RICK KITTLER, PHD, ON

Disparities in Prostate Cancer

‘This could actually predict risk of certain outcomes’
As soon as you see a rapidly rising PSA in patients receiving ADT...

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

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

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

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

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

Laboratory Abnormalities—All Grades (Grade 3-4)
• Hematology—anemia ERLEADA™ 70% (0.4%), placebo 64% (0.5%); leukopenia ERLEADA™ 47% (0.3%), placebo 29% (0%); lymphopenia ERLEADA™ 41% (2%), placebo 21% (2%)
• Chemistry—hypercholesterolemia ERLEADA™ 76% (0.1%), placebo 46% (0%); hyperglycemia ERLEADA™ 70% (2%), placebo 59% (1%); hypertriglyceridemia ERLEADA™ 67% (2%), placebo 49% (0.8%); hyperkalemia ERLEADA™ 32% (2%), placebo 22% (0.5%); Rash—Rash was most commonly described as macular or maculo-papular. Adverse reactions were 24% with ERLEADA™ versus 6% with placebo. Grade 3 rashes (defined as covering >30% body surface area [BSA]) were reported with 8% of patients treated with ERLEADA™ and 7% of patients treated with placebo. The median onset was day 113. There were no Grade 3 or 4 adverse reactions.

Drug Interactions
Effect of Other Drugs on ERLEADA™—Co-administration of a strong CYP2C8 or CYP3A4 inhibitor is predicted to increase the steady-state exposure of the active moieties. No initial dose adjustment is necessary; however, reduce the ERLEADA™ dose based on tolerability (see Dosage and Administration [2.7]).

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

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

PSA doubling time ≤10 months.

Study Design: SPARTAN was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial of patients with non-metastatic CRPC (N=1207). Patients had a PSA doubling time ≤10 months and serum testosterone levels ≤50ng/dL. All patients in the SPARTAN trial received a concomitant GnRH analog or had a bilateral orchectomy. All patients enrolled were confirmed to be non-metastatic by blinded central imaging review. Patients were randomized 2:1 to receive ERLEADA™ 240 mg orally once daily + ADT or placebo orally once daily + ADT. The primary endpoint was metastasis-free survival (MFS), defined as the time from randomisation to the time of first evidence of blinded independent central review-confirmed distant metastasis, defined as new bone or soft tissue lesions or enlarged lymph nodes above the iliac crest, or death due to any cause, whichever occurred first. ADT = androgen-deprivation therapy; CRPC = castration-resistant prostate cancer; GnRH = gonadotropin-releasing hormone; HR = hazard ratio; PSA = prostate-specific antigen; SPARTAN = Selective Prostate Androgen Receptor Targeting with ARN-509.

References:

Visit erleadahcp.com

Please see Brief Summary of full Prescribing Information for ERLEADA™ on subsequent pages.
Brief Summary of Prescribing Information for ERLEADATM (apalutamide)
ERLEADATM (apalutamide) tablets, for oral use

See package insert for Full Prescribing Information

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

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

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

In a randomized study (SPARTAN), falls occurred in 16% of patients treated with ERLEADA compared to 9% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure. Fractures occurred in 12% of patients treated with ERLEADA and in 7% of patients treated with placebo. Grade 3-4 fractures occurred in 3% of patients treated with ERLEADA and in 1% of patients treated with placebo. The median time to onset of fracture was 314 days (range: 20 to 953 days) for patients treated with ERLEADA. Routine bone density assessment and treatment of osteoporosis with bone targeted agents were not performed in the SPARTAN study.

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

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

ADVERSE REACTIONS
The following are discussed in more detail in other sections of the labeling:
- Falls and Fractures [see Warnings and Precautions].
- Seizure [see Warnings and Precautions].

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

SPARTAN, a randomized (2:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had non-metastatic, castration-resistant prostate cancer (NM-CRPC). In this study, patients received either ERLEADA at a dose of 240 mg daily or a placebo. All patients in the SPARTAN study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchiectomy. The median duration of exposure was 16.9 months (range: 0.1 to 42 months) in patients who received ERLEADA and 12.3 months (range: 0.1 to 37 months) in patients who received placebo.

Overall, 8 patients (1%) who were treated with ERLEADA died from adverse reactions. The reasons for death were infection (n=4), myocardial infarction (n=3), and cerebral hemorrhage (n=1). One patient (0.3%) treated with placebo died from an adverse reaction of cardiopulmonary arrest (n=1). ERLEADA was discontinued due to adverse reactions in 11% of patients, most commonly from rash (3%). Adverse reactions leading to dose interruption or reduction of ERLEADA occurred in 33% of patients; the most common (>1%) were rash, diarrhea, fatigue, nausea, vomiting, hypertension, and hematoma. Serious adverse reactions occurred in 25% of ERLEADA-treated patients and 23% in patients receiving placebo. The most common serious adverse reactions (>2%) were fracture (8%) in the ERLEADA arm and urinary retention (4%) in the placebo arm.

Table 1 shows adverse reactions occurring in ≥10% on the ERLEADA arm in SPARTAN that occurred with a 2% absolute increase in frequency compared to placebo. Table 2 shows laboratory abnormalities that occurred in ≥15% of patients, and more frequently (>5%) in the ERLEADA arm compared to placebo.
Rash
In SPARTAN, rash associated with ERLEADA was most commonly described as macular or maculo-papular. Adverse reactions of rash were reported for 24% of patients treated with ERLEADA versus 6% of patients treated with placebo. Grade 3 rashes (defined as covering > 30% body surface area [BSA]) were reported with ERLEADA treatment (5%) versus placebo (0.3%).
The onset of rash occurred at a median of 62 days of ERLEADA treatment. Rash resolved in 81% of patients within a median of 60 days (range: 2 to 709 days) from onset of rash. Four (4%) of patients treated with ERLEADA received systemic corticosteroids for treatment of rash. Rash recurred in approximately half of patients who were re-challenged with ERLEADA.

Hypothyroidism
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 Day 113. There were no Grade 3 or 4 adverse reactions. Thyroid replacement therapy was initiated in 7% 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 CYP2C8 or CYP3A4 Inhibitors
Co-administration of a strong CYP2C8 or CYP3A4 inhibitor is predicted to increase the steady-state exposure of the active moieties (sum of unbound apalutamide plus the potency-adjusted unbound N-desmethyl-apalutamide). No initial dose adjustment is necessary however, reduce the ERLEADA dose based on tolerability [see Dosage and Administration (2.2) in Full Prescribing Information]. Mild or moderate inhibitors of CYP2C8 or CYP3A4 are not expected to affect the exposure of apalutamide.

Effect of ERLEADA on Other Drugs
CYP3A4, CYP2C9, CYP2C19 and UGT Substrates
ERLEADA is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C8 in humans. Concomitant use of ERLEADA with medications that are primarily metabolized by CYP3A4, CYP2C19, or CYP2C9 can result in lower exposure to these medications. Substitution for these medications is recommended when possible or evaluate for loss of activity if medication is continued. Concomitant administration of ERLEADA with medications that are substrates of UDP-glucuronosyl transferase (UGT) can result in decreased exposure. Use caution if substrates of UGT must be co-administered with ERLEADA and evaluate for loss of activity [see Clinical Pharmacology (12.3) in Full Prescribing Information].

P-gp, BCRP or OATP1B1 Substrates
Apalutamide 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) by 30% (36/120) and rosvastatin (a BCRP/OATP1B1 substrate). Concomitant use of ERLEADA with medications that are substrates of P-gp, BCRP, or OATP1B1 can result in lower exposure of these medications. Use caution if substrates of P-gp, BCRP, or OATP1B1 must be co-administered with ERLEADA and evaluate for loss of activity [see Clinical Pharmacology (12.3) in Full Prescribing Information].

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

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

Females and Males of Reproductive Potential
Contraception
Males
Based on the mechanism of action and findings in an animal reproduction study, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA. [see Use in Specific Populations].

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.

Geriatic Use
Of the 803 patients who received ERLEADA in SPARTAN, 87% of patients were 65 years and over and 49% were 75 years and over. Grade 3-4 adverse reactions occurred in 46% (323/697) of patients 65 years or older and in 51% (197/391) of patients 75 years or older treated with ERLEADA compared to 35% (124/355) of patients 65 years or older and 37% (70/187) of patients 75 years or older treated with placebo. No overall differences in effectiveness were observed between these patients and younger patients.

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

PATIENT COUNSELING INFORMATION
Adviser the patient to read the FDA-approved patient labeling (Patient Information).

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) agonist 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 patients having sex 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 Use in Specific Populations].

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

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Addressing the Disparities in Prostate Cancer Care and Outcomes

Dr. Kittles discusses the race-based health disparities in prostate cancer, and one genetic-environmental crossover that is clinically significant.

There are significant race-based disparities in prostate cancer care and outcomes. Recent research has shed more light on the divergent causes of these disparities. ONCOLOGY spoke with Rick Kittles, Professor and Founding Director of the Division of Health Equities within the Department of Population Sciences at City of Hope Comprehensive Cancer Center in Duarte, California, where he is also Associate Director of Health Equities. Among other health disparity topics, Dr. Kittles conducts research on why African-Americans have a disproportionately higher burden of prostate cancer compared to European-Americans.

Q: First, could you lay out the research questions that you address, as they relate to health disparities and prostate cancer specifically among African-Americans? What are the main issues?

Dr. Kittles: There are several issues dealing with prostate cancer disparities that we focus on. What we are attempting to do is try to understand why there’s an increased burden and incidence of prostate cancer for men of West African descent in particular. There are mortality differences, too, and other different outcomes compared with other populations. We’re trying to understand if there is a strong genetic component to this, or is it environmental or the interaction of both of these factors? We’re doing a lot of genetic studies and behavioral and dietary studies in this area.

Q: You and your colleagues recently conducted a study analyzing the role of

The region of risk is on the 8q24 region of chromosome 8.
calcium and vitamin D in prostate cancer pathogenesis and progression. Could you tell us about the genesis of this study and what you found?

Dr. Kittles: The calcium study emerged after we started studying vitamin D. Vitamin D, calcium, and parathyroid hormone interact and regulate each other in one way or another, and this relates not only to what we historically have known in terms of bone mineralization and bone development, but also to immune surveillance. This is something that we started to really focus in on—specifically the role vitamin D plays in immune surveillance. Our calcium study showed that there was this higher incidence or higher risk of aggressive prostate cancer among African-American men whose daily calcium intake was over 800 mg.[1] This was quite surprising, but there have been other studies that have shown similar results.

Q: Can you talk about vitamin D research and how vitamin D might be linked to prostate cancer?

Dr. Kittles: Is vitamin D linked to prostate cancer? Some have said that there’s an association and others say there is not. A lot of the differences in results has to do with how you are collecting and analyzing data. Our group has found that there are many different modifiers of serum vitamin D levels, and there are differences in levels of prostatic vitamin D, the amount of vitamin D in the prostate. And those levels, whether they are sufficient or deficient, could lead to differences in gene expression, many of which are related to immune response, inflammation, and immune surveillance. Vitamin D deficiency can lead to altered immune surveillance in the prostate tissue, which could potentially lead to prostate cancer.

Q: Are there other factors that may affect this higher prevalence of prostate cancer among African-Americans that you have found in your research?

Dr. Kittles: When we look at the difference between African-American men and men of European descent, we find that genes are playing a strong role. In fact, upwards of maybe 40% to 50% of the difference we see is genetic. There are some strong genetic signals that emerged over the last 10 years related to a region on chromosome 8 that appear to be enriched in men of West African descent. (The region of risk on chromosome 8, specifically, is the 8q24 region.) There may be some sort of increased inherited predisposition based on ancestry that could be driving a lot of the differences that we see. We don’t know the mechanism of action, but we do know that the markers and biomarkers are pretty consistent and replicable.

Q: Using those genetic markers, has your group or other groups followed up this work to potentially screen men for higher risk of prostate cancer or does this still need to be confirmed in additional studies?

Dr. Kittles: Well, a lot of this work on biomarkers was work from a consortium, what we call GWAS or genome-wide association studies on prostate cancer where multiple groups around the country put their
Although we have known for decades that African American men with prostate cancer are at an extreme disadvantage, scientists are still seeking the translational answers that might reverse this reality. The literature includes a wide variety of genetic, social, and environmental theories that they hope will explain, individually or in combination, the higher risk and poorer outcomes seen in these patients. Dr. Kittles has discussed some of these in his interview, and focuses specifically on a genetic predisposition and vitamin D. This and other factors have been examined, including diet, exercise, testosterone levels, androgen receptor variations, immunological responses, and many more.

A major component includes access to medical care and treatment. In some equal access situations, such as the military, disparities in survival seemed to be lessened and in some cases eliminated. We published an article in 2004 looking at outcomes of African-American men in the Henry Ford system regarding local prostate cancer outcomes. Some of the discrepancies appear to be related to choices of therapy. When African American men, who represented 30% of the men in the system, chose the same treatment as Caucasians, they had similar survival. [1] Interestingly, Dr Oliver Sartor, reported recently that African-American men with advanced prostate actually had a survival advantage over Caucasian men when treated with immunotherapeutic regimen of sipuleucel-T (Provenge). As we continue to explore all the research on prevalence and prognosis, we may find that we can increase favorable outcomes based on multiple factors. I applaud Dr. Kittles’s work and appreciate the comments.

Q: Are you conducting other studies to identify other potential factors or the role of the environment in this health disparity connection?

Dr. Kittles: The vitamin D study was actually a gene environment study. We’re looking at genes, their pathways, the steroid synthesis pathway, and the steroid signaling pathways. We are also looking at dietary behavioral factors that influence vitamin D levels in serum and in the prostate. This is a really good model of a disparity project that has a strong gene-environment interaction. We are also studying methylation and dietary folate, folic acid in particular. We are looking at some of the clinical outcomes as they relate to the heterogeneity among these tumors. What we’re finding

E. David Crawford
Unraveling the Research on Prostate Disparities

Vitamin D metabolites migrate to the prostate. 25(OH)D is metabolized to 1,25(OH)2D, which binds to vitamin D receptor (VDR) in conjunction with coactivators. The complex created by vitamin D and VDR modulates immune response by regulating the target genes of vitamin D expression.
is that there’s no overburden of particular genetic changes in these prostate tumors. There’s a subset of different types of signals and mutations in various tumors in the African-American men who have prostate cancer. What we’re trying to do now is to uncover some of the outcomes from these particular signatures. For example, HER2, which is a clear breast cancer subtype and is used as a biomarker in breast cancer, actually has a therapeutic potential. We need to identify markers like this for prostate cancer.

**Q:** More recently, you had a study that looks at different cancer cell lines and highlighted disadvantages for minorities in accessing personalized therapy strategies for prostate and other tumor types. Can you tell us about that work and what you found?

**Dr. Kittles:** The challenges and problems have been the lack of diversity in biorepositories and biospecimens. This has limited the progress in disparities research. What we wanted to do was really examine if, in fact, cell lines that were labeled or characterized as African-American were really from African-American patients. And, in fact, many were not,[2] and so this is hopefully bringing some attention to this fact that we still, in particular for prostate cancer, have this enormous disparity difference among ethnic groups. We really need to focus in on collecting more diverse samples for our research models of prostate cancer, and also other tumor types.

**Q:** Lastly, can you talk about your efforts and efforts by the broader scientific community to make bioscience research more inclusive to different ethnic populations?

**Dr. Kittles:** My whole career has been focused on studying disparities in Black and Hispanic populations. I focus on going out, educating the community, getting them excited about research, and then getting them to participate. For me, there is no challenge in terms of getting access to samples, of getting people excited about the research. I think a lot of times the community really just needs to see themselves in the research. When I say that I mean they need to see something that is impactful for them, something that they want to see resolved in their community. They also want to see themselves reflected in the research, as it relates to participating researchers, clinicians, nurses, and students. Let’s say the principal investigator of a study is not of African-American descent and staff isn’t either. This does play a role in the ability of the researcher to recruit a diverse population and get diverse samples.

**Q:** Anything else you would like to add on your research and increasing diversity in scientific research?

**Dr. Kittles:** I think this issue of increasing diversity in scientific research is going to have a major role in the future of research here in the United States. As everybody knows, the country is becoming more and more diverse. If we do not have adequate representation, not just in biomedical samples and biospecimen repositories, but also in representation in the pipeline and workforce, that lack of diversity is going to have some major ramifications downstream. I get excited when I go out into the community and talk about these issues. I’m trying to get folks to be more aggressive in terms of their advocacy for themselves and support for diversity in the biomedical workforce.

**FINANCIAL DISCLOSURE:** Dr. Kittles has no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.
Anti-Angiogenesis Therapy in Ovarian Cancer: Which Patient Is It Most Likely to Benefit?

Anca Chelariu-Raicu, MD, PhD, Robert L. Coleman, MD, and Anil K. Sood, MD

ABSTRACT: Angiogenesis is known to play an important role in normal ovarian physiology as well as in growth and progression of ovarian cancer. The first FDA approval of bevacizumab in 2004 was for metastatic colorectal cancer in combination with chemotherapy; this was a key point for several subsequent approvals of antiangiogenic drugs. The efficacy of bevacizumab treatment is modest, however, and most ovarian cancer patients eventually develop acquired resistance, which highlights the need for new targeted therapies and/or combination strategies. Understanding the multitude of variables in response to antiangiogenic therapy would offer potential strategies for selecting patients most likely to benefit from such therapy.

Introduction

The principles of antiangiogenic therapy are rooted in observations made by Folkman and others over 40 years ago.1 Since then, antiangiogenic therapies have been incorporated into clinical care for many cancer patients. The vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR) pathway is arguably the most advanced for clinical development. This pathway has been extensively studied for its role in development of malignant ascites and tumor progression.2 The VEGF molecule is a key angiogenic factor, which is involved in development of physiologic and pathologic neovascularization. VEGF is a growth as well as proliferation factor for endothelial cells and it binds to VEGFR-1 and VEGFR-2 as well as the cofactors neuropilin-1 (NRP-1) and NRP-2.3 VEGFR-2 is expressed mostly on endothelial cells; VEGFR-1 can be expressed on macrophages, tumor cells, and fibroblasts.4 While one of the main antiangiogenic approaches is to block VEGF using a monoclonal antibody, other drugs including VEGF pathway inhibitors such as small-molecule tyrosine kinase inhibitors (eg, sunitinib, sorafenib, pazopanib, regorafenib, lenvatinib, vandetanib), soluble VEGF decoy receptor (eg, aflibercept), and human monoclonal antibody against VEGFR-2 (ramucirumab) have also been developed.

Among the various antiangiogenic drugs, bevacizumab, a humanized anti-VEGF monoclonal antibody, is the most widely studied across tumor types and specifically in epithelial ovarian cancer. Beginning in 2004, the US Food and Drug Administration (FDA) granted several approvals for antiangiogenic drugs with a main indication in metastatic disease for colorectal cancer, non–small-cell lung, renal cell, cervical, and ovarian cancers, and glioblastoma. Recently, in June 2018, bevacizumab was approved for the first time also for frontline therapy for ovarian cancer in combination with platinum and taxane-based chemotherapy. Despite positive initial response rates using bevacizumab in advanced ovarian cancer, patients unfortunately develop relapsed disease within weeks to months. Nevertheless, preclinical data suggest that prolonged administration of bevacizumab as maintenance therapy after platinum-based chemotherapy prolongs progression-free survival (PFS).5 This review summarizes the major clinical
trials that led to the approval of antiangiogenic drugs and gives a brief view into novel combinations of bevacizumab with other targeted therapies in an attempt to enhance the efficacy of bevacizumab.

**Standard of Care**

Ovarian cancer is the most deadly gynecologic malignancy with 5-year survival rates ranging from 47% for all stages compared to only 29% for those with advanced-stage disease (III or IV) and is responsible for approximately 14,000 deaths in the United States annually.[6] The standard-of-care treatment remains primary tumor reductive surgery followed by adjuvant platinum and taxane-based chemotherapy. However, the recurrence rate is approximately 80%, even for patients who respond to initial treatment.[7]

**Bevacizumab as Upfront Therapy**

GOG-218 and ICON7 were the first two positive advanced-stage frontline ovarian cancer randomized phase III trials that added bevacizumab to chemotherapy.[8,9] In both GOG-218 and ICON7, bevacizumab was added to the standard of care, which consists of 6 cycles of platinum and taxane-based chemotherapy. In GOG-218, the duration of bevacizumab treatment was up to 22 cycles using a dose of 15 mg/kg, and in ICON7, 18 cycles of bevacizumab were given using a dose of 7.5 mg/kg. Although the two trials used different treatment duration and dosing, they both showed an increase in PFS. In GOG-218, the median PFS after adding bevacizumab in frontline and maintenance was increased by 4 months, from 10.3 to 14.1 months (hazard ratio (HR), 0.72; 95% CI, 0.63–0.82).[8] In ICON7, PFS at 36 months was 20.3 months with standard therapy plus bevacizumab (HR, 0.81; 95% CI, 0.70–0.94; P = .004).[9] The same study suggested that the benefit of adding bevacizumab was the greatest for patients with high risk of progression (International Federation of Gynecology and Obstetrics [FIGO]) stage III > 1 cm or IV or suboptimally debulked surgery) where the estimated median PFS was 10.5 months with standard therapy, as compared with 15.9 months with bevacizumab (HR, 0.68; 95% CI, 0.55–0.85; P < .001).[1] Another intriguing observation of the study was that the effect on PFS was lost when the therapy with bevacizumab was withdrawn.[9,10] In this context, the optimal strategy for bevacizumab might be to continue the treatment until disease progression, as indicated by the data in the OCEANS trial results, the effects of adding bevacizumab to chemotherapy incorporating bevacizumab with the same toxicity.[12] As already mentioned from the OCEANS trial results, the effects of adding bevacizumab to chemotherapy and continuation as maintenance were reproducible. This was also the case in patients enrolled in the GOG-213 trial, where the median overall survival (OS) in the chemotherapy plus bevacizumab group was 42.2 months (95% CI, 37.7–46.2) vs 37.3 months (95% CI, 32.6–39.7) in the chemotherapy group (HR, 0.829; 95% CI, 0.683–1.005; P = .056).[12] Results from the ENGOT-ov15/AGO-OVAR 17 trial will most probably give an answer to the optimal treatment duration with bevacizumab, as this trial consists of 2 experimental arms, one being frontline chemotherapy combined with bevacizumab for 15 months while the second arm incorporates bevacizumab with the same frontline chemotherapy, but for a longer period (30 months). Considering the increase in PFS and OS after administration of bevacizumab in frontline therapy in GOG-218 and ICON7, the European Medicines

**TABLE 1 Antiangiogenic Drugs Approved by FDA (2004–Present)**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic colorectal cancer (with chemotherapy)</td>
<td>Bevacizumab, regorafenib, aflibercept ziv-aflibercept, ramucirumab</td>
</tr>
<tr>
<td>Metastatic nonsquamous non–small–cell lung cancer (with chemotherapy)</td>
<td>Bevacizumab, ramucirumab</td>
</tr>
<tr>
<td>Recurrent glioblastoma (monotherapy)</td>
<td>Bevacizumab</td>
</tr>
<tr>
<td>Metastatic renal cell carcinoma</td>
<td>Bevacizumab, sunitinib, sorafenib, Pazopanib, axitinib, lenvatinib, cabozantinib</td>
</tr>
<tr>
<td>Metastatic, persistent, recurrent cervical cancer (with chemotherapy)</td>
<td>Bevacizumab</td>
</tr>
<tr>
<td>Ovarian cancer (recurrent and frontline)</td>
<td>Bevacizumab</td>
</tr>
<tr>
<td>Gastrointestinal stromal tumors (monotherapy)</td>
<td>Sunitinib, regorafenib</td>
</tr>
<tr>
<td>Pancreatic neuroendocrine tumors (monotherapy)</td>
<td>Sunitinib</td>
</tr>
<tr>
<td>Unresectable hepatocellular carcinoma (monotherapy)</td>
<td>Sorafenib, lenvatinib, ramucirumab, regorafenib, cabozantinib</td>
</tr>
<tr>
<td>Advanced medullary thyroid cancer (monotherapy)</td>
<td>Sorafenib, vandetanib, lenvatinib</td>
</tr>
</tbody>
</table>
The incorporation of antiangiogenic therapy in the treatment of solid tumor malignancies dates back to 2004, when bevacizumab, an anti-vascular endothelial growth factor (VEGF) monoclonal antibody, received US Food and Drug Administration (FDA) approval in advanced colorectal cancer after demonstrating an improvement in both overall and progression-free survival (PFS).[1] Studies in epithelial ovarian cancer have shown a correlation between VEGF expression and more advanced disease leading to worse survival rates.[2] After initial skepticism, bevacizumab was finally granted FDA approval in 2011 for recurrent ovarian cancer and has since received approval in 2018 as front-line therapy after initial surgical resection.[3] Other antiangiogenic agents of interest include pazopanib, nintedanib, cediranib, and navicizumab, all of which are currently being evaluated in clinical trials.

Although bevacizumab demonstrated a modest improvement in PFS, the unique toxicity profile of antiangiogenic therapies and the lack of an overall survival benefit must be considered when selecting patients most appropriate for treatment. Common adverse effects can be divided into these major categories: generalized, cardiovascular, gastrointestinal (GI), and dermatologic. Generalized symptoms primarily include fatigue, headache, dyspnea, arthralgia, and myalgia.[4] In the phase III PALETTE trial that evaluated using pazopanib in treating advanced soft-tissue sarcoma, the incidence of all-grade and grade > 3 fatigue was 65% and 13%, respectively.[5] Although not FDA approved for use in ovarian cancer, the debilitating fatigue associated with pazopanib often warrants dose modification to improve tolerability. Cardiovascular symptoms such as hypertension and venous thromboembolism can be concerning in a primarily postmenopausal population. Frequent blood pressure (BP) monitoring is essential when treating patients with baseline hypertension, and all patients should have adequate BP control prior to initiating treatment with anti-VEGF therapies. Common GI symptoms include diarrhea and abdominal pain. More severe GI adverse events (ie, perforation, fistula, and/or necrosis) have been reported in 2.9% of patients with ovarian cancer, and identifiable risk factors include history of inflammatory bowel disorder and previous bowel resection.[6] Palmar-plantar erythrodysesthesia has been reported in patients receiving anti-VEGF therapies, and early identification of symptoms is essential in preventing dose interruptions. Impaired wound healing can result in serious or fatal complications; therefore, anti-VEGF therapies should be held at least 28 days prior to and after elective invasive procedures.[4] Considering the potentially substantial toxicities associated with bevacizumab and other anti-VEGF agents, their incorporation into the standard treatment of ovarian cancer should be reserved for patients with high-risk clinical features and minimal comorbidities.

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**For references visit cancernetwork.com/Ovarian-Ang**

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from patients enrolled in GOG-218 were sequenced, showing that patients with mutations in homologous recombination repair (HRR) had significantly prolonged PFS and OS when compared to those without mutations.[15] These data show that genetic testing plays an important role with regard to prognostic implications and should be discussed with all patients. This is particularly relevant for treatment with poly (ADP-ribose) polymerase (PARP) inhibitors.[16] There was no positive or negative correlation between HRR and the use of bevacizumab as maintenance therapy in this study.[15] In the AGO-OVAR 12 study, another multitargeted compound, nintedanib (a potent inhibitor of VEGFR, fibroblast growth factor receptor [FGFR], and PDGFR), was investigated. Patients with advanced ovarian cancer were given standard-of-care chemotherapy, carboplatin and paclitaxel, and randomized to nintedanib or placebo. The median PFS was significantly improved in the experimental arm compared with placebo (17.2 vs 16.6 months) (HR, 0.84; 95% CI, 0.72–0.98). Patients treated with nintedanib reported grade 3 adverse effects such as diarrhea (21% vs 2%), thrombocytopenia (12% vs 5%), and anemia (12% vs 6%).[17] Another trial with trebananib, a selective angiopoietin-1 (Ang1) and Ang2 neutralizing peptibody, examined its effects in combination with standard chemotherapy, carboplatin and paclitaxel, and randomized to nintedanib or placebo. The median PFS was significantly improved in the experimental arm compared with placebo (7.4 months vs 5 months) (HR, 0.60; 95% CI, 0.42–0.81). Patients treated with trebananib had a median duration of response of 18 months vs 8 months (HR, 0.45; 95% CI, 0.27–0.74). Another trial, TRINOVA-1, aimed to determine whether adding trebananib to weekly paclitaxel until disease progression would improve PFS. This trial showed that inhibition of Ang1/Ang2 determined a prolongation of PFS but not over the benefit of bevacizumab.[20] A third randomized phase III trial, ENGOT-ov-6/ TRINOVA-2, which had a similar study design to TRINOVA-1, evaluated PFS and OS after adding trebananib to pegylated liposomal doxorubicin (PLD) in patients with recurrent ovarian cancer (platinum sensitive and resistant). Patients in the experimental arm had a median PFS of 7.6 months (95% CI, 7.2–9.0) vs 7.2 months (95% CI, 4.8–8.2) in the placebo arm (HR, 0.92; 95% CI, 0.68–1.24). Trebananib demonstrated anticancer activity indicated by improved objective response rate (46% vs 21% in the placebo arm [odds ratio, 3.43; 95% CI, 1.78–6.64]). Median duration of response was also improved in the trebananib arm (7.4 months; 95% CI, 5.7–7.6) vs placebo (3.9 months; 95% CI, 2.3–6.5).[21] **Bevacizumab and Other Antiangiogenic Drugs Used in the Relapse Setting, Platinum Sensitive** While the antiangiogenic frontline therapy was seen from different perspectives by the FDA and the EMA, bevacizumab was initially granted FDA approval for use in recurrent ovarian cancer based on the AURELLA trial. The experimental arm of this trial consisted of adding bevacizumab to chemotherapy until disease progression. Patients who received bevacizumab had a median PFS of 6.7 vs 3.4 months in patients receiving chemotherapy alone (HR, 0.48; 95% CI, 0.38–0.60) and median OS of 16.6 vs 13.3 months, respectively (HR, 0.85; 95% CI, 0.66–1.08).[19] Another trial, TRINOVA-1, aimed to determine whether adding trebananib to weekly paclitaxel until disease progression would improve PFS. This trial showed that inhibition of Ang1/Ang2 determined a significant increase in PFS (HR, 0.829; 95% CI, 0.823–0.835). Median PFS was 10.5 months vs 7.6 months for bevacizumab vs placebo (HR, 0.81; 95% CI, 0.70–0.93). Median PFS was 12.4 months vs 8.4 months in the placebo arm.[11] In the GOG-213 trial, a different chemotherapy backbone (paclitaxel and carboplatin) was used and it was not placebo-controlled due to its primary endpoint being OS. In addition, surgical randomization for candidates deemed appropriate for secondary surgery was done for about 16% of the intent-to-treat population. This trial also demonstrated an increase in the median PFS in the bevacizumab plus chemotherapy arm compared with chemotherapy alone (13.8 months vs 10.4 months). Of note, GOG-213 showed a positive trend in median OS from 37.3 months in the chemotherapy group to 42.2 months in the chemotherapy plus bevacizumab group (HR, 0.829; 95% CI, 0.683–1.005; P = .056), which when adjusted for platinum-free interval and participation in the surgical objective, was significantly associated with OS (HR, 0.823; 95% CI, 0.680–0.996, P = .0447). [12] While the patients in the OCEANS trial did not receive bevacizumab with the frontline treatment, a third trial, MI-TO16B-MaN NGO OV2B-ENGOT OV17, enrolled patients with carboplatin-sensitive relapsed disease who had had previous bevacizumab treatment. They found that bevacizumab in combination with a platinum-based doublet is associated with significantly prolonged PFS and a good safety profile.[22] Results from AGO OVAR 2.21, which evaluated patients with relapsed disease who previously had bevacizumab in frontline, were presented.
during the ESMO 2018 meeting. In this study, both arms contained bevacizumab added to a platinum-based chemotherapy; one arm consisted of gemcitabine and carboplatin and the other arm consisted of PLD and carboplatin. Being the first phase III trial in ovarian cancer comparing two bevacizumab-containing regimens, the study showed that the carboplatin/PLD/ bevacizumab combination resulted in superior PFS compared with carboplatin/ gemcitabine/bevacizumab (HR, 0.80; 95% CI, 0.68–0.96; \( P = .0128 \)).[23]

Only one antiangiogenic VEGF receptor 1-3 inhibitor investigated in recurrent platinum-sensitive ovarian cancer patients so far has shown anti-tumor activity. In the 3-arm ICON6 trial, participants were randomly assigned to receive placebo plus chemotherapy then placebo maintenance (arm A), cediranib 20 mg once daily plus chemotherapy then placebo maintenance (arm B), or cediranib 20 mg once daily plus chemotherapy then cediranib 20 mg once daily for maintenance (arm C). Median PFS was 11 months for arm C vs 8.7 months for arm A (HR, 0.56; 95% CI, 0.44–0.72). The difference in OS was nonsignificant (\( P = .3 \)) across the 3 arms.[24] Although the improvement in PFS to a median of 11 months with cediranib as maintenance is similar to that reported with bevacizumab maintenance after chemotherapy, the risk of hypertension, fatigue, diarrhea, and nausea in patients taking cediranib in combination with chemotherapy makes this a worse candidate compared to intravenous bevacizumab.

**Other Emerging Antiangiogenic Therapies in Combination With Anti-VEGF Drugs**

Using antiangiogenic drugs to target the VEGF molecule or angiogenic receptors such as VEGFR, FGFR, and PDGFR proved to be an effective strategy for inhibiting tumor angiogenesis. The effects on PFS and OS are modest, as most patients develop adaptive resistance to anti-VEGF therapy and eventually present with progressive disease. Novel concepts that combine antiangiogenic drugs with other emerging approaches such as Delta-like ligand 4 (DLL4)-blocking antibody,[25,26] and colony stimulating factor 1 receptor (CSF1R) found on macrophages,[27] are showing promising results in decreasing tumor burden in vivo.[25-27] Previous studies that investigated the DLL4 pathway showed that DLL4 blockade improves PFS for patients with recurrent platinum-sensitive relapsed ovarian cancer. Different combinations of PARP inhibitors and antiangiogenic drugs are studied in the NRG-GY005 (NCT02502266) phase II/III and NRG-GY004 (NCT02446600) phase III trials in which a PARP inhibitor added to anti-VEGF therapy restored response to antiangiogenic therapy and an 83% lower tumor burden compared to treatment with anti-VEGF therapy and paclitaxel alone.[27]

**Other Interesting Combinations**

Phase III clinical trials showed that adding PARP inhibitors in maintenance therapy improves PFS for patients with recurrent epithelial ovarian, fallopian-tube, or primary peritoneal cancer who had received prior platinum-based chemotherapy.[32,33] The SOLO-1 study demonstrated that the risk of disease progression or death was 70% lower with olaparib than with placebo (HR, 0.3; 95% CI, 0.23–0.41; \( P < .001 \)) in patients with newly diagnosed advanced ovarian cancer who have a complete or partial response after platinum-based chemotherapy.[16] Taking into account the response rate to PARP inhibitors, the combination of PARP inhibitor with bevacizumab is the premise of the PAOLA-1 phase III clinical trial. Specifically, olaparib and bevacizumab are used in frontline maintenance in advanced ovarian cancer. Different combinations of PARP inhibitors and antiangiogenic drugs are studied in the NRG-GY005 (NCT02502266) phase II/III and NRG-GY004 (NCT02446600) phase III trials in which a PARP inhibitor is given alone or in combination with cediranib maleate in the experimental arms to determine efficacy compared with standard platinum-based chemotherapy in platinum-sensitive relapsed ovarian cancer. VEGF inhibitors in combination with immunotherapy are also being investigated. The rationale for combining immunotherapy with VEGF inhibitors is that the latter induce abundant tumor vasculature and inhibit directly T-cell function.

[34] There are several promising trials in development evaluating immunotherapy
in combination with VEGF inhibitors such as NRG-GY009 (NCT02839707), ATLANTE (NCT02891824), and IMagyn050 (NCT03038100).

Possible Markers of Response to Antiangiogenic Therapy

Treatment with antiangiogenic agents can be quite expensive and can have substantial side effects. One potential solution for optimizing the treatment is to identify useful biomarkers that can allow selection of patients most likely to benefit from such therapy and potentially to detect early escape from anti-VEGF therapy. Circulating molecular and cellular biomarkers in blood would be ideal candidates, as such markers can be followed longitudinally. However, circulating protein levels (e.g., VEGF or other angiogenic molecules such as placental growth factor [PIGF]) have not been particularly effective.[35]

Circulating endothelial cells (CECs) are mobilized in murine models as well as in humans in response to VEGF.[36,37] This is especially important because the level of CECs should decrease in response to anti-VEGF therapy. Although the suppression of mobilized endothelial cells was observed in patients with confirmed response to anti-VEGF therapy, an increase in value before clinical progression was not noted.[38]

Some have attempted to identify molecular subgroups of high-grade serous ovarian cancer that could predict response to anti-VEGF therapy. For example, Gourley and colleagues identified three major subgroups in the ICON7 participants based on mRNA analysis of human tissue samples. In two of the subgroups, the angiogenic genes were upregulated, while the third subgroup presented more complex features including repression of the angiogenic genes and upregulation of the immune genes. With regard to OS, the latter group had a superior OS compared to the other two subgroups. However, addition of bevacizumab therapy in this latter group was associated with worse PFS and OS compared to chemotherapy alone. This study suggests that an immune subgroup “geno-signature” with the repressed angiogenic-related expression could better select patients in whom antiangiogenic therapy could be avoided. Addition of bevacizumab in the proangiogenic group was associated with a nonsignificant trend for improved PFS compared with controls (median, 17.4 vs 12.3 months, respectively).[39]

Given the lack of reliable plasma biomarkers, imaging modalities such as CT and MRI scans are the most common assessment tools to evaluate efficacy. However, other functional imaging methods such as dynamic contrast-enhanced (DCE)-MRI and CT perfusion can provide information on tumor perfusion, vascularity, and permeability and could be useful as early markers of treatment efficacy.[38,40,41] The ACRIN 6695 study investigated whether CT perfusion biomarkers are associated with PFS in patients with advanced ovarian cancer treated with carboplatin and dose-dense or conventional paclitaxel. The patients were enrolled from the prospective phase III GOG-0262 clinical trial in which bevacizumab use was left to the physician’s choice and was overwhelmingly preferred based on the results from previous clinical trials in patients with advanced ovarian cancer. The study showed that changes in vasculature parameters within 4 weeks of initiating therapy in one or more CT-perfusion biomarkers were associated with shorter PFS, proving that these biomarkers can be considered good imaging candidates to provide early prognostic information.[41]

Future Directions

The number of antiangiogenic drugs developed during the last 30 years is impressive and is associated with improved patient outcomes. Nevertheless, due to emergence of adaptive resistance, additional therapies are needed. Steps forward would be made with the identification of predictive biomarkers that could help assess the response among patients and a better understanding of mechanisms of adaptive resistance. While neutralization of VEGF was the first approach for targeting the tumor microenvironment, additional approaches (e.g., immune therapy) have been also quite successful. In this context, the potential of tumor vessel normalization using antiangiogenic drugs to improve the effectiveness of immunotherapy should be explored further. Collectively, such microenvironment-targeted approaches hold promise for further improving the outcomes of women with ovarian cancer.

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Start of ELCAP
Throughout the last half of the 20th century, despite enormous research efforts, lung cancer remained the most feared as well as lethal cancer across the world. Starting in 1991, a multidisciplinary group of investigators (ELCAP) at Weill Cornell Medical College (WCMC) in New York, mindful of challenge, proposed to leverage the transformative breakthrough in performance of low-dose radiation CT imaging to obtain full thoracic images in a single breath hold to identify early, curable lung cancer. Their research demonstrated that it worked remarkably well.[1] However, they were to find convincing a skeptical world already inured by decades of failed lung cancer detection efforts was to be their greatest challenge.

The research team wanted to learn about previous efforts. For this purpose, they conducted extensive discussions with veterans of the previous, ill-fated National Cancer Institute (NCI)-sponsored randomized trial evaluating the effectiveness of sputum cytology and annual chest x-rays (CXR) as an early detection method.[2] A particularly insightful expert was the chief study statistician, B. Flehinger. Dr. Flehinger had developed a mathematical model to estimate the potential cure rates for lung cancers that were much smaller than were detectable by CXR, but in a range that could be detected by low-dose CT (LDCT). [3,4] Based on the preliminary experience, the investigators hypothesized that the LDCT detection rate of small lung cancer could be as high as 80% of cancers between 4 mm and 10 mm and the Flehinger model suggested that for such cancers, the cure rate could be as high as 80%, much higher than the 18% rate the model predicted for CXR screening.

Based on this preliminary WCMC modeling experience, early detection of curable lung cancer using LDCT seemed feasible. The investigators understood that to compare the quantitative benefit of CT to CXR screening, three probabilities need to be determined for each imaging modality:

1) Probability of detecting a noncalcified nodule (NCN) in a person
2) Probability of diagnosing lung cancer by size and stage
3) Probability of curing all persons diagnosed with lung cancer under screening

They also recognized that, for each imaging modality, these three probabilities need to be determined separately for the baseline round and for all subsequent repeat rounds of screening.[1,5,6] The profound difference between the probabilities for the baseline (“prevalence”) round and the subsequent rounds of repeat screening (“incidence”) had been recognized by Morrison and others.[7] The terms “prevalence” and “incident” had been adapted from acute disease descriptors (eg, myocardial infarction), but any cancer has typically been present but not detectable for a considerable time and thus is a prevalent case, whether detected on baseline or repeat screening.

Thus, the ELCAP investigators do not use the terms prevalence or incident cancers, but rather report whether the cancer was detected in the baseline or repeat rounds.

While the probabilities for the baseline round are different from those of repeat rounds of screening, each repeat annual round is a replicate of the other repeat rounds. Thus, a single repeat round would suffice to provide the probabilities, provided the sample size was sufficiently large. The investigators decided that the screening interval should be annual,[5,6] based on analysis of the lung cancer growth rates of lung cancers.[8]

The group’s first study was called the Early Lung Cancer Action Program (ELCAP).[1,6] Its goal was to determine the first two probabilities for LDCT and CXR by recruiting a prospective cohort of 1,000 current and former cigarette smokers, aged 60 years or older with at least 10 pack-years of cigarette smoking, who were asymptomatic for lung cancer. Each ELCAP participant was to receive a baseline LDCT and CXR followed by a repeat screening 12 months later. Upon receiving Institutional Review Board approval in 1992 at WCMC and then at New York University Medical Center, ELCAP recruitment started, thanks to
seed philanthropic funding. A grant application was submitted to the NCI, but it was recognized that this would probably take several years to receive a grant award, and as predicted it was awarded in 1995. [5]

During the conduct of the ELCAP trial, participants with noncalcified nodules (NCNs) on LDCTs were presented at weekly multidisciplinary Thoracic Tumor Conferences. Quarterly ELCAP meetings of investigators at both institutions were held to rigorously manage the conduct of this trial. The literature at that time focused on “solitary noncalcified pulmonary nodules,” [9,10] but it was soon recognized that on LDCT, multiple small NCNs were frequently detected in a single participant, and more importantly only few of them represented lung cancers. Thus the focus changed from detecting solitary NCN to detecting one or more NCNs. More importantly, it was recognized that most NCNs remained stable while the lung cancer was identified in rapidly growing LDCT-detected NCNs. [11] Furthermore, standard diagnostic testing and follow-up of NCNs was based on CXR experience, but the ELCAP investigators rapidly moved away from performing a biopsy on all NCNs. Instead for NCN less than 10 mm in size on baseline LDCT, follow-up CT in 3 months was performed to assess growth. [1] If, on follow-up LDCT, the observed NCN growth rate was suggestive of a malignancy, an immediate nodule biopsy was recommended. For larger NCNs (≥ 10 mm) the standard recommendation, which called for biopsy, was followed.

Dr. D. Yankelevitz, an ELCAP investigator, recognized the potential of CT to reliably measure growth rates of small lung cancers on follow-up CTs and led the research projects to confirm that short-term follow-up LDCT scans were very useful in distinguishing between the many small benign NCNs and the few malignant ones. [11-16] This critical innovation was initially supported by philanthropy but then subsequently validated by NCI grant awards, [17] a textbook example of the power of public/private interactions.

The seminal finding of using short-term follow-up LDCT for differentiating lung cancer from benign nodules also highlighted how the efficiency of screening diagnostic workup could be optimized and how it could be integrated into protocols. [18,19] This innovation was rapidly recognized and also integrated by a wide range of other screening research groups. [20,21] In particular, the NELSON trial in the Netherlands and Belgium integrated volume assessment into their protocol. [22]

With the large number of participants with NCNs on LDCT with the need for follow-up scheduling of CT scans, the investigators recognized that data and image management soon became overwhelming, even for a study of 1,000 participants at two institutions. Fortunately, the principal investigator, C. Henschke, was an experienced computer programmer and statistician, and was thus able to rapidly develop and write the needed computer management programs to document, store, and analyze the data for the ELCAP study.

**ELCAP Baseline Screening**

In 1998, recruitment of 1,000 baseline participants was completed and the baseline results were analyzed and published in the *Lancet* in 1999. [1] Among the 1,000 participants, NCNs were found by LDCT in 233 (23.3%) and by CXR in 68 (6.8%). Lung cancers were diagnosed in 27 by LDCT and 7 by CXR among the 1,000 participants (2.7% vs 0.7%, P = .0005). Of the 27 lung cancer patients identified by LDCT, 23 (85.1%) were stage I lung cancers while CXR identified only 4, missing 19 (82%) of them. LDCT also found 4 additional cancers, 2 endobronchial cancers, and 2 mediastinal cancers that were not identified by CXR.

Using published long-term survival rates by stage, [23,24] the ELCAP investigators projected a possible cure rate of 80% (a lung cancer fatality rate of 20%) for patients with lung cancer diagnosed in a program of LDCT screening. To robustly estimate the cure rate, however, additional screenings and longer follow-up time were needed.
innovation is said to be disruptive and the experience in applying low-dose computed tomography (LDCT) to find early lung cancer certainly validated that old bromide. In Dr. Henschke and colleagues’ review, we have the encapsulation of 20 profoundly transformative years in the history of biomedical research. In 1999, lung cancer was a terribly lethal scourge that humbled countless research efforts to improve outcomes. Aside from the courageous interventions of a generation of surgeon generals, a spirited tobacco control community, and a few Japanese epidemiologists, the disease burden of tobacco use was unrelentingly deadly.

The Lancet paper computed tomography (CT) screening report from Dr. Henschke’s team in 1999 was electric and galvanized camps of skeptics and believers alike[1]. This report came at the time of an ongoing and charged reconsideration of screening benefits with breast cancer, as well as prostate cancer. This situation with lung cancer was also colored by memories of initial enthusiasm for chest X-ray screening that did not hold up to more in-depth analysis.

An important, but underappreciated aspect of the New York screening team’s effort was a commitment to continue to pursue research evidence to refine the early lung cancer detection process. This momentum was sustained by a series of workshops that occurred every 6 months for the next 20 years and included advocates, as well as skeptics, from a broad array of medical and scientific disciplines.

Over this time in excess of 300 screening-related manuscripts were published coming from International Early Lung Cancer Action Program (I-ELCAP) collaborative groups in their consortium on aspects from imaging to health policy. Leveraging a remarkably robust informatics capability, the collaboration ultimately accrued over 82,000 screening subjects, including access to over 300,000 thoracic CT scans from participants on five continents. Hundreds of investigators worked with this consortium, including surgical leaders such as Drs. Robert Ginsburg, Nasser Alorki, and Raji Flores. Through coordinated efforts with Drs. William Travis and Adi Gazdar and others from the International Association for the Study of Lung Cancer Pathology Committee, every case of lung cancer detected by ELCAP was reviewed by the pathology panel. That experience led to the changes in international pathology classification and corresponding changes to international staging classifications.

Drs. Harvey Hecht, Matt Cham MD, Joseph Shemesh, and Jagat Narula revealed the dynamic of screen-detected coronary artery disease, while a corresponding revelation of frequent asymptomatic pulmonary parenchymal disease was reported by Javier Zulueta and his Spanish colleagues, principally from the University of Navarra. The list of other new observations is long, from Mary Salvatore’s findings with interstitial pulmonary fibrosis, to the routine findings of abnormal breast density on screening CTs with Laurie Margoilies and colleagues, to recent emerging information about screening for nonalcoholic steatohepatitis (NASH) in the context of low-dose computed tomography screening, with Andrea Branch and colleagues. These activities were thoughtfully acknowledged in Dr. Henschke’s review[2].

An excellent example of the power of this consortial approach was highlighted in a report to the Annals of Internal Medicine on the consequences of selecting the size threshold of detected non-calcified pulmonary nodule relative to the efficiency of a screening management approach. To address this question, Henschke was able to analyze the outcomes of 21,136 screening cases from a 5-year period of observation to inform the decision as to what threshold would be most appropriate[3] and then further confirm these thresholds using the National Lung Screening Trial Database.[4] Having such robust evidence to refine the efficiency of the screening process reflects how far the I-ELCAP investigators have moved this field.

As Dr. Henschke relates, her group’s work also stimulated competitive and collaborative efforts across the globe with outstanding screening research teams emerging launching the National Lung Screening Trial and the NELSON study, as well as coordinated efforts in Canada, Poland, Spain, Switzerland and many other nations[5-7]. This vibrant experience, while not perfect, did in fact align the contributions of hundreds of talent researchers and advocates to change the world’s perception of and aspirations for lung cancer to the benefit of many.

FINANCIAL DISCLOSURE: Dr. Mulshine has no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

For references and acknowledgements visit cancernetwork.com/lung-screen-pro

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ELCAP Annual Screening

The annual repeat screenings were completed, analyzed, and submitted in 1999, but only published in Cancer in 2001. [6] As annual rounds are repeated year after year for each participant, while the baseline round is performed only once for each participant, results from annual screening rounds are critical to assess screening performance.

Among the 1,184 annual repeat screening, new or growing NCNs were identified in 30 (2.5%) participants. Seven of the 30 participants were diagnosed with lung cancer, of which 6 (85.7%) had stage I disease. There were far fewer new NCNs on annual repeat screening than on the baseline screening (2.5% vs 23%, **P < .0001**) and the percentage of screen-diagnosed lung cancers was also different (0.59% vs 2.7%, **P < .0001**). The percentage of screen-diagnosed stage I disease, however, was similar (85.7% vs 85.1%, **P = 1.00**), although the median tumor size was smaller in annual rounds of screening (8 mm vs 10 mm, **P = .45**). Based on this evidence and pathologic findings,[25,26] future protocols for workup in the baseline and annual repeat rounds of screening were different.[18,19,27]

A critical quality assessment parameter for any cancer screening program is the frequency of cancers identified by symptom-prompted workup between the scheduled rounds of repeat screening. Another 2 participants had symptom-prompted workup for pneumonia which led to the diagnosis of lung cancer prior to the first annual round of screening. Both had endobronchial tumors, one stage I small-cell carcinoma and one stage II squamous-cell carcinoma. Thus, the percentage of patients with stage I lung cancer, including screen-diagnosed and symptom-prompted diagnoses, was slightly lower on annual repeat than on baseline screening (77.8% vs 85.1%, **P = .63**). This was expected as a higher percentage of aggressive cancers are identified in repeat rounds of screening. [26,27]

Prior to 2000, radiologists reviewed the CT images displayed on radiographic films that provided 12 CT images per film.[1,7] Typically, 30 CT images were obtained for each screening participant, using 10-mm slice thickness, although reconstruction at 5-mm overlapping intervals was used to improve the image resolution. With advances in CT technology, particularly with multislice scanners, submillimeter slice thickness acquisitions are now obtained, providing as many as 800 CT images for each participant, and these images are displayed on large computer monitors, which, though expensive, provide far greater detail. Today, in addition to viewing axial images, coronal, sagittal, and maximum intensity projections are routinely provided, further enhancing visualization. These advances have markedly increased identification of tiny NCNs, thus reducing symptom-prompted diagnoses between annual rounds of screening. These marked improvements have also prompted reconsideration of using longer intervals between repeated rounds of screening.[21,28]

Expansion of ELCAP Screening to New York (NY)-ELCAP and International (I)-ELCAP

Immediate international requests for collaborations on LDCT screening followed the publication of the 1999 Lancet article. [1] In response, the ELCAP investigators initiated an International Conference on Screening for Lung Cancer in the fall of 1999 and these conferences have been continued, with the 40th conference held in April 2019.[29,30] At the first conference, participants called for the development of a multi-institutional protocol that, when presented at the next conference 6 months later, was unanimously adopted and then published.[18,19]

The screening protocol was critical, as with the marked advances of CT scanner and viewing technology, radiologists could detect NCNs as small as 2 mm but very few of these NCNs are lung cancers. The exquisite sensitivity of LDCT to identify small lung cancers, compared to CXR, further accentuated the difference in the first two probabilities of the baseline and annual repeat rounds and the need for recognition of these differences in the baseline and repeat protocol.[26,27] These advances also highlighted the need to update the threshold criteria for workup on baseline and on annual repeat screening.[18,31-33] Many additional insights were developed using the enlarging International [I]-ELCAP database, and these recommendations have been incorporated in the updated online protocol.[19] These recommendations are provided for findings made on screening scans of mediastinal masses, emphysema, coronary artery calcifications, aortic valve calcifications, pulmonary artery enlargement, interstitial lung disease, breast density and masses, liver density, and bone. In developing these recommendations, the investigators worked closely with...
clinicians in different medical specialties and stressed that, different from routine medical practice, these findings were not prompted by symptoms but identified as a result of screening and thus recommendations and workup need to be tailored accordingly. Some of these recommendations have been incorporated, for example, into national guidelines. The importance of using a protocol with detailed recommendations was highlighted by the comparison of I-ELCAP and National Lung Screening Trial (NLST) results, which showed that the use of a regimen of screening markedly decreased unnecessary workup.

In view of the international demand for LDCT screening, A.P. Reeves, a Professor of Electrical Engineering and Computer Science at Cornell University, who had been working with the ELCAP team on tumor growth analyses, suggested expansion to a web-based management system that would enable more efficient and comprehensive data and images collection from any site connected to the internet. It would also be able to provide a platform for screening management tools, training, and reporting. Thus, the original ELCAP management system was converted into the updated, web-based ELCAP management system.

This web-based ELCAP management system together with the I-ELCAP protocol made it possible to rapidly expand LDCT screening worldwide. ELCAP investigators developed educational sessions for radiologists and coordinators, and provided the ELCAP management system, free of charge, to all participating institutions. Core features of this system have been widely adopted by other screening data systems. The ELCAP management system has developed a comprehensive, new site onboarding process using a blend of web content, face-to-face interactions at its biannual workshop process, as well as a comprehensive archive of relevant screening publications.

These estimated cure rates for annual LDCT screening for lung cancer have been confirmed at the international conferences, held every 6 months since 1999, including the latest 40th conference held in April 2019, which provided the 20-year follow-up results.

I-ELCAP Long-Term Survival for Diagnosed Lung Cancers Under Screening

The expansion of ELCAP provided sufficient data to robustly estimate the probability of cure for patients diagnosed with lung cancer under lung cancer screening (baseline, annual screen-diagnoses as well as symptom-prompted diagnoses rounds). The cure rate, estimated by the 10-year Kaplan-Meier survival rate of 484 patients, was 88% (95% CI, 84%–91%), regardless of the cancer stage or treatment. Patients who were diagnosed with clinical stage I lung cancer and resected within 1 month of diagnosis had a higher estimated cure rate (92% [95% CI, 88%–95%]).

I-ELCAP Long-Term Survival for Diagnosed Lung Cancers Under Screening

The benefit of LDCT screening was individualized as to the age, smoking history, and other pertinent information of each individual considering screening. Using the ELCAP baseline information together with the long-term Kaplan-Meier survival rates, the benefit of a single round of screening was determined based on the person’s age and smoking history. This benefit was due to the increased survival by undergoing the first round of LDCT screening. This approach can be extended to calculate the individual benefit or survival gain from each subsequent annual round of screening.

The ELCAP Management System

The ELCAP management system provided a scalable system to disseminate the standardized data elements needed for each new participating institution to have the first 200 scans read jointly by the coordinating center with follow-up adjudication discussions and then review of the next 300 scans. Other quality interactions around lung cancer pathology review, assessment of other thoracic detected disease conditions, as well as nursing and navigation measures are available.

By 2000, LDCT screening rapidly expanded throughout New York State as NY-ELCAP and internationally as I-ELCAP programs. The US Preventative Services Task Force recommends that long-term smokers receive annual screening from ages 55-80 years.
for consistent, high-quality screening implementation and management. It documented the initial contact of each participant and allowed for all subsequent steps of the screening process, scheduling, reading the LDCT, recommendations for follow-up, and follow-up. This information is needed by coordinators, navigators, nurses, radiologists, and treating physicians on a participant-prompted, timely basis. The system efficiently collected screening data obtained in the process of a clinical screening program and also provided quality control, follow-up management, and reminders. Beyond the clinical needs, the system enabled collection of screening research data, collected in the context of clinical care, for rigorous scrutiny of needed updates and analysis of outcomes.

The ELCAP management system was provided to each participating institution, free of charge. Training for setting up screening programs was provided to each site and is also provided at the international conferences held every 6 months. Training included dual reading by the institution and coordinating center with identification of critical differences as the ELCAP management system provided both the data and images.[37] By the 40th International Conference on Screening held in New York on April 12–13, 2019,[29] the I-ELCAP database has clinical data and images on baseline and repeat rounds on over 82,000 participants throughout the world. The database includes the information on diagnostic work-up, treatment, and follow-up on all participants diagnosed with lung cancer, and also identifies additional diagnoses of metachronous lung cancers during annual follow-up of patients who had been cured of their first lung cancer.

The process of having international meetings every 6 months open to all interested in screening and providing international collaboration for an international health concern has engendered many international collaborations and has enabled an entire family of researchers from many medical, mathematical, engineering, statistics, computing, and other disciplines to work together to continually improve the benefit of LDCT screening for people at risk of lung cancer and other diseases.

The flexibility and utility of the ELCAP cohort design allowed for rapid accumulation of data and thus expansion of knowledge of how to optimize the clinical screening process and the resulting treatment advances.[27,35,41] In fact, considering the latest very low-dose techniques of CT scanners and the findings that can be made on LDCT, LDCT screening should be considered as providing a comprehensive health check of the lungs, heart, and other visualized organs in the LDCT screening,[42] which might prove to be highly cost-effective.[43]

Both the conferences and the management system anticipated the era of “open science, open-source” and have illustrated the power and benefit of an open science approach.[44] The open-science and open-source approach is a formalized approach of the fundamental philosophical underpinning of the Early Diagnosis and Treatment Research Foundation that has provided the ELCAP management system and the international conferences. The ELCAP management system has been made available as an “open source” system for LDCT screening of US veterans who are at high risk of lung cancer and other lung and heart diseases through a grant from the Bristol Myers-Squibb Foundation.[45]

The resulting updated VA-Partnership to increase Access to Lung Screening (VA-PALS)-ELCAP management system is the MUMPS-based software.[46] The ELCAP and updated VA-PALS-ELCAP management systems both use structured forms and radiology reporting, as did the original system, The structured reporting provides the common terminology for characterization of all NCNs, allows for quality assurance assessments, and pooling of data across multi-institutions around the world. In the future, the follow-up recommendations can be automatically generated based on the established screening protocol.

The initial information for each participant is documented in the intake form. Pertinent background information potentially helpful in the interpretation of the LDCT images is collected on the background form, which can be obtained by phone prior to the appointment, at the time the LDCT is performed, or later. As radiologists are responsible for reporting on findings of the entire LDCT, structured reporting of all LDCT findings are documented in the CT evaluation form: NCNs, other lung abnormalities (eg, interstitial lung findings, small airways abnormalities), cardiac abnormalities (eg, coronary artery calcifications and aortic valve calcifications), breast abnormalities (breast density, masses, and other findings), and abdominal abnormalities (eg, liver, adrenal, kidney, esophagus, pancreas, spleen). Input can be done directly or by a dictation template. Upon completion of the CT evaluation form, the written report is automatically generated. The follow-up form is used for documenting whenever the participant returns for a LDCT along with any changes in smoking pattern and diagnosis or hospitalization since the last visit. Biopsy, PET, and treatment forms are available for documenting subsequent diagnostic procedures and interventions.

**Advances Stimulated by LDCT Screening**

LDCT screening has been disruptive, as its much earlier identification of lung
cancers led to updating of recommendations in related disciplines such as smoking cessation, workup of NCNs, recognition of subtypes of NCNs, and pathology criteria of early lung cancer, staging, and treatment.

As a result of the initial ELCAP study, the investigators recognized that LDCT screening enhanced smoking quit rates and did not encourage resumption of smoking.[47,48] These results led to the strong recommendation that smoking cessation programs should be provided with all LDCT screening programs.[49]

Screening led to ever-increasing understanding of small, early lung cancers as to their appearance, growth, and pathologic characteristics that heretofore had not been well-explored due to insufficient data. The impact of CT scanner technology on tumor growth assessment was demonstrated by the limitations due to the tumor appearance and those due to the quantitative measurements of the scanner itself.[50,51] The importance of measurement error in nodule growth assessment was an important factor leading to the formation of the Quantitative Imaging Biomarker Alliance sponsored by the Radiological Society of North America (RSNA).[52] Hopefully, recognition of these limitations will stimulate development of better quantitative tools so that NCN growth can be determined within weeks rather than months, as this will lead to marked improvement of the efficiency of LDCT and to reducing unnecessary biopsies and/or surgery.

Differences in NCN subtypes, solid, part-solid, and nonsolid, were recognized early in the development of screening protocols.[53-56] The terminology was developed by the ELCAP investigators. [56] After review of the I-ELCAP and NLST databases and then of the world literature,[57-62] recommendations for workup of the different subtypes was developed and incorporated into the I-ELCAP protocol.[19] The usefulness of watchful waiting for nonsolid NCNs and concerns about over-diagnosis was addressed by these publications. The key conclusion was that overtreatment should be avoided and that current surgical recommendations for nonsolid NCNs involve watchful waiting as supported by the revised surgical staging classification of the American Joint Committee on Cancer/International Association for the Study of Lung Cancer (AJCC/IASLC) and address the concerns of over-diagnosis.[63-65] These critical findings allowed for watchful waiting, showing that by annual CT follow-up, cancers identified in nonsolid NCNs remained 100% curable even if they developed a solid component during the year.

Other advances were due to the recognition that the LDCT of the chest provides additional information about the lungs as well as the other visualized organs. The Surgeon General reports had documented the impact of active tobacco smoking and involuntary exposure to tobacco smoke on many other organs, including heart disease, chronic pulmonary diseases, and cancers of other organs.[66-69] Secondhand tobacco smoke exposure was shown to increase the risk of lung cancer, emphysema, and cardiovascular disease,[68] which was also assessed in the context of LDCT screening.[70,71] These results suggest that secondhand tobacco smoke should be included as a risk factor. I-ELCAP was also able to demonstrate that women in the United States were found to be more susceptible to lung cancer,[72,73] but when diagnosed with lung cancer, had a lower risk of dying.[73] The lower risk of women dying of lung cancer was confirmed in the NELSON study.[21]

Pathologic criteria for diagnosis of small, early lung cancer needed updating. The ELCAP investigators had developed a pathology protocol and initiated expert pathology panel reviews in 2000.[74] funded in part by the American Cancer Society. Results of these panel reviews of the pathologic specimens available through I-ELCAP have been published.[25,26,75] These reviews led to the new pathologic classification of adenocarcinoma and to the revised World Health Organization classification.[76-79]

When ELCAP started, the 6th staging classification edition was being used.[24] From the beginning, ELCAP and I-ELCAP also documented the modified tumor size categories as many small cancers were identified: < 10 mm, 11–20 mm, and 21–30 mm. These categories have now been incorporated in the 8th staging edition introduced in 2018.[80,81] Different from the 8th classification, however, in I-ELCAP’s modified staging, multiple adenocarcinomas without lymph node metastases are considered as multiple primary stage I cancers, not as higher stages as currently classified in the 8th classification, based on the evidence resulting from analyses of screening results.[75] The 8th edition of staging does not recognize the
impact of nodule consistency (solid, non-solid, part-solid). I-ELCAP investigators have shown in their recent publications that tumor consistency is both an important diagnostic and prognostic factor that needs to be considered in the tumor, node, and metastasis (TNM) staging, particularly for lung cancers < 30 mm in maximum diameter.[82,83] Based on careful documentation and analyses, investigators have found that clinical staging for tumors 30 mm or smaller should be classified based on the tumor size on CT, as neither lymph node enlargement or F-18-fluorodeoxyglucose (FDG)-PET uptake were helpful in identifying lymph node metastases. These publications called for updates of the 8th classification of the IASLC staging database. I-ELCAP investigators have found that clinical staging for tumors 30 mm or smaller should be classified based on the tumor size on CT, as neither lymph node enlargement or F-18-fluorodeoxyglucose (FDG)-PET uptake were helpful in identifying lymph node metastases. These publications called for updates of the 8th classification as data for the smallest size category was limited, despite the impressive contribution of the IASLC staging database.

Breast cancer treatment provides an excellent paradigm of the impact of screening on diagnosis and treatment. Prior to screening, mastectomy with radical lymph node dissection was the standard of care, but currently there are many alternative and less radical treatments. The recommendation of lobectomy has not changed in more than 50 years. Two randomized surgical trials started in 2007,[84,85] but their results are not expected until after 2020. In the meantime, new technologies are being developed (eg, robotic surgery, navigational bronchoscopy, percutaneous ablation) that are continuously being introduced, often with limited data for small lung cancers, the Initiative for Early Lung Cancer Research on Treatment (IELCART) was started using a prospective cohort design as previously used for I-ELCAP.[96] The ELCAP management system has been adapted for treatment considerations and also allows for randomization for future innovative randomized trials within its structure. IELCART is envisioned to be as productive as I-ELCAP has been in producing ongoing evidence.

Summary
The low-cost and efficient ELCAP design provided the fundamental clinically relevant information about the benefit of LDCT screening. In the 20 years since our initial ELCAP report in 1999, a vibrant community of LDCT investigators has emerged. Their efforts have ranged from providing the NLST in the United States, the largest randomized screening trial performed, which started in 2002, to the NELSON trial in Europe, which started in 2004.[20,21] The design of the NELSON trial and its use of volumetrics was strongly influenced by extensive discussions of the leading NELSON and ELCAP investigators at I-ELCAP conferences and through personal communications.[22,29] Both the NLST and NELSON trials, when published in 2011 and 2019,[20,21] not only confirmed the ELCAP results reported in 1999, but the NLST also provided a large library of CT images with associated clinical outcomes for research.[97] Important insights of the different screening trial designs and outcome parameters were gained,[98-102] and spinoff screening management optimization approaches were developed.[103-105] Other international trials have reported long-term follow-up of studies with randomized and cohort trial designs across the world that have confirmed the high long-term benefit of CT screening,[28,106-109] thus providing even further assurances as to the robustness of the LDCT screening benefit.

Other screening protocols have emerged since our initial publication in 1999, such as the American College of Radiology Lung Imaging Reporting and Data System (Lung-RADS) and the European Consortium protocols.[103,104] Comparisons of efficiency of these protocols as to the number of workups per diagnosis of lung cancer show that the I-ELCAP is currently the most efficient,[105] but we are excited that each of these efforts provides innovative approaches that benefit all screening participants. As further evidence and technology emerges, it is hoped that protocols will continue to be updated and compared using standardized criteria that measure efficiency and eventually these efforts should lead to further uniform improvements.

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For references and acknowledgements, visit cancernetwork.com/lung-screen-pro

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Management of Midostaurin-CYP3A4 Drug-Drug Interactions in Patients With Acute Myeloid Leukemia

Danielle Schlafer, PharmD, BCOP

Background
Acute myeloid leukemia (AML) is the most common acute leukemia in adults, with an estimated 21,450 new cases diagnosed annually in the United States.[1] Approximately one third of patients with newly diagnosed AML harbor a mutation in the \textit{fms-like tyrosine kinase} 3 (\textit{FLT3}) gene, which encodes a receptor tyrosine kinase involved in proliferation and survival of hematopoietic progenitor cells.[2] Mutations in \textit{FLT3} are associated with poor outcomes with traditional chemotherapy. In particular, the internal tandem duplication \textit{FLT3} mutation is associated with decreased disease-free survival and shorter overall survival (OS) vs patients with wild-type \textit{FLT3}.[3,4]

Midostaurin, a first-generation multitargeted tyrosine kinase inhibitor, was the first \textit{FLT3} inhibitor to be Food and Drug Administration (FDA) approved for use in AML in the United States.[5] It is indicated for use in the treatment of patients with newly diagnosed \textit{FLT3}+ AML in combination with standard induction and consolidation chemotherapy. Its August 2017 approval ended a 17-year drought in new drug approvals for AML and was the first in a wave of targeted agents to be approved for the disease, including the second-generation inhibitor gilteritinib, approved in November 2018 for single-agent treatment of relapsed/refractory \textit{FLT3}+ AML.[6]

The availability of these agents represents a paradigm shift in the treatment of \textit{FLT3}-mutated AML, and clinicians should be aware of their unique toxicity profiles and prescribing considerations. Of particular interest is the management of drug-drug interactions mediated via cytochrome P450 (CYP) 3A4, as the use of interacting supportive care medica-
Dosing and Adverse Events

FDA approval of midostaurin was based on the phase III RATIFY trial, which randomized 717 patients with newly diagnosed FLT3+ AML to receive midostaurin or placebo (50 mg twice daily on days 8 to 21) in combination with standard induction and consolidation chemotherapy followed by single-agent maintenance therapy (50 mg twice daily on days 1 to 28). The midostaurin arm demonstrated improved OS (median 74.7 months vs 25.6 months; $P = .009$) and event-free survival (EFS) (median 8.2 months vs 3.0 months; $P = .002$) vs placebo.[7]

Adverse events observed in the RATIFY study were comparable between the midostaurin and placebo treatment groups.[7] The most frequent grade 3 or higher adverse events were hematologic toxicities, febrile neutropenia, infection, diarrhea, hypokalemia, pain, and increased alanine aminotransferase. Rates of grade ≥3 anemia (92.7% vs 87.8%, $P = 0.03$) and rash (14.1% vs 7.6%, $P = .008$) were higher with midostaurin versus placebo. While grade ≥3 nausea/vomiting (61% vs 53%) were more common, rates of grade ≥3 nausea (83% vs 70%) and diarreha (13.8%), contributing to a 79% discontinuation rate. In contrast, there were no incidences of grade 3/4 nausea/vomiting in patients who received the 50-mg twice-daily schedule, and the discontinuation rate was lower at 45%.[8]

Additional safety concerns reported with midostaurin include QTc prolongation, which was higher in patients receiving midostaurin vs placebo, with elevations >480 ms and >500 ms occurring in 10.1% vs 5.7% and 6.2% vs 2.6% of patients, respectively. Pneumonitis and interstitial lung disease, including some fatal cases, have been reported in patients receiving midostaurin as a single agent or in combination with chemotherapy.[5] Monitoring recommendations are summarized in Table 1.

Pharmacokinetics and Drug-Drug Interactions

Midostaurin and its two active metabolites, CGP62221 and CGP52421, exhibit time-dependent pharmacokinetics with an initial increase in minimum concentrations during the first week of therapy followed by a decrease to steady-state levels.[5,9] When administered at 50 mg twice daily for 14 days sequentially after chemotherapy, trough concentrations of midostaurin and CGP62221 decrease to undetectable levels during off-treatment periods, while CGP52421 displays a long half-life and is maintained at detectable levels between dosing phases.[8] Midostaurin is primarily metabolized by CYP3A4, which catalyzes hydroxylation and demethylation to active metabolites.[10] Drug excretion is 95% via the hepatobiliary route, with 91% as metabolites and 4% excreted unchanged.[5]

Coadministration of midostaurin with strong CYP3A4 inducers leads to reduced concentrations of midostaurin and its metabolites, with more than ten-fold decreased exposure.[9] The US package insert recommends avoiding coadministration of midostaurin with strong CYP3A4 inhibitors because of concern for reduced efficacy.[5] Concomitant administration of strong CYP3A4 inhibitors leads to increased exposure to midostaurin and its active metabolites. Inhibition of CYP3A4 by ketoconazole resulted in a 1.8-fold increase in midostaurin maximum concentration and delayed formation and excretion of its active metabolites.[9]

Due to a theoretical concern for increased toxicity, drug labeling recommends the using alternative therapies that do not inhibit CYP3A4 or monitoring patients for increased risk of toxicity if coadministration with strong inhibitors cannot be avoided.[5] While the use of strong CYP3A4 inducers (eg, rifampin, phenytoin) is relatively uncommon, the use of strong

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**TABLE 1 Management of Select Midostaurin Adverse Events[5]**

<table>
<thead>
<tr>
<th>Event</th>
<th>Management Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/vomiting</td>
<td>Administer with food&lt;br&gt;Administer prophylactic antiemetics prior to each dose&lt;br&gt;(eg, prochlorperazine 10 mg orally bid; ondansetron 4 to 8 mg orally bid)&lt;br&gt;Provide prescription for as-needed antiemetics</td>
</tr>
<tr>
<td>QTc prolongation</td>
<td>Electrocardiographic monitoring, particularly if given concomitantly with medications known to prolong QT interval&lt;br&gt;Monitor for pulmonary symptoms&lt;br&gt;Maintain potassium and magnesium within normal limits</td>
</tr>
<tr>
<td>Interstitial lung disease</td>
<td>Monitor for pulmonary symptoms&lt;br&gt;Discontinue in patients who develop signs/symptoms of interstitial lung disease</td>
</tr>
</tbody>
</table>

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*Frequency not defined in package labeling. Consider more frequent monitoring during the first week of therapy and if midostaurin given concomitantly with CYP3A4 inhibitors or QT-prolonging medications.*
Use of concomitant CYP3A4 inhibitors as prophylaxis against fungal infection was permitted in the RATIFY study, without midostaurin dose adjustment. Fluconazole, posaconazole, and voriconazole were the most commonly prescribed agents. Use of concomitant strong CYP3A4 inhibitors occurred throughout induction, consolidation, and maintenance in 60.8%, 45.6%, and 10.8% of patients, respectively.[12] Midostaurin plasma levels were measured in a subset of 188 patients, demonstrating a 1.44-fold increase in midostaurin exposure in patients who received concomitant strong CYP3A4 inhibitors vs those who did not. The median dose intensity was similar (>94% of intended dose) regardless of concomitant strong CYP3A4 inhibitor therapy. Midostaurin-related adverse events were not significantly increased in patients receiving concomitant use of strong CYP3A4 inhibitors.[12] Considering these results, clinicians should be reassured that concomitant use of strong CYP3A4 inhibitors is not a contraindication to midostaurin therapy, but they should continue to be vigilant in monitoring for midostaurin-related toxicities. Aggressive prophylaxis and treatment of nausea and vomiting are warranted. Patients should be counseled on the use of scheduled prophylactic antiemetics and provided with an appropriate breakthrough antiemetic regimen.[5,13] Given the potential for QTc prolongation with several classes of antiemetics and select azole antifungals (Table 2), clinicians should strongly consider regular electrocardiographic monitoring and electrolyte replacement when initiating midostaurin and throughout therapy. Since QTc prolongation has been reported with the strong CYP3A4 inhibitors posaconazole and voriconazole, isavuconazole is a potentially attractive alternative given its moderate CYP3A4 inhibition and lack of QTc prolongation.[14] One case report described the successful concomitant administration of midostaurin and isavuconazole with no observed increase in toxicity.[15] It should be noted, however, that data are somewhat limited for prophylactic use of isavuconazole in immunocompromised patients, with some conflicting reports of breakthrough invasive fungal infections.[16-20]

Midostaurin is currently the only FDA-approved treatment for newly diagnosed FLT3+ AML, demonstrating improved survival in a patient population with historically poor outcomes. Drug-drug interactions should be carefully reviewed at treatment initiation and throughout therapy with consideration of patient-specific risk factors and comorbidities. Alternative therapies should be considered when feasible. When no acceptable alternatives exist, midostaurin may be successfully coadministered with CYP3A4 inhibitors with cautious monitoring.

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

**For references visit cancernetwork.com/midostaurin-int**

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**TABLE 2 Comparison of Select Antifungal Agents[14,21–24]**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Form(s)</th>
<th>CYP3A4 Effect</th>
<th>Treatment Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posaconazole</td>
<td>Oral (tablet; solution)</td>
<td>Strong inhibitor</td>
<td>Hepatic dysfunction; QTc prolongation; Oral solution poorly absorbed; must be taken with a full meal</td>
</tr>
<tr>
<td></td>
<td>Intravenous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Oral (tablet)</td>
<td>Strong inhibitor</td>
<td>Hepatic dysfunction; QTc prolongation; Vision changes; Rare cases of dermatologic malignancy with long-term use; Fluorosis with long-term use</td>
</tr>
<tr>
<td></td>
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<td>Moderate inhibitor</td>
<td>Hepatic dysfunction; QTc shortening; Therapeutic drug monitoring not well established</td>
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<td>Well-tolerated; Approved for Candida prophylaxis in hematopoietic cell transplant patients</td>
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<td>B liposome</td>
<td>None</td>
<td>Nephrotoxicity; Infusion reactions; Electrolyte wasting</td>
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The 2019 American Society of Clinical Oncology (ASCO) Annual Meeting, which took place May 31–June 4 in Chicago, drew more than 32,000 oncology specialists from around the world. The theme of this year’s ASCO conference was *Caring for Every Patient, Learning from Every Patient*. Among the topics of interest covered were new approaches to surmount limited access to cancer care and the latest advances in targeted therapies for pancreatic, prostate, and pediatric cancers.

More than 2,400 abstracts were presented at the meeting. These are some notable examples[1]:

**BREAST CANCER**

**Low-fat Dietary Pattern and Long-Term Breast Cancer Incidence and Mortality: The Women’s Health Initiative Randomized Clinical Trial**

A low-fat diet is linked to lower rates of breast cancer, according to results from the Women’s Health Initiative Dietary Modification trial (Abstract 520), a randomized, controlled clinical trial performed at 40 US centers.[2] In total, 48,835 postmenopausal women aged 50 to 79 years were randomized to either a usual diet comparison group (60%) or a dietary intervention group (40%). The intervention group set goals to decrease fat intake to 20% of total energy and boost consumption of vegetables, fruits, and grains.

After 8.5 years of dietary intervention, breast cancer incidents and breast cancer deaths in the intervention vs control group were lower, but not significantly so. Deaths after breast cancer from any cause, however, significantly decreased in the intervention group during the intervention (hazard ratio [HR], 0.65; 95% CI, 0.45–0.95), as well as on total follow-up of 16.1 years. Moreover, the decrease continued at 19.6 years of follow-up, along with a significant drop in deaths from breast cancer (HR, 0.79; 95% CI, 0.64–0.97).

“Adoption of a low-fat dietary pattern associated with increased vegetable, fruit, and grain intake demonstrably achievable by many significantly reduced the risk of death from breast cancer in postmenopausal women,” wrote authors led by Rowan Chlebowski, MD, PhD, of the Los Angeles BioMedical Research Institute at Harbor-UCLA Medical Center. “These findings provide the first randomized clinical trial evidence that a dietary change can reduce a postmenopausal woman’s risk of dying from breast cancer.”[2]
BLADDER CANCER
EV-201: Results of Enfortumab Vedotin Monotherapy for Locally Advanced or Metastatic Urothelial Cancer Previously Treated with Platinum and Immune Checkpoint Inhibitors

Following treatment failures with platinum-based and/or immunotherapy with checkpoint inhibitors, there are no effective treatment options for locally advanced or metastatic urothelial cancer. Treatment with enfortumab vedotin (EV) yielded responses—no growth or tumor shrinkage—in 44% of patients with locally advanced or metastatic types of urothelial cancer, according to the results of an open-label phase II study. [3,4] Furthermore, 12% of patients experienced a complete response with no detectable cancer signs. (Abstract LBA4505). The median overall survival time in this study of 125 patients was 11.7 months. In total, 41% of patients with locally advanced or metastatic urothelial cancer did not respond to a checkpoint inhibitor responded to EV, and 38% of those with liver metastases responded. EV was well tolerated, with fatigue being the most common adverse effect (30%).[3]

“These phase II results replicate the phase I results very closely, which is not often the case in clinical trials,” said lead author Daniel P. Petrylak, MD, a Professor of Medicine (Medical Oncology) and Urology at Yale Cancer Center, in an ASCO press release. “The fact that we have a therapy that can help people who don’t benefit from checkpoint inhibitors is very gratifying.”[4]

MULTIPLE MYELOMA
E3A06: Randomized Phase III trial of Lenalidomide vs Observation Alone in Patients with Asymptomatic High-Risk Smoldering Multiple Myeloma

Treatment with single-agent lenalidomide vs observation resulted in a 72% reduction in progression-free survival (PFS) at 3 years in patients with intermediate- to high-risk smoldering multiple myeloma, according to the results of a phase III trial.[5,6]

The overall response rate in the phase II study was 47.7%. In the phase III study, it was 48.9% for the lenalidomide group only. In phase II, the median follow-up was 71 months, and in phase III, it was 28 months. No differences in quality of life were observed.[5,6]

“There is no question that patients with multiple myeloma need immediate treatment to reverse evidence of organ damage, but a challenge we’ve struggled with is trying to identify patients without organ damage who are at highest risk of disease progression, and trying to intervene,” lead author Sagar Lonial, MD, of Winship Cancer Institute of Emory University, said in an interview with ASCO.[6]

“We showed, in the largest randomized study to date in smoldering myeloma, that we can prevent the development of symptomatic myeloma in a significant fraction of patients,” he commented.[6]

COLORECTAL CANCER
Long-Term Survival After Laparoscopic vs Open Resection for Colorectal Liver Metastases

Laparoscopic vs open surgery did not change survival rates in patients with colorectal cancer who were having liver metastases removed, according to results of the phase III Oslo-COMET trial (Abstract LBA3516). Of note, no difference between groups was observed with respect to extent of complete tumor removal or amount of tissue resected past the observable tumor.[7]

“After many years of improvements in laparoscopic surgery, we now have results showing that survival is as good with this procedure as with open surgery, and morbidity is lower, so we expect that this will cause a shift to even more operations on the liver being done laparoscopically,” stated team leader Bjørn Edwin, MD, PhD, from the Intervention Centre and the Department of HPB Surgery at Oslo University Hospital, Norway, in an ASCO press release.[8]

Medicaid Expansion Impact on Racial Disparities in Cancer Care

Finally, in news that was encouraging to all in attendance, researchers showed that implementation of Affordable Care Act (ACA) Medicaid expansions led to more timely cancer treatment in African Americans, thus reducing racial dispar-
In the study, which included 34,067 patients (median age, 57 years; 12% African American), racial disparities were noted pre-expansion. Specifically, African Americans were 4.9 percentage points (%pt) less likely to be administered timely treatment. The Medicaid expansion trended toward a rise in timely treatment for all patients ($P = .05$). This expansion, however, was correlated with a higher benefit for African American patients (6.9 %pt) vs Caucasian patients (1.8 %pt).

Patients selected had advanced or metastatic cancer (non–small-cell lung, breast, urothelial, gastric, colorectal, renal cell, prostate, and melanoma) and were diagnosed between January 1, 2011, and December 31, 2018, using the nationwide Flatiron Health electronic health record-derived database. “Timely treatment” was defined as first-line treatment started within 30 days of advanced or metastatic diagnosis. Covariates controlled for included race, age, sex, practice type, cancer type, stage, and unemployment rate.

“Implementation of Medicaid expansions as part of the ACA differentially improved African American cancer patients’ receipt of timely treatment, reducing racial disparities in access to care,” concluded the authors, led by Blythe J. S. Adamson, PhD, MPH, a Senior Quantitative Scientist at Flatiron Health in New York.

Researchers are excited about new treatment options for those patients with bladder cancer who don’t benefit from checkpoint inhibitors.
Introduction
Despite overall declining age-standardized cancer incidence rates in men and stable rates in women, growing and aging populations combined with improvements in cancer survival have led to mounting numbers of cancer survivors in the United States.[1] More than 16.9 million US residents with a history of cancer were alive on January 1, 2019, and this number is projected to grow to more than 22.1 million by January 1, 2030.[2] The most prevalent cancers in 2019 are prostate (3,650,030), colon and rectum (776,120), and melanoma (684,470) among males, and breast (3,861,520), uterine corpus (807,860), and colon and rectum (768,650) among females.[2] Many cancer survivors must cope with the physical effects of cancer and its treatment, potentially leading to functional and cognitive impairments as well as other psychologic and economic sequelae.[3] Among survivors, long-term, late effects such as subsequent cancers are of concern. Information on late and long-term complications at the population level, however, is limited.

Recognition of multiple primary cancers goes as far back as 1921, when a report showed that there were 4.7% multiple primary cancers found in 3,000 cases of malignancy.[4] Many factors can influence the reported numbers of multiple primaries, including the definition utilized, patient population studied, and follow-up time.[5] Depending on the definition, overall reported frequency of multiple primary cancers varies between 2.4% and 17%. Underlying causes for multiple primary cancers may include host and lifestyle-related factors, environmental and genetic factors, and treatment-related factors. Significant temporal changes have been found in the prevalence of cancer risk factors (ie, smoking, alcohol consumption, obesity) as well as advances in diagnostic sensitivity and improved screening programs that may affect the incidence of second or more cancers. In this review, the literature on multiple primary cancers is analyzed with a focus on clinical situations where a treating physician should take into consideration the possibility of multiple primaries.

ABSTRACT: The frequency of patients living after a cancer diagnosis continues to increase due to the rising incidence of cancer as well as the improved survival of cancer patients thanks to advances in cancer research and treatment. The risk of multiple primary cancers is also increasing due to increasing numbers of cancer survivors, long-term side effects of chemotherapy and/or radiation therapy, increased diagnostic sensitivity, and persisting effects of genetic and behavioral risk factors. Multiple primary cancers are defined as more than one synchronous or metachronous cancer in the same individual. Although several different definitions of multiple primaries have been proposed, the main definitions come from the Surveillance, Epidemiology, and End Results (SEER) Program and the International Association of Cancer Registries and International Agency for Research on Cancer (IACR/IARC). Depending on the definition, overall reported frequency of multiple primary cancers varies between 2.4% and 17%. Underlying causes for multiple primary cancers may include host and lifestyle-related factors, environmental and genetic factors, and treatment-related factors. Significant temporal changes have been found in the prevalence of cancer risk factors (ie, smoking, alcohol consumption, obesity) as well as advances in diagnostic sensitivity and improved screening programs that may affect the incidence of second or more cancers. In this review, the literature on multiple primary cancers is analyzed with a focus on clinical situations where a treating physician should take into consideration the possibility of multiple primaries.
Colon) as multiple sites. The IACR/IARC rules are more exclusive; only one tumor is registered for an organ, irrespective of time, unless there are histologic differences. The SEER database recommends use of a 2-month period to distinguish between synchronous and metachronous multiple primaries, whereas IARC suggests a 6-month period.[8,9] The rules of the SEER program are used mainly by North American cancer registries while the rules of IACR and the IARC are used internationally. A summary definition of multiple primary cancers is included in the Table.[9]

**Etiologic Factors**

Cancer, a multistage process of initiation, promotion, malignant transformation, and progression, often involves damage to DNA. Mutations in critical areas of genes that regulate cell growth, cell death, or DNA repair may lead to the selective growth of damaged cell lines and accumulation of further genetic damage. Once enough damages accumulate in the DNA, cancer may develop. Factors associated with increased risk of developing more than one primary cancer may include genetic susceptibility and familial cancer syndromes, environmental and lifestyle exposures (e.g., tobacco, alcohol use), hormonal factors, immune deficiency and infection, carcinogenic effects of prior cancer treatments, and finally, interaction among all of these factors.[5,11,12]

**Genetic Susceptibility and Familial Cancer Syndromes**

About 1% to 2% of all cancers are associated with hereditary cancer syndromes. Affected individuals have a heritable germline mutation in every cell, which may have arisen early in development. Many of these syndromes are autosomal dominant, with a 50% chance that someone carrying the gene will pass it on to their child.[11] Identification of a germline mutation in a cancer survivor portends increased risk for specific second primary cancers. The most relevant cancer predisposition syndromes in routine oncology care include hereditary breast and ovarian cancer syndrome, Lynch syndrome/hereditary nonpolyposis colon cancer, multiple endocrine neoplasia type 1 and type 2, von Hippel-Lindau disease, and Li-Fraumeni syndrome.[13] Heritable cancer syndromes should be suspected when several generations of a family are diagnosed with certain cancers at a relatively young age or when several individuals in a family develop multiple primary cancers. When a heritable cancer syndrome is suspected, genetic counseling should be discussed because this may identify mutations in known cancer susceptibility genes.

**Environmental and Lifestyle Exposures**

Environmental and lifestyle influences such as tobacco use, excess alcohol intake, and dietary patterns may play a significant role in the development of multiple primary cancers. Tobacco use is one of the most well-recognized causes of multiple primary cancers, with strong associations between cancers of the lung and upper aerodigestive tract (oral cavity, pharynx, larynx, and esophagus).[14] Lung cancer survivors also demonstrate increased risks of cancers of the head and neck and bladder and second primary lung cancers.[15] This is reflective of a phenomenon called “field cancerization,” in which some of the multiple patches of transformed cells in the respiratory and urinary tract may evolve into second (or more) cancers. Other cancers related to tobacco use include stomach, liver, pancreas, kidney, uterine cervix, and myeloid leukemia.[16] Alcohol consumption has been associated with increased risk of cancers including oral cavity and pharynx, esophagus, liver, colon, larynx, and female breast. For some cancers, the risks associated with excessive alcohol consumption and tobacco use are much higher than for either exposure alone.[17,18] Tobacco- and alcohol-related cancer sites are estimated to account for more than 35% of all subsequent malignancies.[12] Dietary factors and being either overweight or obese are reflected in the aggregation of cancers of the breast, uterine corpus, ovary, colon, esophageas, gallbladder, kidney, pancreatic, and thyroid.[19,20]
Hormonal Factors
Hormonal factors play an important role in the development of female breast cancer and several cancers of the female reproductive system. Individuals may be at increased risk of developing multiple primary cancers due to hormonal factors. Studies of multiple primary cancers have found increases in relative risks for breast, ovarian, and uterine corpus cancers, which may be attributable to common hormonal risk factors related to menstrual and pregnancy history and use of hormonal medications. This may result not only from factors related to menstrual and pregnancy history but also from use of hormonal medications and genetic susceptibility factors that increase risk for several cancers. [11]

Immune Deficiency and Infection
Some established, growing evidence supports a causal role of immunodeficiency and infections in increased risk for primary and secondary cancers. Immunodeficiency syndromes, either acquired or inherited, have been associated with an increased risk of non-Hodgkin lymphoma, Kaposi sarcoma, and squamous cell cancer on sun-exposed areas of the skin. [11] Human papillomavirus (HPV) infections are the main cause of cancer of the uterine cervix and have been implicated in other cancers of the anogenital tract (ie, vulva, vagina, perineum, anus, penis) for which there is evidence of mutually increased risk. HPV, especially HPV-16, has been implicated in oropharyngeal cancers. [21] Patients infected with human immunodeficiency virus (HIV) are at increased risk of non-Hodgkin lymphoma, Kaposi sarcoma, and cervical and anal cancer. Although case reports document multiple cancers in HIV-infected individuals, the relative risk for multiple primary tumors in patients with HIV-related immunodeficiency is unknown. [11]

Carcinogenic Effects of Prior Cancer Treatments
The carcinogenic potential of chemotherapy and radiation therapy is well known. The association between some alkylating chemotherapy agents and risk of developing acute leukemia, which typically occurs in the first 10 years after treatment, is well-established. [22] Other drug classes associated with increased risk of acute myeloid leukemia include topoisomerase II inhibitors, anthracyclines, and platinum-based therapies. [23, 24] The second cancers associated with radiation therapy include acute leukemia, chronic myelogenous leukemia, and breast, lung, thyroid, and nonmelanoma skin cancers. Second cancers of the bone and connective (soft) tissues occur within or adjacent to the irradiated area among patients treated with high-dose radiation. Dose and type of radiation, the intrinsic susceptibility of exposed tissues, and patient characteristics influence the risk for radiation-associated cancers. The risk is generally higher when developing tissue is exposed at a younger age. [25]

Clinical Relevance to the Practicing Oncologist
Depending on the definition, the frequency of multiple primaries is in the range of 2% to 17%. The number of patients with multiple primary cancers seems to be growing based on the National Cancer Institute SEER Program. [26] With advances in early detection, supportive care, and effective cancer treatments and with longer follow-up, the number of multiple primaries will continue to increase. Over the past few decades, the meaningful increases in the 5-year relative survival rate for all cancers continues to be offset by the long-term late effects of cancer and its treatment. One of the most life-threatening sequelae is the diagnosis of a new cancer. Patients with a prior cancer diagnosis usually undergo several follow-up tests and examinations often over a period of several years to rule out relapse of their disease. With the increasing use of more sophisticated and sensitive imaging methods, such as PET/CT, more and more cancer survivors are now found to have new suspicious lesions in their thyroid, colon, breast, esophagus, bile duct, and head and neck that might have been missed otherwise. [27, 28] Practicing oncologists should be aware of this rather not uncommon presentation in their cancer surveillance patients and watch for the clinical features that may be indicative of a second primary cancer. Late and atypical metastatic spread pattern for a given primary tumor, discordant tumor burden/tumor marker levels, isolated single new metastatic lesions, continued exposure to environmental carcinogens (eg, smoking, alcohol), and history of prior carcinogenic chemotherapy (eg, etoposide, anthracyclines) or radiation therapy may be some of the manifestations indicative of the presence of a second primary cancer.

After histologic confirmation of a second primary cancer, the decision for...
active treatment may be difficult in the advanced and surgically unresectable second primary presentation. The challenge is to find an anticancer therapy strategy that covers both cancer types without increased toxicity or relevant pharmacologic interactions and without negative impact on the overall outcome. There are no well-established, evidence-based guidelines in this setting. These patients are always excluded from clinical trials by the eligibility criteria unless they have been low grade/stage and were successfully treated at least 3 to 5 years ago. To reflect more of a real-life population and to enable participation of patients with a second primary cancer history in clinical trials, the exclusion criteria, especially for early-phase clinical trials, should be modified to only exclude patients who currently require active anticancer therapy. Admittedly, this may add marked complexity to assessing efficacy and progression and may therefore not be suitable for phase III clinical trials. Moreover, there is a lack of reliable safety and efficacy data for the drug–drug interactions of antineoplastic (ie, cytotoxic, biologic, immunotherapy) treatment options being considered for a given patient. Decisions about if and how to treat these patients should be based on multidisciplinary tumor board discussions and should be individualized.

The increased knowledge about patients with hereditary cancer and cancer survivors will hopefully allow for the development of specific management and surveillance measures. Few studies have specifically addressed the prevention of multiple primary cancers in cancer survivors. There is also a lack of specific screening guidelines in this setting. Currently, all cancer survivors are recommended to follow applicable national guidelines for cancer screening for average-risk individuals in the general population (ie, not cancer survivors) such as those provided by the American Cancer Society, American Society of Clinical Oncology, National Comprehensive Cancer Network, and the US Preventive Services Task Force.[29]

Finally, it is important that patients diagnosed with cancer have information about possible late and long-term effects of treatment and their symptoms, as well as possible signs of recurrence and second tumors. A physician-guided follow-up plan should include information about recommended cancer screening, surveillance for recurrence, and the schedule on which tests and examinations should be performed. In addition to recommendations that are specific to their primary cancer, age at initial diagnosis, and potential risks related to treatment, it is important that cancer survivors follow the recommendations for cancer prevention and early detection in the general population, including tobacco avoidance or cessation, physical activity, nutrition and diet, healthy weight, and all standard cancer screenings.[30,31]

**Conclusion**

Overall, the incidence of multiple primary cancers is increasing due to advances in cancer treatment. Different mechanisms such as family history, genetic defects, hormonal factors, alcohol, tobacco, and environmental influences have been implicated in the development of multiple primary cancers. Diagnosis and treatment for multiple cancers remains a challenge because of variable definitions of multiple primaries, lack of specific screening guidelines, and the lack of well-established treatment guidelines. Management of these patients should be individualized through a multidisciplinary approach. Further research is needed to better understand and define prevention, screening, diagnosis, treatment, and survivorship issues in this area.

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For references visit cancernetwork.com/multi-tumors

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Therapy Options in Treating Acute Lymphoblastic Leukemia in Adults

Reviewing clinical strategies in the age of individualized medicine

Recently, ONCOLOGY discussed therapy options for adult acute lymphoblastic leukemia (ALL) with Dr. Elias Jabbour, MD, Professor of Medicine in the Department of Leukemia at the MD Anderson Cancer Center in Houston, Texas. Dr. Jabbour is involved in the development of chemotherapies and other therapies for leukemias, including ALL.

**Q:** What are the current standard-of-care therapy options for newly diagnosed patients with ALL, including newly approved therapies?

**Dr. Jabbour:** First, I think lots of progress has been made in therapies for adult ALL and believe we are going to improve the cure rate of this disease to levels achieved for pediatric ALL. I am confident of this because we don’t see every patient the same way and are moving to a la carte treatment. We do have many new drugs available, the first subset of which is tyrosine kinase inhibitors. When added to chemotherapy in Ph+ [Philadelphia chromosome-positive] ALL, these drugs lead to improvement in survival. In fact, the current 5-year survival rate of 75% has never been seen before. Then we have another group of drugs, the monoclonal antibodies, for the treatment of relapsed and refractory settings. In the frontline setting, rituximab, when added to chemotherapy, improved survival in the ALL 3b subtype. We also have other drugs like inotuzumab, ozogamicin, and blinatumomab that are approved in the relapsed setting. These drugs will be moving to the frontline setting and are very promising.

As there are different disease subsets of ALL, we rely heavily on their biology to identify certain subgroups of patients. This allows us to tailor our approach according to the baseline features of these disease subsets. Ten years ago, there was a publication describing what is now called Philadelphia-like ALL. [1] These are patients with the same gene expression as Philadelphia-positive ALL but they don’t have the Philadelphia chromosome and therefore are Philadelphia-like. Patients who have this ALL subtype do poorly with chemotherapy, but with newly available approaches, we may be able to improve their outcome. At the T-cell level, we are looking into different subsets such as adenosine triphosphate (ATP) ALL, which has a poor prognosis. We are now testing new drugs to improve the outcome of these patients.

So, in treatment we have induction, consolidation, maintenance, and intrathecal chemotherapy to prevent CNS relapses. The consolidation therapy can be done with chemotherapy or a transplant and with maintenance therapy. We should not forget that we need to prevent CNS relapses by administering intrathecal chemotherapy.

This is what we have in the frontline setting for the management of ALL patients. Now, when we discuss the frontline setting, we also have to discuss biomarkers and how we choose therapy. So, what are the biomarkers that we use to distinguish the group of patients with ALL from each other? When you have a patient with ALL, it is important to identify the immune phenotype, whether it is a B-cell or T-cell subtype. Once we know it’s a B-cell ALL,
An 83-year-old man presented with significant weight loss, progressive abdominal distension, and discomfort. His past medical history included resection of a localized, invasive primary cutaneous malignant melanoma in the right shoulder 5 years ago.

A physical examination revealed normal vital signs, and no skin lesions were observed. The liver was palpable 8 cm below the right costal margin. He had no signs of jaundice, and no signs of encephalopathy were found. His Eastern Cooperative Oncology Group (ECOG) performance status score was 2 during evaluation and all of the workup.

Laboratory tests at presentation showed abnormal liver function parameters: aspartate aminotransferase (AST) 81.7 IU/L (normal, 13–39 IU/L); alanine aminotransferase (ALT), 83.2 IU/L (normal, 7–52 IU/L); \( \gamma \)-glutamyl transferase (GGT), 488 IU/L (normal, 9–64 IU/L); alkaline phosphatase (ALP), 441 IU/L (normal, 34–104 IU/L); total bilirubin (TBIL), 1.13 mg/dL (normal, 0.3–1 mg/dL); and direct bilirubin (DBIL), 0.71 mg/dL (normal, 0.03–0.18 mg/dL). Lactate dehydrogenase (LDH) was 1,125 IU/L (normal, 9–64 IU/L); and direct bilirubin (DBIL), 0.71 mg/dL (normal, 0.03–0.18 mg/dL). No other significant abnormalities in laboratory tests were found.

An abdominal CT scan showed hepatomegaly and a diffusely infiltrated liver.

**FIGURE 1** 18F-FDG PET/CT: (A) and (B) MIP image shows an increased-in-size liver with a very heterogeneous hypermetabolism. In the fusion images, a diffusely infiltrated liver is seen with some areas of photopenia due to necrosis (*). US: (C) liver shows a coarse echotexture with multiple hyperechogenic foci due to diffuse metastatic infiltration. An area of extensive necrosis (*) and a focal well-defined tumor are also present (arrow).

\( ^{18} \text{F-FDG PET/CT} = \text{F-18-fluorodeoxyglucose (18F-FDG) with positron emission tomography (PET) and computed tomography (CT)}; \text{MIP} = \text{maximum intensity projection}; \text{US} = \text{ultrasound}.\)

**What is the best therapy to start in a patient with PD-L1–negative (0%) BRAF wild-type metastatic melanoma?**

A. Chemotherapy  
B. BRAF/MEK inhibitors combination  
C. Ipilimumab monotherapy  
D. Single anti–PD-L1 agent (ie, nivolumab or pembrolizumab) or combined immunotherapy with an anti–CTLA-4 antibody (ie, nivolumab plus ipilimumab)
with no ascites or lymphadenopathies. F-18-fluorodeoxyglucose (18F-FDG) with PET and CT (18F-FDG PET/CT) revealed an enlarged liver with very heterogeneous hypermetabolism and some areas of photopenia due to necrosis (Figure 1-A and 1-B). Additionally, a hypermetabolic nodule in the right lung and multiple nodular lesions in the spleen were noted. A complementary liver ultrasound showed multiple hyperechogenic foci due to diffuse metastatic infiltration (Figure 1-C).

The patient underwent a percutaneous liver biopsy, and the histologic examination revealed liver parenchyma infiltrated by melanoma neoplastic cells. The melanin pigment was diffusely disseminated throughout the sinusoids (Figure 2-A) but also showed a nodular pattern (Figure 2-B and 2-C). Immunohistochemistry revealed 0% expression of programmed death ligand 1 (PD-L1) in tumor cells and in tumor infiltrative lymphocytes. The tumor was negative for BRAF-V600 mutations.

**Discussion**

Melanoma of the skin is the 19th most common malignant neoplasm worldwide, with 287,723 new cases estimated for 2018.[1] Metastatic melanoma accounts for 4% of all new cases.[2] In recent years, the prognosis of this stage has undergone a dramatic transformation with the advent of immunotherapy and BRAF/MEK targeted therapy.[3] Although hepatic metastases are a common event in metastatic melanoma, from 14% to 20% of clinical series and 54% to 77% of autopsy series,[4] diffuse hepatic infiltration (DHI) of the liver is an exceptional event, with only 12 cases reported in the literature.[5–15] Due to the rarity of this entity, there is not a uniform definition of DHI.

Using conventional imaging studies (CT/MRI), hepatomegaly without defined focal lesions is the usual manifestation of DHI.[16] PET/CT scans may show diffuse hepatic tracer uptake, described sometimes as “hepatic superscan,” which, although suggestive of extensive liver infiltration by malignancy, can be caused by ipilimumab-induced hepatitis or infections like tuberculosis or Q fever.[17,18] Microscopically, DHI is characterized by diffuse intrasinusoidal invasion and tumor emboli. Foci of infarction can also be present.[19] DHI is more commonly associated with hematologic malignancies, breast cancer, small-cell lung cancer, and gastric adenocarcinoma.[20] There are no specific treatment recommendations for DHI, as compared to other forms of metastatic disease. Prognosis of DHI is usually fatal, with most patients dying in the first couple of weeks after diagnosis.[20,21]

Until 2010, treatment options for metastatic melanoma were limited to chemotherapy with a dismal prognosis, with median overall survival that ranged from 7 to 11 months. Dacarbazine was considered the standard first-line treatment, as no other chemotherapy regimens, targeted therapy (bevacizumab or sorafenib), or cytokines (interleukin-2 or interferon alfa) achieved an increase in overall survival.[22] In 2011, two phase III randomized clinical trials changed that landscape, introducing two new treatment modalities for metastatic melanoma. In patients with the BRAF-V600E mutation, the BRIM-3 trial demonstrated an improvement in overall survival with the use of vemurafenib, a BRAF inhibitor, as compared to dacarbazine in the first-line therapy set-

**FIGURE 2** Hematoxylin and eosin 20x; (A) liver parenchyma infiltrated by melanoma neoplastic cells, melanin pigment is disseminated throughout the sinusoids and hepatocytes (arrow); (B) Liver parenchyma infiltrated by melanoma neoplastic cells in a nodular pattern (arrow); (C) The presence of melanin pigment is disseminated throughout the liver parenchyma (arrow).
Thus, chemotherapy is no longer the standard of care in the first-line setting of metastatic melanoma.

The addition of MEK inhibitors to anti–BRAF therapies increases overall response rate, progression-free survival, and overall survival. Three BRAF inhibitors (vemurafenib, dabrafenib, and encorafenib) and three MEK inhibitors (cobimetinib, trametinib, and binimetinib) have gained US Food and Drug Administration (FDA) approval for metastatic melanoma. Their use, however, is restricted to the BRAF-V600E/K-mutated population, which accounts for approximately 50% of melanoma patients. The implementation of these therapies outside those indications remains investigational.[27]

Anti–PD-L1 therapies revolutionized the treatment of metastatic melanoma. Two anti–PD–1 antibodies are available for the treatment of this disease: pembrolizumab and nivolumab. These therapies first demonstrated superiority to chemotherapy in terms of overall survival in the second-line setting in the phase III CheckMate 067 trial.[30] A selection of this and other practice-changing anti–PD-1-based clinical trials is shown in the Table.

Two landmark clinical trials positioned anti–PD-1 therapies over ipilimumab. The KEYNOTE-006 trial was a 3-arm trial that randomized patients to two different schedules of pembrolizumab 10 mg/kg every 2 weeks or every 3 weeks or to 4 doses of ipilimumab 3 mg/kg every 4 weeks. Most patients had not received treatment for advanced disease: 12% were given chemotherapy, 3% immunotherapy, and 18% BRAF/MEK inhibitors. Both pembrolizumab arms had similar outcomes and outperformed ipilimumab. Moreover, the pembrolizumab arms experienced less grade 3–5 adverse events, compared to those who received ipilimumab.[31,32]

CheckMate 067 was another 3-arm phase III study that randomized patients to nivolumab 3 mg/kg every 2 weeks, nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for 4 doses, followed by nivolumab 3 mg/kg every 2 weeks, or ipilimumab 3 mg/kg every 3 weeks for 4 doses. Compared to ipilimumab, the nivolumab monotherapy arm experienced better overall response rate, progression-free survival, and overall survival. The grade 3/4 adverse events were similar to those of pembrolizumab in the KEYNOTE-006 trial.[33–35] Taken together, the improvement in outcomes alongside the less-toxicity profile support the use of anti–PD-L1 inhibitors over CTLA-4 inhibitors, even in the PD-L1-negative population.

As there are no formal contrasts between anti–PD-1 monotherapy and anti–PD-1 plus CTLA-4 combination therapy, both are considered category 1 first-line options.[36] Treatment selection depends on therapeutic goals, tolerability of adverse events, and the patient’s age and performance status.

Regarding therapeutic goals, objective response rates were slightly better with the anti–PD-1/CTLA-4 combo than with the anti–PD-1 monotherapy; however, the onset of response was the same for both treatments, at approximately 2.8 months.[31,33] In the aforementioned CheckMate 067 trial, the combination nivolumab plus ipilimumab arm performed the best in every survival outcome, with median overall survival not reached in this arm in the last published update.[35] Those benefits came with the downside of two times the grade 3/4 adverse

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**TABLE Selected immunotherapy clinical trials for advanced melanoma**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Treatment Naïve*</th>
<th>BRAF-V600 Mutated</th>
<th>PD-L1 Negative</th>
<th>Performance Status</th>
<th>N</th>
<th>Treatment Arms</th>
<th>Primary Endpoint</th>
<th>ORR</th>
<th>3-year OS</th>
<th>Median PFS</th>
<th>Grade 3/4 AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01721772 *(CheckMate 066)[30]</td>
<td>III</td>
<td>100%</td>
<td>0%</td>
<td>64.6%&lt;sup&gt;3&lt;/sup&gt;</td>
<td>ECOG 0, 1</td>
<td>418</td>
<td>• Nivolumab ((n = 210))</td>
<td>OS</td>
<td>42.9%</td>
<td>51.2%</td>
<td>2.2 mos</td>
<td>17.6%</td>
</tr>
<tr>
<td>NCT01844505 *(CheckMate 067)[34]</td>
<td>III</td>
<td>100%</td>
<td>31.5%</td>
<td>65.6%</td>
<td>ECOG 0, 1</td>
<td>945</td>
<td>• Nivolumab ((n = 316)) *Nivolumab + Ipilimumab ((n = 314))</td>
<td>OS and PFS</td>
<td>44%</td>
<td>52%</td>
<td>11.5 mos</td>
<td>21%</td>
</tr>
<tr>
<td>NCT01866319 *(KEYNOTE-006) *[32,41]</td>
<td>III</td>
<td>66%&lt;sup&gt;2&lt;/sup&gt;</td>
<td>36.2%</td>
<td>19.5%</td>
<td>ECOG 0, 1</td>
<td>834</td>
<td>• Pembrolizumab (q2wk (n = 279)) *Pembrolizumab (q3wk (n = 277)) *Ipilimumab (q3wk (n = 276))</td>
<td>OS and PFS</td>
<td>37%</td>
<td>48.1%</td>
<td>5.6 mos</td>
<td>10.1%</td>
</tr>
</tbody>
</table>

*Previously untreated advanced disease.

<sup>2</sup>Previous systemic therapy included no more than one line: chemotherapy, BRAF/MEK inhibitor, immunotherapy (interferon, peg-interferon, IL-2).

<sup>3</sup>Negative or indeterminate.

<sup>4</sup>AE = adverse events; ECOG = Eastern Cooperative Oncology Group; IL-2 = interleukin-2; NR = not reported; ORR = objective response rate; OS = overall survival; PD-L1 = programmed death ligand 1; PFS = progression-free survival.

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PD-L1 expression is the cornerstone of biomarker for treatment selection in non–small-cell lung cancer. [39] In metastatic melanoma, however, results have been inconclusive and many PD-L1–negative tumors respond to anti–PD-1 antibodies. [40] Despite exploratory data from CheckMate 067 that suggested the preplanned PD-L1–negative subgroup derived the greatest benefit from combination immunotherapy, a statistical test for interaction was not positive, and PD-L1 status alone is an insufficient biomarker for treatment selection in metastatic melanoma. [33, 35] An argument can be made that chemotherapy would have given a more rapid response, although response rates are infrequent with that treatment (9.8%–14.5%) and we believed the patient would not withstand the chemotherapy’s adverse effects.

Outcome of this case

The patient was started on pembrolizumab monotherapy as first-line treatment. After receiving 2 cycles, his performance status (ECOG) worsened to grade 3 and liver function parameters deteriorated rapidly (AST, 496.1 IU/L; ALT, 533.6 IU/L; GGT, 988.0 IU/L; ALP, 1068.2 IU/L; TBIL, 2.15 mg/dL; DBIL 0.71 mg/dL). LDH was 1915 IU/L, while platelets and coagulation tests remained in the normal range. The patient’s clinical course continued to worsen. He went to best supportive care, and he died 3 weeks after his last dose of pembrolizumab. This case exemplifies that DHI is a rapidly fatal condition, regardless of the treatment you choose.

FINANCIAL DISCLOSURE: Dr. Castro-Alonso received a travel grant from Bristol-Myers Squibb (BMS). Dr. M. Bourlon has been a speaker for MSD and BMS. She has also been an advisor and received a grant from BMS. 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.

For references visit cancernetwork.com/QC-Hep-melanoma
ALL Therapy options interview
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for example, we need to know whether the patient is Philadelphia-positive. We check for the Philadelphia-like biology by checking the expression of certain markers such as cytokine receptor-like factor 2, overexpression involving checkpoint kinase 2 activation, or other arrangements including ABL1, ABL2, and cytokine receptors. Then we have the standard rubric of risk of ALL that usually has a good outcome. We look at CD20 expression, and we can add rituximab to frontline therapy for these patients. In T-cell ALL, we have to identify what we call the early T-cell precursor ALL, T-cell ALL, or Early T-precursor [ETP]-ALL. These include patients who have a certain immune phenotype, that is, CD1a-negative, CD5-dim (<75%), and CD8-negative, and one or more myeloid markers. These patients do not do well with a standard ALL regimen, and we are exploring new drugs such as venetoclax, but transplant should be offered in the frontline setting. In the past, we used to classify patients by WBC count, sex, and other factors. Today, based on biology, we are able to retune and redefine our ALL patient subgroups and design our treatment approach accordingly. When we have the diagnosis and baseline features, for example, we need to design a treatment approach for these patients.

Of course, the question of consolidation depends on the subtype of the patient. For example, in Philadelphia-positive ALL, we should offer transplantation up front, particularly in patients who cannot achieve complete molecular remission. Then we have transplant in first remission is reserved for patients who have bad features.

To summarize, we have different subsets of ALL. We identify the biology of the disease. We understand the severity of certain subsets and design consolidation and treatment approaches based on a patient’s baseline features.

Transplant in first remission is reserved for patients who have bad features.

Q: You mentioned minimal residual disease. Can you talk about how this is typically measured and if it is something now assessed in all patients? Or is this still only done at academic centers?

Dr. Jabbour: There’s nothing minimal about finding disease, because even having minimal disease is a sign of the cancer being refractory to treatment. If you look at the outcome with chemotherapy in ALL, if you give agent induction, about 90% of patients respond. But then, the vast majority do relapse, and our long-term outcome is only about 40% to 50% survival. This means there’s disease left that we may not be able to measure just based on morphology, indicating relapsed disease. Persistent minimal disease is the equivalent of relapse and treatment failure. This is not a biomarker but rather the persistence of disease whether detected at 4 weeks of a complete response or at 12 weeks. A meta-analysis with over 13,000 patients was published in 2017.[2] It showed that pediatric or adult ALL patients, regardless of how you measure MRD, have poor outcomes. Therefore, we need to understand, whether we are in a community practice or in academia, that we cannot treat ALL without having in mind MRD assessment and how to address it. Finally, the US Food and Drug Administration approved a drug based on MRD last year. This was the approval of blinatumomab for the treatment of both pediatric and adult B-cell ALL in first or second complete remission with MRD > 0.1%. New trials are being designed taking into account MRD, because MRD can be a great target endpoint for long-term outcome. When you run a trial assessing a new drug, instead of waiting 7 years for survival results, you can use MRD as a surrogate endpoint because it coordinates with outcome.

In practice, we should test for MRD. Another question is how to test for it and when? The agreement is that within 12 weeks of starting treatment, patients should be MRD-negative. There is a lot of debate here because some
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As illustrated throughout this conversation, the landscape and approach to treating ALL has seen changes related to a better understanding of disease biology, more sensitive tools to describe treatment responses with application of MRD-testing, and new agents incorporated into treatment algorithms. While inotuzumab ozogamicin, blinatumomab, and CAR-T cells are effective, consideration of their toxicity profiles and cost/access need to be taken into account.

**Neurotoxicity risks and individual patient profiles must be carefully considered in making treatment decisions for those diagnosed with ALL.**

The antibody-drug conjugate inotuzumab ozogamicin carries the risk of VOD – a risk also well described post-transplant. This risk should be factored into treatment planning; other non-modifiable risk factors, and those that may be modified, should be taken into account for patients who will move to transplant after receiving inotuzumab ozogamicin. Limiting pre-transplant exposure to inotuzumab, where possible, and selection of transplant conditioning therapy may be opportunities to reduce risk of VOD in this population.

Due to a short half-life of around 2 hours, blinatumomab administration consists of a continuous 28-day infusion of medication. In appropriate situations this can be managed in the ambulatory care setting after an initial hospitalization (7-day infusions may be prepared to reduce patient visits), but centers using this agent should establish clear transitions of care from the inpatient to outpatient setting to avoid interruptions in drug administration (unless, of course, drug administration is being held for toxicity). Blinatumomab administration requires close monitoring for cytokine-release syndrome (CRS) and neurotoxicity.

Speaking of CRS and neurotoxicity – these are also serious warnings associated with CAR-T therapy. At this time, centers must be certified and undergo training specific to the recognition and management of these complications in order to utilize CAR-T therapies. Patients and caregivers should be educated on the signs and symptoms of neurotoxicity as delayed onset in some patients who may not need to undergo a transplant. But there could be false-negative results. Having MRD-negative can be positive by next-generation sequencing where we look at the sequence of the immunoglobulin receptor at a very low level and follow it. This is being standardized and is approved by the Food and Drug Administration as a reliable test for MRD. This assay is more time-consuming and expensive compared to flow cytometry. Flow cytometry doesn’t require a baseline sample, and the sensitivity is 10E-4 (1 leukemic cell/100,000). With the PCR-based test, the sensitivity is 10E-5 (1 leukemic cell/100,000). To go more in depth, we have a new test based on next-generation sequencing where we look at the sequence of the immunoglobulin receptor at a very low level and follow it. This is being standardized and is approved by the Food and Drug Administration as a reliable test for MRD. This test allows us to reach a sensitivity of 10E-6.

If you look at the data from the PCR test or from flow cytometry, patients who are MRD-negative can be positive by next-generation sequencing. It’s important because today if someone is MRD-negative, you may say that patient is doing well and that patient may not want to go for transplant. But there could be false-negative results. Having MRD assessed in more depth is one way to identify those patients who may not need to undergo a transplant.

So, next-generation sequencing is gaining more momentum today, but still the message I want to highlight is to check for MRD. Do not continue to treat ALL without assessing clinicians say that maybe we should test for MRD at 4 weeks. That argument makes some sense, but it requires validation from different groups. For now, all of us who treat ALL have agreed that if you have levels of 10E-4 and above at 12 weeks, the outcome is really poor and these patients should be considered as refractory.

Of course, any time you have a patient who is MRD-positive is bad. How do we measure MRD? In the United States, the most common test is 6- to 8-color flow cytometry where we look at the expression of certain antigens on B cells and we define a normal population present. These tests require good expertise from the pathologist who reviews the flow cytometry results. We should send the first sample from the bone marrow to the pathologist. In Europe, they use a polymerase chain reaction (PCR)-based test with a look at the IgH [immunoglobulin heavy chain] receptor on the B cells. This requires a baseline clone and subsequent clones, and a good sample, to assess for MRD. This PCR-based assay is more time-consuming and expensive compared to flow cytometry. Flow cytometry doesn’t require a baseline sample, and the sensitivity is 10E-4 (1 leukemic cell/100,000). With the PCR-based test, the sensitivity is 10E-5 (1 leukemic cell/100,000). To go more in depth, we have a new test based on next-generation sequencing where we look at the sequence of the immunoglobulin receptor at a very low level and follow it. This is being standardized and is approved by the Food and Drug Administration as a reliable test for MRD. This test allows us to reach a sensitivity of 10E-6.

For references, visit cancertreatment.com/ALL-treat-Jab

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for MRD. Next-generation sequencing requires a baseline sample, as well as follow-up, just like the PCR-based test. One last test for MRD for Philadelphia-positive patients is to use PCR to check for BCR-ABL, and that has been standardized. The importance of MRD is that if you get to 3 months of treatment and a patient is in complete molecular response (CMR) with no disease left, this is great because we have shown that the outcome is excellent without transplantation in these patients. In contrast, if a patient is MRD-positive, you may need to go for transplant because the outcome is not so great.

Today, assessment for MRD and the results of MRD tests will dictate our approach to therapy moving forward. In the United States, we have a drug called blinatumomab, which is a CD3 bispesific engager that binds to CD19. The drug was approved based on multicenter phase II studies called the BLAST trial. Patients with MRD were given blinatumomab, and 80% responded. Today, someone with MRD-positive disease should be offered blinatumomab. They should not go for transplant unless they had blinatumomab and converting them to MRD-negative status had been tried, because we know outcomes with transplant are better in MRD-negative patients with ALL.

Q: It sounds like you are saying transplantation is not the goal for all patients. Can you talk in more detail about which patients are likely going to need a transplant versus those who will not?

Dr. Jabbour: Transplant is indicated in the frontline setting for patients who have hypodiploid ALL, for patients with 11q23 mutation, and for patients who have Philadelphia-like ALL, as well as for patients with Philadelphia-positive disease after blinatumomab who don’t achieve a CMR at 3 months, and finally, for patients with ETP-ALL. These are the patients for whom I would go to transplant in first remission.

A: Acute Lymphoblastic Leukemia

Acute lymphocytic leukemia (ALL), is an aggressive type of leukemia in which too many lymphoblasts or lymphocytes are found in the bone marrow and peripheral blood.

If ALL is not treated, typically it quickly progresses. It can spread to the lymph nodes, CNS, spleen, liver, and other organs.

ALL occurs in children and adults. Although treatment in children can achieve a good cure rate, prognosis has been less optimistic for adults with ALL.

Most recent estimates for 2019 are 5,930 new cases and 1,500 deaths in the United States.


Q: Can you talk about the different therapy options and for which patients these are appropriate in the relapsed, refractory setting?

Dr. Jabbour: In the relapsed setting, we’re making progress and have had several drugs approved in the last couple of years. One is inotuzumab ozogamicin, which is a CD22 antibody plus ozogamicin, a toxin. We also have blinatumomab, a bispecific engager antibody, and CAR [chimeric antigen receptor] T cells. Inotuzumab ozogamicin is targeted to CD22 expressed on B cells. When the drug binds to CD22, it is internalized and the ozogamicin is freed in the cell, and then causes double-stranded DNA breaks and kills the B cells. Blinatumomab is a bispecific engager that binds to CD3 on T cells and CD19 on B cells and activates T cells to kill the B cells. The CAR T cells are a big innovation in which a patient’s T cells are collected, re-engineered to express a receptor to CD19, and then infused back into the patient where they proliferate and kill the B cells.

Inotuzumab was approved based on a randomized trial that recruited patients who were refractory and randomized to either inotuzumab ozogamicin or standard of care. [3] There was an improvement in responses of 80% and better overall survival of 7.7 months. Blinatumomab was first approved based on a phase II study, and then based on a trial in patients with Philadelphia-negative ALL randomized to either standard of care or blinatumomab.[4] Patients on blinatumomab had higher response rates, higher MRD negativity, and better overall survival. That led to the full approval of this drug. In addition, the drug was tested in Philadelphia-positive disease. For both Inotuzumab and blinatumomab, better outcomes are obtained in first salvage compared to second salvage.

At MD Anderson, we took a step beyond that, knowing that these drugs are not myelosuppressive and can be combined with low with low-dose chemotherapy.[5] When we did that, we had a response of 80% overall, and of 90% in first salvage; we improved survival as well: on average, the median survival was 14 months. If you look at first-salvage patients, survival at 2 years is beyond 50%, which is really good. With a 50% survival for patients at first salvage, and compared to historical data with inotuzumab or blinatumomab, the survival is about 7 months and here it’s 14 months, so we doubled the survival. I think the drugs are good, but it would be better to use them in combination, because we
can have a better outcome and better safety profile. For example, with inotuzumab, there is veno-occlusive disease (VOD). The combination allows us to use a lower dose of inotuzumab. Instead of using 1.8 mg/m² per cycle, we now use the third of the dose with a total dose given of 2.7 mg/m². With this kind of combination with the lower dose, we see less VODs. Furthermore, we use blinatumomab in a sequential fashion that allows us to distant transplant while deepening the responses and avoid VODs, and we have survival at 2 years of 50%. I don’t think these strategies are competing. Immunotherapies are great, but they can be used in combination.

This brings me to the last treatment strategy, which are CAR T cells. Again, these are T cells from the patient that are engineered to kill the patient’s B cells. Approval was based on a phase II multicenter trial with more than 100 patients screened, but not all were enrolled.[6] The patients who did receive the infusion had responses that were still durable at 18 months and led to approval of the strategy. This therapy comes at the price of toxicities, mainly neurologic events, and cytokine syndrome. We see better efficacy in patients with minimal disease compared to patients with bulky disease. The approval is for patients only up to age 25, and we need more work on the adults. But I see a future role for the CAR T cells, maybe as a replacement for allogeneic stem cell transplantation. These are complementary approaches that will lead to significant improvement in outcomes for these patients.

Q: Finally, could you highlight some of the novel agents that are in the late stage of development for ALL?

Dr. Jabbour: We learned a lot from the relapsed, refractory setting experience with these drugs, and today we are testing these drugs in the frontline setting. We have an ongoing trial, for example, in older patients. Older patients do not do well because of bad organs and aggressive disease where survival is usually 4 to 6 months. We tested the combination of low-dose chemotherapy, inotuzumab, and blinatumomab in this group and found a highly tolerable regimen with a high response rate and a survival rate at 3 years of 54%, contrasting with 10% to 15% historically. Therefore, we are making progress by moving these drugs to the frontline setting and going into randomized trials to confirm their efficacy. Furthermore, we know that in young patients intensive chemotherapy can be toxic and can cause long-term complications. If these immunotherapy drugs are really well tolerated, maybe we can simplify the chemotherapy and use these drugs in the frontline setting.

FINANCIAL DISCLOSURES:
Dr. Jabbour has received funding grants from Amgen, Pfizer, Takeda, Adaptive, Novartis, Spectrum, AbbVie, and BMS.

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Overview: FDA Approval of Olaparib Maintenance for BRCA-Mutated Ovarian Cancer

Naveed Saleh, MD, MS | Clinically reviewed by Mehmet Sitki Copur, MD, Editor-at-Large

The US Food and Drug Administration (FDA) recently approved a new indication for olaparib (Lynparza) for maintenance treatment in adult patients with germline or somatic BRCA-mutated advanced epithelial ovarian cancer.[1] Important information about new and previous ovarian cancer indications for olaparib is detailed here.

New Indication as Maintenance Treatment
FDA approval of olaparib maintenance treatment on December 19, 2018, was supported by results from the SOLO-1 trial (NCT01844986), a randomized, double-blind, placebo-controlled trial spanning several centers. SOLO-1 examined the efficacy of olaparib vs placebo in subjects with BRCA-mutated advanced epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy.

In the trial, patients were randomized in a 2:1 ratio to receive olaparib tablets 300 mg po bid (n = 260) or placebo (n = 131). In total, 388 patients exhibited a centrally confirmed germline BRCA1/2 mutation, with 2 patients exhibiting a centrally confirmed somatic BRCA1/2 mutation. The primary endpoint was progression-free survival (PFS) assessed by investigators. Substantial improvement in PFS was demonstrated with olaparib vs placebo.[1]

After a median follow-up of 41 months, the risk of disease progression or death was 70% less with olaparib vs placebo. The estimated median PFS was not met in the olaparib arm and was 13.8 months in the placebo arm (hazard ratio [HR], 0.30; 95% CI, 0.23–0.41; *P* < .001). In total, 60% of women taking olaparib did not experience cancer growth or return vs 27% of women taking placebo.

Of note, overall survival data were not yet realized in the study.

PFS2, a secondary endpoint defined as time from randomization to a second progression event, was a median of 41.9 months with placebo and, once again, not yet met with olaparib (HR, 0.50; 95% CI, 0.35–0.72; *P* < .001).

Adverse events secondary to the drug were usually low-grade. The most common adverse effects were nausea, fatigue, abdominal pain, vomiting, and anemia, among others. Recommended dosage is 300 mg po bid (total, 600 mg/d), with or without food.[2]

Importantly, the FDA also approved the BRACAnalysis CDx test (Myriad Genetic Laboratories, Inc.), a companion diagnostic tool used to isolate patients with germline BRCA-mutated advanced epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer who are eligible for olaparib. The effectiveness of the tool was based on the SOLO-1 trial population for whom deleterious or suspected deleterious germline BRCA-mu-
tated status was confirmed using prospective or retrospective testing with the BRACAnalysis CDx test.[1]

**Other Indications for Ovarian Cancer**

On August 17, 2017, the FDA approved olaparib tablets for the maintenance treatment of adult patients with recurrent epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy.[3] In 2014, they had approved the capsule form of the drug for the treatment of patients with deleterious or suspected deleterious germline \textit{BRCA}-mutated advanced ovarian cancer who have been administered 3 or more prior lines of chemotherapy.

FDA approval stemmed from the randomized, placebo-controlled, double-blind trials spanning many centers, SOLO-2 (NCT01874353) and Study 19 (NCT007553545), which involved patients with recurrent ovarian cancers who responded to platinum-based therapy.

In SOLO-2, 295 patients with recurrent germline \textit{BRCA}-mutated ovarian cancer, fallopian tube cancer, or primary peritoneal cancer were randomized in a 2:1 ratio to receive olaparib 300 mg po bid or placebo. The PFS as assessed by investigators showed a significant boost in those subjects taking olaparib vs placebo (HR, 0.30; 95% CI, 0.22–0.41; \(P < .0001\)). Estimated PFS was 19.1 months in the olaparib group and 5.5 months in the placebo group.[3]

Another notable finding of the SOLO-2 study was that after 2 years of taking olaparib, 43% of women did not experience disease progression vs 15% of women who took placebo.[4]

In Study 19, 265 patients with platinum-sensitive recurrent ovarian cancer—plus or minus \textit{BRCA} mutations—were assessed. A total of 136 patients were administered 400 mg olaparib bid and 129 patients were administered placebo bid. Results of Study 19 indicated that patients receiving olaparib vs placebo experienced a significant increase in PFS as assessed by investigators (HR, 0.35; 95% CI, 0.25–0.49; \(P < .0001\)). The approximate median PFS was 8.4 months in those taking olaparib and 4.8 months in those taking placebo.

Finally, in both studies, adverse reactions were limited and similar to those seen in SOLO-1. Similarly, the recommended olaparib dosage for both maintenance therapy and next-line treatment is 300 mg po bid, taken with or without food.[3]

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

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Two cancer cell subsets may drive tumor progression

At a high level, cancer cells can be categorized into two subsets:

- Mature, differentiated cancer cells
- Undifferentiated cancer stem cells (CSCs)

Differentiated cancer cells sustain and increase the volume of local tumors but lack the ability to self-renew. CSCs, however, possess the ability to originate tumors and metastasize.²,³

Therapies that target both subsets could help prevent tumor recurrence

While conventional chemotherapies may effectively target differentiated, proliferating cancer cells, CSCs can remain viable and reestablish tumors. The persistence of CSCs despite therapy could help explain why some tumors recur even after an initial reduction in size.⁴ Therefore, targeting both CSCs and differentiated cancer cells may be a rational therapeutic strategy.¹


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