer. ClinicalTrials.gov Identifier: NCT03646162. Genentech Research, Glendora, Arizona, 20 locations in the U.S.
- Pre-Operative Radio Therapy for High-Risk Prostate Cancer (PORT-PC Trial) (PORT-PC). ClinicalTrials.gov Identifier: NCT03862118. Weill Cornell Medicine, New York, New York.

REFERENCES
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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. 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.

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References:

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