ONCOLOGY®

PRACTICAL, PEER-REVIEWED PERSPECTIVES

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GASTROINTESTINAL CANCER

JOHN L. MARSHALL, MD, ON

Molecular Profiling and the Promise of Precision Medicine

“[It] is all about precision medicine
and biomarker-driven therapies.”

Lung Cancer Factors Associated With Treatment Refusal and Impact of Treatment Refusal on Survival of Patients With Small Cell Lung Cancer

Prostate Cancer Integrating PARP Inhibitors Into Advanced Prostate Cancer Therapeutics

Multiple Myeloma A 65-Year-Old Man With Back Pain and Imaging Findings of Spinal Cord Compression

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Precision Medicine Takes Center Stage in GI Cancer

The recent advances in immunotherapy have revolutionized cancer care and ushered in an era of true precision medicine. But to best utilize these extraordinary therapies, oncologists must be able to recognize specific biomarkers and oncologic drivers associated with an individual patient's cancer diagnosis. This is true, in particular, for oncologists specializing in the care of gastrointestinal (GI) cancers.

In this issue of *ONCOLOGY*®, we spoke with John L. Marshall, MD, director of the Ruesch Center for the Cure of Gastrointestinal Cancers at Georgetown Lombardi Comprehensive Cancer Center as well as co-chair of the *6th Annual School of Gastrointestinal Oncology*® (SOGO®), hosted by Physicians' Education Resource, LLC (PER®), about the rise of molecular profiling in GI cancer.

"It is so important for us as oncologists to make sure we're doing good molecular testing," says Marshall. "You need to do it right from the beginning of metastatic disease. Broad molecular profiling is quickly becoming the standard of care so that you [are able to] know all of the chess pieces on the chessboard. They're not common and unless you look under every single rock, you'll never find it.

"I think [the future] is all about precision medicine and biomarker-driven therapies," adds Marshall, noting that cancer physicians of the future may specialize in mutations and biomarkers rather than tumor type. "There's one member of my division who thinks that we should be RAS-ologists or [microsatellite instability] MSI-ologists instead of a GI or breast oncologist or a hematologist. I'm not sure we're there yet. But you can sort of feel like we're heading in that direction."

Also in this issue, we published original report investigating the factors associated with treatment refusal and its impacts on survival of patients with small cell lung cancer. The report highlights that more patients than ever are refusing treatment and discusses recommendations for better messaging for health providers and policy makers alike.

We also present a case report of a 65-year-old patient with spinal cord compression and a clinical quandary examining the role of post-mastectomy radiotherapy in locally advanced breast cancer. Read on to find out the optimal treatment for both of these challenging cases.

Within these pages, you will also read a review of the clinical data supporting the use of PARP inhibitors as a therapeutic option for patients with advanced prostate cancer. The recent approvals of both rucaparib (Rubraca) and olaparib (Lynparza) offer new hope for this subset of patients that historically have seen adverse outcomes.

I hope you find our journal helpful in caring for your patients through what is likely one of the most challenging times in their lives. As always, thank you for reading.

Mike Hennessy Sr

*Chairman and Founder of ONCOLOGY®'s
parent company, MJH Life Sciences™*

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Minority Enrollment to Clinical Trials: Road to Increased Access

Julie M. Vose, MD, MBA

For the outcome of clinical trials to have validity, participants should represent the patients that will be using the medical products, though this is often not the case. Racial and ethnic minorities are underrepresented in cancer clinical trials for a variety of reasons. This is a concern because people of different ages, races, and ethnicities may react differently to medical products.

The estimated extent of racial disparities in clinical trial access varies in the literature, yet recent reports—such as the FDA's 2018 Drug Trials Snapshots—indicate the presence of a remarkable imbalance. A total of 5157 patients participated in oncology trials that led to approvals of 17 new drugs. Overall, 38% of all participants were women, 68% were White, 15% were Asian, 4% were Black or African American, 4% were Hispanic, and 50% were 65 years and older.¹ These proportions sharply contrast with the racial distribution in the general United States population (76.6% White, 13.4% Black or African American, 5.8% Asian, 18.1% Hispanic or Latino). Further, only 36% of the trial participants were residents in the United States, which is a reflection of the increasingly

international nature of phase 3 oncology trials designed to support the worldwide marketing plans of the study sponsor. According to US Census Bureau projections, more than half of the population in the United States is expected to be other than non-Hispanic White by 2045.² In the absence of proactive planning, corrective measures, and systematic and effective intervention, the disparity between the clinical trial population and the changing population of patients with cancer in the United States is likely to worsen in the coming decades.

What can be done to reverse this trend and enhance clinical trial enrollment by minorities? Increasing minority representation in the health care professions will enhance the ability of the patients to feel more comfortable with the recommended options, including clinical trial participation. In addition, the outreach of health care opportunities to neighborhoods closer to patients' homes will allow access to those without consistent transportation. Eligibility criteria that allow for patients with more comorbidities to enroll when possible will also increase minority enrollment as well as represent a more real-world population on the study.

Another recent improvement is the congressional approval of the Clinical Treatment Act, which requires Medicaid to cover the routine clinical care costs of patients associated with participation in clinical trials. Since Medicaid serves a large portion of individuals from racial and ethnic minority groups, this legislation will remove some barriers to participation in clinical trials for this patient population. With a more representative patient population, the results of these clinical trials will have more accurate outcomes in real-world patients with the illness in question. In addition, the racial and ethnic minority groups will benefit with this increased access to clinical trials and cutting-edge health care opportunities. ■

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1. 2018 Drug Trials Snapshots Summary Report. FDA. January 2019. Accessed February 23, 2021. <https://www.fda.gov/media/120253/download>
2. Vespa J, Armstrong DM, Medina L. *Demographic Turning Points for the United States: Population Projections for 2020 to 2060*. Current Population Reports. US Census Bureau. February 2020. Accessed February 23, 2021. <https://www.census.gov/library/publications/2020/demo/p25-1144.html>

ONCOLOGY® has recently added a “Clinical Trials in Progress” segment. This addition to the print publication is meant to highlight and increase awareness about open trials. **Scan to see manuscript submission guidelines.**

MEET OUR EXPERT

Marshall is chief of the Division of Hematology/Oncology at Medstar Georgetown University Hospital and director of the Ruesch Center for the Cure of Gastrointestinal Cancer as well as co-chair of the *6th Annual School of Gastrointestinal Oncology® (SOGO®)*, hosted by Physicians' Education Resource®, LLC (PER®)

Molecular Profiling and the Promise of Precision Medicine

"You can't miss these opportunities. They don't come every day."

Roughly 26% of global cancer incidence and 35% of all cancer-related deaths worldwide are related to gastrointestinal (GI) disease.¹ Traditional treatment—consisting of surgery, radiotherapy, and chemotherapy—has shown limited efficacy and is accompanied by toxicities that often negatively affect a patient's quality of life. However, the rise of molecular profiling and next-generation sequencing has allowed investigators to identify and characterize genetic mutations, amplifications, and protein expression, leading to a new era of targeted and personalized therapy for patients with GI cancers. The ability to more accurately profile tumors has led to dramatic increases in survival and quality of life while reducing adverse effects (AEs)—so much so that the American Society of Clinical Oncology has named molecular profiling in GI cancers as its 2021 Advance of the Year.²

In a recent interview with *ONCOLOGY®*, John L. Marshall, MD, director of the Ruesch Center for the Cure of Gastrointestinal Cancers, discussed the importance of profiling every patient and the improved outcomes made possible by the use of immunotherapy.

Q: In your opinion, what is the biggest story in GI cancers right now?

MARSHALL: Molecular profiling continues to be the story. How do we subdivide our patients into their different molecular subtypes for therapies? With multidisciplinary care, how do we approach neoadjuvant therapies and combined modality approaches? We're all trying to put each other out of business: We're trying to put the surgeons out of business with [more effective] chemoradiation; we're trying to put the radiation oncologists out of business with better chemotherapy and better surgery. So, we're all trying to make the same or better outcomes while affecting patients less: fewer AEs, shorter treatments, less toxicity. So [the question becomes,] "How do we do that? How do we deliver the same or better outcomes with less patient toxicity?"

Q: Use of immunotherapy has become more and more important in treating GI cancer. What are you learning that's allowing you to make more use of the immune system?

MARSHALL: We have to remember, first, that only 10 years ago, no one on the planet, except for a

few people, thought immunotherapy would ever have an impact at all. We thought that idea was crazy. Why bother? But these checkpoint inhibitors were [such an incredible] breakthrough, to the point where now we say, "How come they're not working everywhere?" We should get them to work in every cancer, but we know that that's not happening so far. With GI cancers—unlike, say, lung cancer, melanoma, or kidney cancer, in which major breakthroughs have occurred quickly—it's been a little bit of a slower set of stairs to climb.

We have made a landmark breakthrough with microsatellite instability (MSI)—high cancers. So, with MSI-high colon cancer, in terms of frontline therapy, immunotherapy is beating chemotherapy. That's big news, because lots of our GI cancers are MSI high. Then, when it comes to PD-L1 positivity, it's gotten kind of confusing for us in GI cancers. Do you need any PD-L1 expression? Do you need a combined positive score of greater than or equal to 1, 5, 10? The answer is different for different settings. So, there's a lot of confusion right now, even among the GI oncology leaders, about who should get immunotherapy and when they should get it, depending on

these molecular markers. But what we really need is a way to turn on what we're calling "cold tumors," tumors that don't seem to be responding to immunotherapy. Are they not responding because the immune system is not seeing the tumor? Or is it because the defenses against the immune system are so strong that the immune system just can't get to the tumor? But our drugs currently are [starting to] break through. So, what we're seeing in liver cancers and bile duct cancers and some others are combinations of immune therapies resulting in improved outcomes. The holy grail right now, however, is in microsatellite-stable colon cancers and pancreatic cancers. These are tough nuts to crack with regard to immunotherapy. A lot of research is ongoing in that field, but so far, we've had no major breakthroughs.

Q: With confusion around the specifics of immunotherapy use, what do you recommend when other physicians come to you and ask when these drugs should be used?

MARSHALL: It all depends on the biomarkers of the patient. Sometimes, you get a result back that would make you say, "Stop everything and give [the immunotherapy to] him now." Other times, you might have a setting where [the treatment is] much less likely to work, where the benefit is lower. So, you save it for later. Patients are highly enthusiastic about these medicines: They watch TV, they watch the advertising. They see the remarkable outcomes from friends and neighbors who are getting these uncertain diseases. So, they want [those outcomes,] too. There has never been a higher awareness of the kind of treatment [than with these immunotherapies]. Doctors want to see the positive outcomes, [too]; we love it when treatments work. But we also know that these medicines are expensive and that in certain circumstances, they are "hail Marys" and they don't work all that well. So, every physician needs to make that a decision that is [individualized for each] patient. Is the treatment approved? Will guidelines support it? Will insurance cover it? What are the chances that it will work?

Q: You mentioned TV advertising and awareness. How do you manage the treatment of a patient who comes in and says they want pembrolizumab (Keytruda)? Or one who says they've seen the latest study and now wants to deviate from their treatment plan?

MARSHALL: Well, it's not difficult to manage, if you just tell them the truth. Tell them, "we've tried it in your cancer, and it didn't work, and there are AEs and risks." To me, it is a fairly easy answer. It doesn't mean you're happy about it. [It's no different than] if a patient came in and said, "Why can't you do surgery on that?" I don't think we as oncologists are obligated to provide a therapy that doesn't work just to maintain hope or to make peace with a patient's soul. It's our job to talk them off that ledge and explain to them why that really is not appropriate or feasible.

Q: In which specific areas do you see immunotherapy having the biggest impact?

MARSHALL: Immunotherapy is having a significant impact on liver cancer. I never thought I would say as a GI cancer expert that the disease we're making the most progress in is liver cancer, because it's been among our most difficult cancers to treat [for a very long time]. So, we're excited about that. We already knew immunotherapy front-line has been showing some benefit, but now evidence from new studies supports first- and second-line [treatment] with checkpoint inhibitors. This just adds to the strength and the focus of [these treatments] being the appropriate therapy. Now, not many oncologists deal with liver cancers (although they are increasing in incidence), so many oncologists out there would send their patients with liver cancer to specialty centers, for example, for transplants or liver-directed therapies. I think, with these new therapies and immunotherapies in the hands of oncologists, we're going to see a lot more liver cancer being treated primarily in the community.

The esophageal study [CheckMate 577;

NCT02743494] is also exciting because we know that gastroesophageal junction cancer is a difficult disease to start with. Here, we're talking about a surgery that can be a big deal for patients. So, what I'm [wondering is whether, as a] next step, something like [immunotherapy could be used] after chemoradiation to replace surgery. That would be something I would love to see. But for right now, after surgery, the patient who hasn't had full or complete response to the chemoradiation is a candidate for immunotherapy. And the data are impressive, indicating that more people are cured of their disease and progression-free survival is quite positive. So, I think it immediately becomes a new standard of care for that subpopulation of patients.

It's been really fun. We've been jealously watching as the lung cancer pie chart gets more and more subsections, showing how different drugs are working for different kinds of lung cancer. We're finally getting that pie chart with colon cancer and other GI cancers getting divided [by druggable targets], with BRAF being the latest major addition. But honestly, right on its heels, is HER2 targeting. There is a new exciting recent approval for HER2-targeting agents in gastric cancer, and we think that will quickly follow in colorectal cancer. So, it is very important for us as oncologists to make sure we're doing good molecular testing. You need to do it right from the beginning of metastatic disease; you need to know MSI, HER2, RAS, BRAF—and there'll be others. Broad molecular profiling is quickly becoming the standard of care. Whether it's a [suspected] NTRK- or HER2-positive colon cancer or whatnot, you [have] got to look into every single patient. And you need to track [results] in your chart, because they can get lost in the electronic medical record somewhere. In your history of present illness, [you have to] make sure you have listed the molecular positives and negatives. For every single patient with every GI cancer, this is critical to making sure you're delivering the best care, given so many new approvals in all of these spaces, and so many options for all of these patients that can have major

benefits. You can't miss these opportunities. They won't come every day. But when you find them, it's pretty cool.

Q: Breakthroughs in the treatment of some of the more difficult GI cancers are notable, but other areas, such as colorectal cancer, seem to be just holding steady. Why do you believe that is the case?

MARSHALL: Well, we go through spells, if you will. You understand the biology better, and then you go after it. Despite all the energy in pancreas cancer, there really hasn't been a lot of progress. Liver cancer is an exception; maybe gastric cancer is an exception; and neuroendocrine cancers are an exception. But we are bringing these fields along. I actually think the problems are research funding and the understanding of the science behind these diseases. One of the cool new discoveries of late is our microbiome. The bacteria that live in our GI tract, in our mouths, and on our skin clearly [contribute to] our health. And the more we look, particularly for colorectal cancer, the more we're seeing that it's that interface between the bacteria and the cancer that might have some special relationship that's creating this biology. Why is right-sided colon cancer different from left-sided? And why the differential expression? We're really not even sure of that yet, but the microbiome may be the answer. My guess is that as we continue to look at that microbiome science, we'll begin to see this explosion of new knowledge, in the next 5 years or so. Maybe we'll learn how to better control the immune system, or maybe how to eat better, or control our microbiomes so that they are the most balanced, the most healthy for us as individuals. So, I'm excited about that. A lot of that research is being pushed by emotion, in that the funding comes from the emotional reaction [of seeing] young people with colon cancer. We're seeing 20-, 30-, 40-year-olds getting colon cancer—and we say, wait, that's not supposed to happen; we should study that. Now we're starting to see the money come to fund the research, drawn by that emotion, which is then triggering success.

Q: What recently reported or soon-to-be reported data excite you?

MARSHALL: One series of studies is looking at frontline immunotherapy in various patients. We're seeing more and more studies of combinations of immunotherapies and chemotherapy, or immunotherapies and other [treatments], in earlier lines of therapy; understanding better how to optimize that treatment early on [is important]. I'm looking forward to seeing some of those studies. In the adjuvant and neoadjuvant world, I think we are all struggling with how to incorporate things like microsatellite instability into neoadjuvant approaches. On the one hand, we have data that say chemotherapy is harmful in the space. On the other hand, we don't [have any better choices], right? We don't have immunotherapy approval in that space for adjuvant approaches. So those studies will be critical to how we approach those patients from the beginning, not just in the metastatic setting. I think those are the main areas now. All of oncology is shifting [away from] a one-size-fits-all to an individualized approach. So, most of the coolest studies out there now are not big randomized trials. The coolest studies are patients with a particular molecular abnormality and a particular drug. For example, we have drugs now that really do a good job with *KRAS* mutations. So, we have umbrella studies, these basket studies individualized for the right patient, [the right] molecular biomarker, and the right drug for the best outcome. That's the coolest thing that's happening.

Again, I think [the future] is all about precision medicine and biomarker-driven therapies. I'd love to be wrong about this, but I don't see a time when one medicine or another is going to have a dramatic impact on a bunch of different cancers or on a larger underenriched patient population. I think those kinds of medicines are still important, but I think our knowledge about cancer and its variable expression—why your cancer would be different than my cancer—and understanding how to apply that [knowledge] is really where the future is. [More often,] we're segregating patients

into smaller and smaller buckets and treating that very specific disease or that very specific molecule rather than [utilizing] an overarching idea of therapy. It's more difficult because you have to find those needles in the haystack, but what's equally encouraging is that we're seeing a similar phenomenon across different subtypes. [Let's take] some molecular drivers, MSI and NTRKs, for example: If you have one of those, almost regardless of what kind of cancer you have, the drugs work. So, this was the dream. In fact, we have fights in our own division about [what constitutes] a GI oncologist—[actually,] one member of my division thinks that we should be RAS-ologists or MSI-ologists instead of a GI oncologist or breast oncologist or hematologist. I'm not sure we're there yet. But you can sort of feel like we're heading in that direction.

Q: How may other breakthroughs have an impact in the field?

MARSHALL: The biggest new technology that is having [an impact] that we weren't expecting is the use of artificial intelligence. We now have big data sets, huge sets of molecular data and clinical outcomes, and [although] we're not smart enough [to interpret all of it], we have machines that are. So, something I'm looking forward to is using artificial intelligence (AI) machine learning to [analyze] what [molecular] profile a patient has and predicting what treatment we should give. I [assure] you that you're better off receiving treatment [suggested by] this AI profiling than [any] other treatment. My hope is that AI technology will make us smarter in this confusing world of oncology, where we have multiple choices and lines of therapy. ■

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Factors Associated With Treatment Refusal and Impact of Treatment Refusal on Survival of Patients With Small Cell Lung Cancer

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ABSTRACT:

BACKGROUND: With fewer than 7% of patients with small cell lung cancer (SCLC) surviving 5 years after diagnosis, the receipt of recommended treatment is of utmost importance for patient survival. Nevertheless, treatment refusal by patients with SCLC has not been studied well. Our study examined factors associated with treatment refusal and the effect of refusal on patient survival.

METHODS: From the National Cancer Database, we analyzed data of 107,988 patients with SCLC diagnosed between 2003 and 2012. Treatment refusals were analyzed separately for chemoradiotherapy among patients with limited-stage disease (LS-SCLC) and chemotherapy among those with extensive-stage disease (ES-SCLC). We used logistic regression to investigate factors associated with treatment refusal. We estimated survival probability using the Kaplan–Meier method and compared survival of those who received and refused treatment using Cox proportional hazards regression analysis.

RESULTS: The refusal rates of chemoradiotherapy among patients with LS-SCLC and chemotherapy among those with ES-SCLC were 1.34% and 4.70%, respectively. From 2003 to 2012, trends show an increase of refusals, especially among the patients with ES-SCLC who were recommended chemotherapy. Multivariable analyses showed that in both SCLC groups, older age at diagnosis (>70 years), female gender, uninsured status, and presence of comorbidities were associated with treatment refusals. Patients with LS-SCLC who refused chemoradiotherapy had a higher risk of mortality than those who received treatment (HR, 4.96; 95% CI, 4.45–5.53); the median survival of those who refused treatment was 3 months vs 18 months for those who received it ($P < .001$). Similarly, patients with ES-SCLC who refused chemotherapy had a higher risk of mortality than those who received treatment (HR, 3.69; 95% CI, 3.48–3.92); the median survival was 1 month vs 7 months, respectively ($P < .001$).

CONCLUSIONS: Treatment refusal among patients with SCLC was associated with worse survival. Strategies to increase patient acceptance of the recommended treatment need to be studied further.

KEYWORDS: Treatment, refusal, small cell lung cancer, survival

Introduction

Of the estimated 234,030 new lung cancer cases diagnosed in the United States in 2018, more than 30,000 cases were identified as small cell lung cancer (SCLC).¹ Analyses of Surveillance, Epidemiology, and End Results Program (SEER) data indicated that the 5-year survival rate of SCLC was less than 7%.¹ In addition, in the last 2 decades, the SCLC survival rate has shown little improvement.²

Therapeutic options for SCLC have not significantly changed in the last 30 years.^{3,4} Concurrent chemoradiotherapy is typically recommended for patients diagnosed with limited-stage SCLC (LS-SCLC), whereas those diagnosed with extensive-stage SCLC (ES-SCLC) are treated predominantly with chemotherapy.^{3,5,6} Lack of patient acceptance of recommended treatment has been implicated by previous studies as a key factor in SCLC survival.^{3,4,7} Nonetheless, there is a lack of research concerning treatment refusal among patients with SCLC.^{4,8}

Our study addressed this gap by examining factors associated with treatment refusal by patients with SCLC in a US national facility-based cancer registry. We also analyzed the trend of treatment refusal over time as well as the effect of treatment refusal on patient survival.

Materials and Methods

Study Population, Design, and Data Source

The National Cancer Database (NCDB) provides national cancer surveillance data through a joint program of the American College of Surgeons' Commission on Cancer (CoC) and the American Cancer Society (ACS).⁹ This database captures approximately 70% of newly diagnosed cancer cases.^{9,10}

We used cross-sectional design in the analysis of factors associated with treatment refusal and retrospective cohort design in the analysis of survival data. The samples for analysis were drawn from the 198,405 SCLC cases diagnosed between 2003 and 2012. **Figure 1** shows the sample selection process. Criteria for data inclusion were: (1) confirmed diagnosis of primary invasive SCLC according to the *International Classification of Disease for Oncology, Third Edition* codes 8041-8045; (2) diagnosis established at a CoC-accredited facility, and patient received all or part of their treatment from 1 or more CoC facilities; (3) diagnosis confirmed with cancer stage, and patient was treated at 1 or more of the following types of CoC facilities: community, comprehensive community, and academic cancer programs; (4) known insurance status; and (5) recommendation for first line of treatment was either chemotherapy or radiation or combination of chemoradiotherapy. We utilized the data of 107,988 eligible patients in our analyses.

Exposures and Outcomes

We included sociodemographic and clinical characteristics as predictor variables. Information on cancer stage was taken from the NCDB analytic stage, which uses standards publicized by the American Joint Committee on Cancer (7th edition).⁹ In the analysis, we followed the recommendation of the International Association for the Study of Lung Cancer by grouping stages I to III as LS-SCLC and stage IV as ES-SCLC.¹¹ Comorbidities were calculated using the Charlson Comor-

FIGURE 1. Sample Selection

*Criteria are nonmutually exclusive.

CoC, American College of Surgeons' Commission on Cancer; NCDB, National Cancer Database.

bidity Index.¹² We used the NCDB definition of median income quartile according to the proportion of income range in the patient's area of residence for income categories. Residence category was based on those established by the United States Department of Agriculture Economic Research Service.⁹

Our outcome variables were refusal of recommended treatment and 5-year overall mortality. Refusal of recommended treatment was defined as standard therapies recommended by a physician(s) and refused by the patient. We analyzed data of those patients with LS-SCLC who were recommended chemoradiotherapy and of those with ES-SCLC who were recommended chemotherapy. Our analysis focused particularly on treatment refusal by

patients who were recommended the above therapies, through the comparison of their median survival to those who accepted recommended treatment. In addition, we examined the effect of treatment refusal on patient survival in the multivariable model.

Statistical Analysis

The χ^2 test was used to examine differences in demographic and clinical characteristics of patients with LS-SCLC and ES-SCLC who refused and received the recommended treatments. We used multivariable logistic regression to examine factors associated with refusal of chemoradiotherapy among patients with LS-SCLC and refusal of chemotherapy among patients with ES-SCLC. Backward selection was used

to fit the multivariable logistic regression model. Changes in the proportion of treatment refusal over time for cases diagnosed between 2003 and 2012 are shown graphically in **Figure 2**. We used the Kaplan-Meier method to estimate survival probabilities and log-rank test to assess survival differences. We performed multivariable Cox proportional hazards (PH) regression to examine the effect of treatment refusal on the risk of mortality, adjusted for other factors. The PH assumption was tested using log-log plots; all predictors met the proportionality assumption. Analyses were performed using SAS software version 9.4 (SAS Institute; Cary, NC).

Confidentiality and Ethics

We used data from a deidentified NCDB file. The ACS and CoC have not verified, and neither is responsible for, the analytic and statistical methods utilized in this study. The statements made in the discussion and the conclusions drawn from these data are solely the authors' responsibility. This study has been classified as exempt by the University of Nebraska Medical Center's Institutional Review Board due to the use of deidentified data.

Results

Demographic and Clinical Characteristics

Of the 107,988 SCLC cases included in the analysis, 40,432 patients were diagnosed with LS-SCLC; and 67,556 with ES-SCLC. Comparison of characteristics of patients who received and refused treatment for LS-SCLC and ES-SCLC are presented in **Table 1**. Separate analyses among those with LS-SCLC and ES-SCLC showed that higher proportions of patients with older age at onset (>70 years), women, and patients treated in a comprehensive community cancer program refused the recommended treatment modalities ($P < .001$). Interestingly, those without comorbidities had a higher proportion of refusal than those with comorbidities.

FIGURE 2. Refusal of Recommended SCLC Treatment by Stage at Diagnosis, NCDB 2003-2012

ES-SCLC, extensive stage SCLC; LS-SCLC, limited stage SCLC; NCDB, National Cancer Database; SCLC, small cell lung cancer.

For the first-line treatment (data not shown), chemoradiotherapy was recommended to 75% of the patients with LS-SCLC ($n = 40,432$). Among patients diagnosed with ES-SCLC ($n = 67,556$), chemotherapy and chemoradiotherapy were recommended to 47% and 45%, respectively.

Trend of Treatment Refusal

In total, 1898 patients declined the recommended chemoradiotherapy for LS-SCLC and the recommended chemotherapy for ES-SCLC. **Figure 2** shows the increase in the proportion of refusal of each therapy over 10 years. Overall, refusal of the recommended chemoradiotherapy among patients diagnosed with LS-SCLC was 1.34% and refusal of the recommended chemotherapy among patients with ES-SCLC was 4.70%. Analysis of 10 years' worth of data shows that the increase in refusal among those with ES-SCLC was higher (50%) than it was among those with LS-SCLC (34%).

Factors Associated With Treatment Refusal

After adjusting for demographic and clinical characteristics, we found that age

at diagnosis, gender, insurance status, and comorbidity score were associated with the refusal of chemoradiotherapy among patients with LS-SCLC (**Table 2**). Patients diagnosed when aged >70 years were more likely to refuse treatment than those aged 50 to 70 years; the adjusted odds ratio (AOR) for refusal of chemoradiotherapy was 3.50 (95% CI, 2.77-4.44). Women were more likely to refuse recommended chemoradiotherapy than men (AOR, 1.29; 95% CI, 1.05-1.58). Compared with those with private insurance, uninsured patients were more likely to refuse treatment (AOR, 3.61; 95% CI, 2.05-6.35). In addition, we found that patients with comorbid conditions were more likely to refuse recommended chemoradiotherapy than those without comorbidities (AOR, 2.54; 95% CI, 1.94-3.31).

The multivariable logistic regression analysis showed that factors similar to those observed in the analysis of LS-SCLC were associated with refusal of chemotherapy among patients with ES-SCLC (**Table 3**). Patients diagnosed when aged >70 years were more likely to refuse chemotherapy than those aged 50 to 70 years (AOR, 2.25; 95% CI, 1.99-2.55). Women were more likely

TABLE 1. Characteristics of Patients With Small Cell Lung Cancer Who Received and Refused Treatment

Characteristics	Limited stage ⁺ (n = 30,585)		P	Extensive stage ⁺⁺ (n = 31,679)		P
	Received n = 29,001 n (%)	Refused n = 409 n (%)		Received n = 29,792 n (%)	Refused n = 1489 n (%)	
Age at diagnosis (years)						
<50	2280 (7.9)	8 (2.0)	<.001	1736 (5.8)	34 (2.3)	< .001
50–70	18,950 (65.3)	142 (34.7)		17,886 (60.0)	573 (38.5)	
>70	7771 (26.8)	259 (63.3)		10,170 (34.1)	882 (59.2)	
Gender						
Male	12,816 (44.2)	156 (38.1)	.014	15,566 (52.3)	651 (43.7)	< .001
Female	16,185 (55.8)	253 (61.9)		14,226 (47.8)	838 (56.3)	
Race						
White	25,972 (89.6)	362 (88.5)	.470	27,047 (90.8)	1358 (91.2)	.542
Black	2370 (8.2)	34 (8.3)		2034 (6.8)	92 (6.2)	
Others/unknown	659 (2.3)	13 (3.2)		711 (2.4)	39 (2.6)	
Median income quartiles, 2008–2012						
< \$38,000	6290 (21.7)	100 (24.5)	.101	6188 (20.8)	317 (21.3)	.664
\$38,000–\$47,999	8116 (28.0)	118 (28.9)		7924 (26.6)	398 (26.7)	
\$48,000–\$62,999	7510 (25.9)	100 (24.5)		7784 (26.1)	402 (27.0)	
\$63,000+	6298 (21.7)	88 (21.5)		6899 (23.2)	330 (22.2)	
Unknown	787 (2.7)	3 (0.7)		997 (3.4)	42 (2.8)	
Category of residence						
Metro counties	21,633 (74.6)	310 (75.8)	.228	22,293 (74.8)	1119 (75.2)	.681
Urban counties	5428 (18.7)	81 (19.8)		5275 (17.7)	264 (17.7)	
Rural counties	723 (2.5)	9 (2.2)		781 (2.6)	43 (2.9)	
Unknown	1217 (4.2)	9 (2.2)		1443 (4.8)	63 (4.2)	
Insurance status						
Uninsured	1262 (4.4)	17 (4.2)	<.001	1436 (4.8)	57 (3.8)	<.001
Private insurance	10,661 (36.8)	46 (11.3)		9056 (30.4)	222 (14.9)	
Medicaid	2416 (8.3)	24 (5.9)		2421 (8.1)	75 (5.0)	
Medicare	14,662 (50.6)	322 (78.7)		16,879 (56.7)	1135 (76.2)	
Charlson/Deyo Comorbidity Index score						
0	18,058 (62.3)	169 (41.3)	<.001	16,269 (54.6)	664 (44.6)	<.001
1	7974 (27.5)	154 (37.7)		9193 (30.9)	530 (35.6)	
2	2969 (10.2)	86 (21.0)		4330 (14.5)	295 (19.8)	
CoC facility						
Community cancer program	4323 (14.9)	75 (18.3)	.036	4438 (14.9)	218 (14.6)	.002
Comprehensive community cancer program	17,704 (61.1)	254 (62.1)		17,941 (60.2)	959 (64.4)	
Academic/research program	6974 (24.1)	80 (19.6)		7413 (24.9)	312 (21.0)	

*Patients with LS-SCLC who were recommended chemoradiotherapy, including those who did not receive for unknown reason.

**Patients with ES-SCLC who were recommended chemotherapy, including those who did not receive for unknown reason.

CoC, American College of Surgeons' Commission on Cancer; ES-SCLC, extensive stage SCLC; LS-SCLC, limited stage SCLC; SCLC, small cell lung cancer.

FIGURE 3. Survival Plots of Chemoradiotherapy for LS-SCLC and Chemotherapy for ES-SCLC

ES-SCLC, extensive-stage SCLC; LS-SCLC, limited-stage SCLC; SCLC, small cell lung cancer.

to refuse recommended treatment than men (AOR, 1.42; 95% CI, 1.27-1.58). Uninsured patients were more likely to refuse chemotherapy than those with private insurance (AOR, 1.76; 95% CI, 1.29-2.40). Patients with ES-SCLC with comorbidities were more likely to refuse chemotherapy than patients without comorbidities (AOR; 1.43; 95% CI, 1.23-1.65). As previous studies had suggested,^{13,14} interactions of race with variables including gender, insurance status, and comorbidity were examined separately for both LS-SCLC and ES-SCLC, but no significant association was found. We used backward selection to fit the multivariable logistic regression model, with cutoff 0.2 to be included in the model and 0.05 to stay in the model. Also, we tested the interaction among variables in the model such as race, gender, insurance status, and comorbidity and found no significant association.

Survival of SCLC Cases

The overall median survival for all patients with SCLC included in the analysis was 9.4 months. Among patients with LS-SCLC who were recommended

chemoradiotherapy, the median survival of patients who refused and received the treatment was 3 months and 18 months, respectively ($P < .001$) (Figure 3). For patients with ES-SCLC, median survival of those who refused chemotherapy was 1 month compared with 7.5 months for patients who received treatment ($P < .001$). Within 1 year following diagnosis (data not shown) among patients with LS-SCLC who were recommended chemoradiotherapy, 67% who received the treatment had survived, compared with 14% of those who declined. The 5-year survival of patients with LS-SCLC who received chemoradiotherapy was 17% compared with only 2% of those who refused (Figure 3). For ES-SCLC, the 1-year survival of patients who received the recommended chemotherapy was 25%, compared with 3% of those who refused.

We included age, gender, primary payer, category of residence, presence of comorbidity, facility, and treatment status in multivariable analyses using Cox PH regression. Results are presented in Table 3 and indicate that among patients with LS-SCLC who were recommended

chemoradiotherapy, those who refused treatment had a higher risk of mortality than those who received treatment (HR, 4.96; 95% CI, 4.45-5.53). Similarly, among patients with ES-SCLC who were recommended chemotherapy, patients who refused treatment had a higher risk of mortality than those who received it (HR, 3.69; 95% CI, 3.48-3.92).

Discussion

Our study found that the majority of first-line treatments received by patients with SCLC in the database met national clinical practice guidelines, which include a combination of chemotherapy and radiation therapy for LS-SCLC and chemotherapy alone for ES-SCLC.^{5,15} Regarding survival among both the LS-SCLC and ES-SCLC groups, patients who accepted recommended treatment had significantly higher survival than those who refused. The overall refusal of the recommended chemoradiotherapy among patients with LS-SCLC was 1.34%, and refusal of chemotherapy among those with ES-SCLC was 4.70%. These proportions are smaller than the overall treatment refusal reported by Ward et al, which was 9% from an

analysis of 11 cancer facilities.¹⁶ Our analyses indicated that over time, there were increases in the proportions of treatment refusal of patients with both LS-SCLC and ES-SCLC. In particular, among patients with ES-SCLC, the refusal of treatment increased by 50% in 10 years. The fact that three-fourths of SCLC diagnoses are for ES-SCLC suggests that our findings on treatment refusal deserve special attention. Aizer et al indicate that compared with other cancers, refusal of treatment among patients with SCLC was more likely to result in death due to cancer.¹⁷

Of factors associated with treatment refusal, age at diagnosis was significantly associated with refusal of both chemoradiotherapy for LS-SCLC and chemotherapy for ES-SCLC. After adjustment for other characteristics, patients receiving a diagnosis at a younger age were less likely to refuse treatment compared with older patients. A meta-analysis among patients with LS-SCLC suggested that due to the toxicity associated with chemoradiotherapy, the survival benefit from treatment was limited to younger patients.¹⁸

However, results of other studies have shown that both older and younger patients respond just as well to a combined modality therapy.^{19,20} Results of a recent study using NCDB data suggested that older patients who received combined modality therapy had a better overall survival than those who had chemotherapy alone.²¹ Younger patients are considered to have better performance status, fewer comorbid conditions, and increased life expectancy, which are all factors that support the decision to agree to cancer treatment.²² Older patients, on the other hand, have increased concerns regarding the tolerability of chemotherapy, treatment duration, and effectiveness and tend to have more comorbid conditions that affect the decision to decline the offered treatment.^{22,23} Analyses of the population and facility-based data

TABLE 2. Multivariable Logistic Regression of Factors Associated With Refusal of Small Cell Lung Cancer Treatment

Characteristics		AOR	95% CI	P
Limited stage SCLC				
Age at diagnosis (years)	50-70	Ref		<.001
	<50	0.47	0.22-1.01	
	>70	3.50	2.77-4.44	
Gender	Male	Ref		.016
	Female	1.29	1.05-1.58	
Primary payer	Private insurance	Ref		<.001
	No insurance	3.61	2.05-6.35	
	Medicaid	2.50	1.51-4.12	
	Medicare	2.41	1.72-3.38	
CDCI score	0	Ref		<.001
	1	1.86	1.49-2.33	
	2	2.54	1.94-3.31	
Extended stage SCLC				
Age at diagnosis (years)	50-70	Ref		<.001
	<50	0.73	0.51-1.04	
	>70	2.25	1.99-2.55	
Gender	Male	Ref		<.001
	Female	1.42	1.27-1.58	
Primary payer	Private insurance	Ref		<.001
	No insurance	1.76	1.29-2.40	
	Medicaid	1.32	1.01-1.74	
	Medicare	1.72	1.46-2.02	
CDCI score	0	Ref		<.001
	1	1.29	1.15-1.46	
	2	1.43	1.23-1.65	

AOR, adjusted odds ratio; CDCI, Charlson/Deyo Comorbidity Index; ref, reference; SCLC, small cell lung cancer.
Note: In the final model variables, race, category of residence, and facility were not significantly associated with treatment refusal among patients with limited stage SCLC and extended stage SCLC.

in previous studies have shown a continuous increase in the proportion of patients with SCLC diagnosed who were aged more than 70 years.²⁴⁻²⁶ If more patients with SCLC are diagnosed at an older age, it may be reasonable to expect that the proportion of treatment refusal will continue to rise, due in part to the aforementioned array of concerns of older patients.

Regarding association with gender,

previous studies have suggested an increased incidence of SCLC cases among women.^{27,28} Women with SCLC were also shown to have better survival than men,^{6,27} with gender differences in survival being linked to patients' perceptions of cancer care.^{29,30} A recent study by Lee et al showed that more women than men chose to refuse active first-line therapy after their diagnosis of SCLC.³¹ These findings

TABLE 3. Multivariable Cox Regression of Factors Associated With Survival of Patients With Small Cell Lung Cancer

Characteristics		AHR	95% CI	P
LS SCLC*				
Age at diagnosis (years)	50-70	Ref		<.001
	<50	0.91	0.86-0.97	
	>70	1.27	1.23-1.32	
Gender	Male	Ref		<.001
	Female	0.82	0.79-0.84	
Primary payer	Private insurance	Ref		<.001
	No insurance	1.17	1.09-1.26	
	Medicaid	1.20	1.14-1.27	
	Medicare	1.18	1.14-1.23	
CDCl score	0	Ref		<.001
	1	1.18	1.14-1.21	
	2	1.36	1.30-1.43	
Facility	Community	Ref		<.001
	Comprehensive community	0.95	0.91-0.98	
	Academic/research	0.91	0.87-0.95	
Combination of chemoradiation	Received	Ref		<.001
	Refused	4.96	4.45-5.53	
ES SCLC**				
Age at diagnosis (years)	50-70	Ref		<.001
	<50	0.95	0.90-1.00	
	>70	1.17	1.13-1.20	
Gender	Male	Ref		<.001
	Female	0.85	0.83-0.87	
Race	White	Ref		.012
	Black	0.93	0.89-0.98	
	Other/unknown	0.95	0.87-1.03	
Primary payer	Private insurance	Ref		<.001
	No insurance	1.17	1.10-1.25	
	Medicaid	1.11	1.06-1.17	
	Medicare	1.12	1.09-1.16	
CDCl score	0	Ref		<.001
	1	1.16	1.13-1.20	
	2	1.41	1.36-1.47	
Facility	Community	Ref		.005
	Comprehensive community	1.01	0.98-1.05	
	Academic/research	0.96	0.93-1.00	
Combination of chemotherapy	Received	Ref		<.001
	Refused	3.69	3.48-3.92	

AHR, adjusted hazard ratio; CDCC, Charlson/Deyo Comorbidity Index; ES, extensive stage; LS, limited stage; ref, reference; SCLC, small cell lung cancer.

*Patients with LS-SCLC who were recommended chemoradiotherapy.

**Patients with ES-SCLC who were recommended chemotherapy.

Note: In the final model variables, category of residence was not significantly associated with survival among patients with LS-SCLC and ES-SCLC.

are in agreement with our results, which suggested that women were more likely to refuse the recommended chemoradiotherapy for LS-SCLC and chemotherapy for ES-SCLC. Refusal linked to gender may occur because women with advanced cancer tend to value quality of life more than just prolonged life.³² As also indicated in the results of other cancer studies, women seem to be more vulnerable to treatment toxicities than men.³⁰ In addition, they were more likely than men to have planned more specific late-in-life activities and were therefore less likely to want, at such a time in their lives, to repeatedly visit medical facilities to complete their cancer treatment series.³³ These perceptions may affect women's decisions to decline recommended cancer treatment. Our findings suggest the need for future studies among women to investigate their perceptions of SCLC treatment and expectations regarding their cancer treatment.

Uninsured patients were 2 to 3 times more likely to decline chemoradiotherapy for LS-SCLC and to decline chemotherapy for ES-SCLC than those with private insurance. Results of other studies among patients with lung cancer cases have suggested that uninsured patients were more likely to refuse offered cancer treatments.^{34,35} In addition, Halpern et al suggested that the uninsured were more likely to be diagnosed with advanced-stage disease.³⁵ The American Society of Clinical Oncology has raised concerns about inequities in cancer care due to insurance status.³⁶ A study by Duh et al estimated that the average cost of intravenous chemotherapy for SCLC was \$788 per visit or \$9449 per treatment course (3 visits per cycle for 4 cycles).³⁷ For uninsured patients, these costs may affect the decision to accept or decline recommended cancer treatment. Furthermore, any factor that delays treatment could result

in a more advanced and aggressive disease. To ensure delivery of quality cancer treatment and optimize patient outcomes, it is important to identify and remove impediments related to the health payer.

Results of survival analysis in this study demonstrate that the 1-year survival of patients with LS-SCLC who received chemoradiotherapy was 5 times higher than those who refused. Among patients with ES-SCLC, those who received chemotherapy were 8 times more likely to survive for 1 year compared with those who refused recommended treatment. The results found by Lally et al and Behera et al, similar to those of our study, previously suggested better survival rates among patients with SCLC who received treatment than those who did not.^{24,38} Regardless of the benefit on survival of receiving treatment, patient autonomy and locus of control remain important aspects of care. Patient-provider communication and patient education are essential in decision-making to increase patient acceptance of standard recommended treatment.

To our knowledge, our study is the most comprehensive one that has analyzed treatment refusal among patients with SCLC using a national facility-based database. We specifically examined the treatment refusal of chemoradiotherapy for LS-SCLC and chemotherapy alone for ES-SCLC, as these have the strongest evidence bases as stage-specific recommended treatment modalities for patients with SCLC. Our findings are relevant for patient management and future studies. The main strengths of our study are in the use of comprehensive clinical information, including cancer stage and treatment recommendations, and the large sample size of SCLC cases included in our analyses. We used the database that includes approximately three-fourths of newly diagnosed cancer cases in the US population.^{9,10}

The main limitations of our study

are those seen with retrospective and database studies in general. Although the database covers a majority of cancer cases in the United States, about a quarter of patients with new diagnoses are not captured in the data.³⁵ However, only marginal differences between NCDB and the SEER data have been acknowledged and should not meaningfully affect our findings.³⁹ Our findings suggest that future studies should focus on factors that might contribute to treatment decisions: for example, patient-physician interactions, patient education regarding cancer treatment and care, and patient support networks.

Conclusions

Although the proportion of patients refusing treatment for SCLC is relatively low, the increase in treatment refusal over time is concerning. Older age at diagnosis, female gender, uninsured status, and comorbidities were associated with higher refusal of chemoradiotherapy among patients with LS-SCLC and with higher refusal of chemotherapy among those with ES-SCLC. It is important for health providers and policymakers to not only make good treatment recommendations but also consider the ways their recommendations are delivered to patients. Interventions that target factors associated with higher treatment refusal may increase acceptance of recommended treatment and ultimately improve patient survival. Due to recent advancements in immunotherapy treatment for SCLC, there may be changes in treatment refusal. There is a need for comparative study to assess any change in treatment refusal among patients with SCLC. ■

FINANCIAL DISCLOSURE: The 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/SCLC_Tx_Refusal

Integrating PARP Inhibitors Into Advanced Prostate Cancer Therapeutics

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ABSTRACT: DNA–damage repair (DDR) pathway mutations can sensitize cancer cells to a class of cancer therapeutics known as PARP inhibitors. Given that DDR alterations can be found in up to one-third of advanced prostate cancers, PARP inhibitors have recently been established in treatment-refractory settings. We provide an updated review of the clinical data supporting the 4 PARP inhibitors that have undergone the most investigation thus far in metastatic castrate-resistant prostate cancer (mCRPC). Two of these agents are currently approved for the treatment of DDR-altered mCRPC. We end with a discussion on integration of approved PARP inhibitors into advanced prostate cancer clinical practice.

KEYWORDS: Prostate cancer, androgen inhibition, poly(ADP) ribose polymerase, PARP inhibitors, DNA damage repair, *BRCA*, homologous recombination

Introduction

Prostate cancer represents the most commonly diagnosed cancer and second-leading cause of cancer death in US men, with a projected 191,930 new cases and 33,330 deaths in 2020.¹ The natural history of prostate cancer can vary; it ranges from more indolent, low-risk disease, in which patients are more likely to die from competing comorbidities, to metastatic-lethal disease or metastatic castrate-resistant prostate cancer (mCRPC), which is characterized by the eventual development of resistance to therapies against the androgen signaling axis.²

Although androgen deprivation therapy (ADT) has been a foundation of pros-

tate cancer treatment for decades, there have been multiple recent advances in the systemic treatment of advanced prostate cancer. For example, the CHAARTED and STAMPEDE trials provided the basis for the addition of docetaxel to ADT in the first-line treatment of metastatic castration-sensitive prostate cancer (mCSPC).^{3,4} The addition of the novel hormonal therapy (NHT) abiraterone (Zytiga) to ADT conferred an overall survival (OS) advantage vs ADT alone in patients with untreated, locally advanced disease or mCSPC.^{5,6} The phase 3 ARCHES and ENZAMET trials demonstrated the superiority of the addition of enzalutamide (Xtandi) to ADT over ADT

alone in mCSPC,^{7,8} while the phase 3 TITAN trial supported the combination of first-line apalutamide (Erleada) and ADT in mCSPC.⁹

Despite the advances in mCSPC that have occurred in the past 5 years, development of castrate-resistant disease often represents the final common pathway and lethal stage of advanced prostate cancer. Currently, multiple systemic agents are available in the armamentarium for mCRPC, including chemotherapy^{10,11}; NHTs, including enzalutamide and abiraterone, both before^{12,13} and after chemotherapy^{14,15}; radium-223¹⁶; and sipuleucel-T.¹⁷ However, only in the past year have targeted therapies against a specific molecular phenotype in mCRPC been established, heralding the first biomarker-driven oral therapy for prostate cancer in the era of precision medicine.

The purpose of this review is to describe the class of PARP inhibitors introduced in prostate cancer and the DNA–damage repair (DDR) pathway mutations that sensitize prostate cancer cells to these agents. We highlight pivotal clinical trials that have resulted in US FDA approvals of PARP inhibitors in mCRPC. We end with a discussion of clinical integration of PARP inhibitors for this promising class of therapeutic agents in prostate cancer.

DNA Damage Repair Mutations and Prostate Cancer Mechanisms of DNA damage Repair and Repair Pathways

Eukaryotic cells have evolved at least 5 major DNA repair pathways for recognizing and repairing endogenous and exogenous sources of DNA damage for the purpose of maintaining genomic integrity.^{18,19} For example, alkylating agents, ionizing radiation, and reactive oxygen species can cause single-strand DNA breaks (SSBs) or single-base damage that is repaired by the base excision repair (BER) pathway, while ultraviolet radiation and chemical mutagens can cause DNA crosslinks and bulky base damages that are repaired by the nucleotide excision repair (NER) pathway. Important enzymes for both BER and NER pathways include the DNA polymerases. Base mismatches formed due to replication errors during DNA replication and recombination are repaired by the mismatch repair (MMR) pathway mediated by key MMR proteins such as MLH1, MSH2, MSH6, and PMS2. Lastly, DNA double-strand breaks (DSBs) caused by ionizing radiation or collapsed replication forks, for example, are repaired by the DSB repair pathway through either homologous recombination repair (HRR) or nonhomologous end joining, the latter of which includes mediators such as Ku70, Ku80, DNA-PKcs, XRCC4, LIG4, XLF, and APLF.

DDR Alterations in Prostate Cancer

Mutations in DDR pathways have been shown to contribute to prostate cancer carcinogenesis and progression¹⁹; both somatic and germline variants, many of which are involved with the HRR pathway, have been increasingly characterized (Table 1). In the initial dataset compiled by The Cancer Genome Atlas, which includes 333 patients with localized, primary prostate cancer cases who underwent radical prostatectomies, comprehensive molecular profiling identified inactivation of multiple DNA repair genes that collectively affected 19% of patients,

TABLE 1. Commonly Altered DNA–Damage Repair Genes in Prostate Cancer

Gene	Frequency (somatic) ^a	Frequency (germline) ^b	Encoded protein function
<i>ATM</i>	3.90%	1.59%	Cell cycle checkpoint kinase (PI3/PI4-kinase family)
<i>ATR</i>	0.60%	0.29%	Serine/threonine kinase, DNA damage sensor
<i>BRCA1</i>	1.10%	0.87%	190 kD nuclear phosphoprotein, forms large multi-subunit protein complex (BASC) involved in DSB repair, recombination
<i>BRCA2</i>	4.90%	5.35%	Binds RAD51 for homologous recombination, DNA repair of DSB
<i>BRIP1</i>		0.18%	DNA helicase maintains chromosomal stability, associates with BRCA1
<i>CHEK2</i>	1.20%	1.87%	Cell cycle checkpoint kinase, phosphorylates BRCA1
<i>FAM175A</i>		0.18%	Component of BRCA1: a complex, central scaffold protein, mediates BRCA1 recruitment
<i>GEN1</i>		0.46%	Endonuclease resolves Holliday junctions during HRR and DNA repair
<i>MLH1</i>	0.60%	0.00%	DNA MMR protein
<i>MRE11A</i>	0.00%	0.14%	DSB repair nuclease
<i>MSH2</i>		0.14%	DNA MMR protein
<i>MSH6</i>		0.14%	DNA MMR protein
<i>NBN</i>	1.20%	0.29%	Component of MRE11-RAD50-NBN (MRN complex) involved in DSB repair, recombination
<i>PALB2</i>	1.30%	0.43%	Recruits BRCA2 and RAD51 to DNA breaks for HRR
<i>PMS2</i>		0.29%	DNA MMR protein
<i>RAD51C</i>	1.50%	0.14%	Part of RAD51 paralogue complexes that act at different stages of BRCA1- or BRCA2-dependent HRR pathway
<i>RAD51D</i>		0.43%	Part of RAD51 paralogue complexes that act at different stages of BRCA- or BRCA2-dependent HRR pathway
<i>XRCC2</i>		0.00%	Part of RAD51 paralogue complexes that act at different stages of BRCA1- or BRCA2-dependent HRR pathway

^aMedian prevalence in unselected prostate cancer population including >500 patients.²¹

^bIncidence in a metastatic prostate cancer cohort of 692 subjects.

DSB, DNA double-stranded break; HRR, homologous recombination repair; MMR, mismatch repair.

including *BRCA2*, *BRCA1*, *CDK12*, *ATM*, *FANCD2*, and *RAD51C*.²⁰ In larger pooled series, the prevalence of somatic and germline DDR gene mutations ranged from 10.0% to 16.4% and 11.4% to 11.8%, respectively, in metastatic prostate cancer.²¹ In mCRPC, somatic mutations in *BRCA1* have been shown to be more common than germline *BRCA1* mutations (2.8% vs 0.8%) and somatic *BRCA1* mutations in an unselected prostate cancer population (2.8% vs 1.1%), whereas somatic and germline mutations were

equally common for *BRCA2* (5% each) in this population. Rates of somatic mutations in mCRPC and unselected prostate cancer populations have also been similar (5.0% vs 4.9%). Germline DDR gene mutations, in general, have been shown to be more prevalent in patients with metastatic prostate cancer than those in the general prostate cancer population.²¹ This is also consistent with results of a multicenter study that demonstrated an incidence of germline DDR gene mutations of 11.8% among men with metastatic prostate can-

cer, much higher than the incidence among men with localized prostate cancer.²²

In a cohort of 150 patients with mCRPC, whole exome and transcriptome sequencing of bone or soft tissue tumor biopsies showed higher frequencies (19.3%) of aberrations in *BRCA2*, *BRCA1*, and *ATM* than in primary prostate cancers.²³ Notably, 12.7% of cases had loss of *BRCA2* (most commonly a result of somatic point mutations and loss of heterozygosity).

PARP and Synthetic Lethality in Prostate Cancer

DNA SSBs are repaired by PARP enzymes.¹⁸ PARP inhibitors block the catalytic activity of PARP enzymes by trapping PARP on DNA at sites of SSBs, which results in the inability to repair DNA SSBs and ultimately the progression to DSBs.^{19,24} In cells that are deficient in HRR capacity and therefore unable to repair DSBs, the addition of PARP inhibition would become synthetically lethal ie, a phenomenon in which the combination of deficiencies results in cell death, whereas a deficiency in only 1 gene does not lead to cell death.^{19,24}

One of the earliest prostate cancer-specific studies that demonstrated the feasibility of PARP inhibition as an anticancer therapy in mCRPC was the phase 2 TOPARP-A trial.²⁵ In this phase 2 investigator-initiated trial, 50 patients with unselected mCRPC who had progressed after 1 or 2 lines of chemotherapy were enrolled to receive the oral PARP inhibitor olaparib at 400 mg twice daily. The primary end point was response rate, defined as a radiographic response according to RECIST, reduction in prostate-specific antigen (PSA) level 50% or greater; and/or reduction in number of circulating tumor cells from baseline. Prospectively planned whole-exome sequencing and transcriptome studies were performed on DNA from fresh-frozen tumor biopsies before treatment. The response rate was 33% of 49 evaluable patients (95% CI, 20%-48%). Sixteen patients (33%)

had tumor aberrations in DDR genes, of whom 14 (88%) had response to olaparib, including 7 patients with *BRCA2* and 4 with *ATM* aberrations (from a total of 5 patients). In these patients receiving olaparib (Lynparza), overall survival (OS) and progression-free survival (PFS) were significantly longer in those with DDR gene mutations than in those who were biomarker negative.

The promising results of TOPARP-A led to the initiation of the open-label, randomized phase 2 trial (TOPARP-B). Included patients have mCRPC that has been previously treated with 1 to 2 taxane regimens; they were selected for tumor DDR mutations by next-generation sequencing (NGS) and were randomized to receive olaparib 300 mg or 400 mg twice daily.²⁶ Of 592 patients with evaluable tumor samples, 161 (27%) had DDR gene aberrations, with *BRCA2* (7%), *ATM* (7%), and *CDK12* (6%) being the most common. As in TOPARP-A, a confirmed composite response end point was used as the primary end point, and the majority of patients had received either abiraterone or enzalutamide or both in addition to prior chemotherapy. Of 92 evaluable patients (46 in each olaparib-dosing cohort), response was seen in 25 patients (54.3%; 95% CI, 39.0%-69.1%) in the 400-mg cohort and 18 patients (39.1%; 95% CI, 25.1%-54.6%) in the 300-mg cohort ($P = .14$). The *BRCA1/2* subgroup had the highest number of composite responses and the longest median radiographic PFS of all DDR gene aberration subgroups. The 400-mg twice daily dose was associated with greater toxicity; in this cohort, 37% of patients had to reduce their dose to 300 mg twice daily, most commonly due to anemia.

PARP inhibitors have now seen advancement from early-phase studies to phase 3 registrational trials in prostate cancer, resulting in their FDA approval and the establishment of this class of agents in the treatment paradigm for mCRPC. The clinical development of PARP inhibitors in prostate cancer has been extensively

reviewed elsewhere.^{24,27} We will focus on an overview of the 4 PARP inhibitors that have undergone the most investigation thus far in mCRPC, with a discussion on integration of approved PARP inhibitors into clinical practice (**Table 2**).

Pivotal Clinical Trials of PARP Inhibitors in mCRPC Olaparib

Olaparib became FDA approved on May 19, 2020, for the treatment of mCRPC following progression on enzalutamide or abiraterone, based on the results of the prospective, open-label, randomized, phase 3 PROFOUND trial.²⁸ At 206 sites in 20 countries, 4425 patients were screened for alterations in 15 prespecified genes, and 778 of 2792 (28%) had qualifying DDR mutations based on NGS from primary or metastatic tumor tissues. Patients with 1 or more alterations in *BRCA1*, *BRCA2*, or *ATM* were assigned to cohort A while those with alterations in the other 12 genes were assigned to cohort B. Patients were randomized 2:1 to receive standard-dose olaparib (300 mg twice daily) or the prespecified physician's choice of enzalutamide (160 mg once daily) or abiraterone (1000 mg once daily and prednisone at a dose of 5 mg twice daily). The primary end point was PFS, with secondary end points of overall response rate (ORR) and OS. A total of 162 and 83 patients were randomized to receive olaparib and control treatment, respectively, in cohort A, while 94 and 48 patients received olaparib and control treatment, respectively, in cohort B.

For cohort A, the median PFS was significantly longer in the olaparib group (7.4 months) than in the control group (3.6 months; HR, 0.34; 95% CI, 0.25-0.47; $P < .001$). Among evaluable patients, the ORR was 33% (28 of 84 patients) in the olaparib group and 2% (1 of 43 patients) in the control group (odds ratio, 20.86; 95% CI, 4.18-379.18; $P < .001$). For the overall population (cohort A and B), olaparib resulted in longer median PFS than control

treatment did (5.8 months vs 3.5 months; HR, 0.49; 95% CI, 0.38-0.63; $P < .001$). In the final OS analysis (secondary end point) of PROFOUND,²⁹ median OS was 19.1 months with olaparib and 14.7 months with control therapy (HR, 0.69; 95% CI, 0.50-0.97; $P = .02$) in cohort A. In cohort B, median OS was 14.1 months with olaparib and 11.5 months with control therapy (HR, 0.96; 95% CI, 0.63-1.49).

Rucaparib

The oral agent rucaparib (Rubraca), a PARP1/2/3 inhibitor, was FDA approved (accelerated approval) based on the TRITON2 study on May 15, 2020, for patients with *BRCA*-mutated mCRPC who have been previously treated with androgen receptor (AR)-directed therapy and a taxane-based chemotherapy.^{30,31} TRITON2 is an ongoing, international, open-label, single-arm, phase 2 study in which patients with pretreated mCRPC were screened by plasma or tumor NGS for a panel of 15 deleterious somatic or germline DDR alterations (Table 2). Patients who had progressed on 1 or 2 prior lines of NHT (ie, abiraterone or enzalutamide) and 1 prior line of taxane-based chemotherapy received rucaparib at 600 mg twice daily. In the *BRCA*-mutated cohort ($n = 115$), confirmed ORR was 43.5% with a PSA response rate of 54.8%, while OS has not yet matured; the 12-month OS rate was 73.0%. The median radiographic PFS was 9.0 months (95% CI, 8.3-13.5 months). Notably, response rates were similar for those with germline or somatic *BRCA* mutations and for *BRCA1* or *BRCA2* alterations.³⁰ In the non-*BRCA*-mutated cohort ($n = 78$), rucaparib had limited activity in those with *ATM*, *CDK12*, or *CHEK2* mutations, with no radiographic or PSA responses in 11 patients with confirmed biallelic *ATM* loss or in 11 patients with germline *ATM* mutations.³¹

A multicenter, randomized, open-label, phase 3 study (TRITON3) is ongoing and randomizing patients with

mCRPC who have *BRCA1/2* or *ATM* gene mutations and have progressed on 1 prior NHT for mCRPC to rucaparib monotherapy or investigator's choice of abiraterone, enzalutamide, or docetaxel (NCT02975934). The primary end point will be radiographic PFS.

Talazoparib

Talazoparib (Talzenna) is a potent PARP1/2 inhibitor that was investigated in mCRPC in the open-label, single-arm, phase 2 TALAPRO-1 study.³² Eligible patients included those with mCRPC refractory to 1 or more lines of taxane-based chemotherapy and 1 or more lines of NHT (ie, enzalutamide or abiraterone) with known/likely pathogenic variants or homozygous deletions in DDR mutations based on tumor-derived NGS. Interim results show an ORR of 28.0% in 75 patients with DDR mutations treated with oral talazoparib 1 mg daily (primary end point). The most common treatment-related adverse events (AEs) were anemia (42.5%) and nausea (32.7%). A phase 3, randomized, double-blind, placebo-controlled study (TALAPRO-2) is currently randomizing patients with mCRPC who have not received prior taxanes or NHT in the mCRPC setting to talazoparib and enzalutamide vs placebo and enzalutamide, with radiographic PFS as a primary end point in unselected patients and in those with DDR deficiencies (NCT03395197).

Niraparib

Niraparib (Zejula) is another oral PARP1/2 inhibitor that has seen active investigation in mCRPC. The phase 2, open-label, single-arm GALAHAD study enrolled patients who had mCRPC refractory to taxane and to AR-targeted therapy as well as biallelic alterations in select DDR genes, as ascertained by plasma or tissue-based profiling; they received niraparib 300 mg daily.³³ The most common grade 3/4 treatment-emergent AEs were mainly hematologic: anemia (29%), thrombocytopenia (15%), and

neutropenia (7%). The ORR was 41% in those with *BRCA* mutations; the median radiographic PFS and OS were 8.2 and 12.6 months, respectively. The ORR in the non-*BRCA*-mutated cohort was 9%; response was observed in only 2 patients, both with *FANCA* mutations. The phase 3, randomized, placebo-controlled, double-blind MAGNITUDE study is currently randomizing mCRPC patients who have not received systemic therapy in the mCRPC setting (except for <4 months of abiraterone prior to randomization) to niraparib and abiraterone vs placebo and abiraterone (NCT03748641). Patients will be stratified into DDR gene-mutated and non-DDR gene-mutated cohorts, and the primary end point will be radiographic PFS.

Incorporating PARP Inhibitors Into Clinical Practice for mCRPC

PARP inhibitors have already been approved for multiple malignancies, including ovarian cancer, breast cancer, and pancreatic cancer.^{34,35} The recent approvals of olaparib and rucaparib offer promising efficacy in patients with treatment-refractory mCRPC, in whom therapeutic options have been limited. As this class of agents continues to undergo rapid clinical development and clinical implementation, several factors must be considered when incorporating PARP inhibitors into routine prostate cancer management.

Choosing the Right Patient

Aside from microsatellite instability, which is found in less than 3% of all prostate tumors, DDR mutations represent a predictive biomarker that can currently guide targeted therapies in patients with advanced prostate cancer.³⁶ In the phase 3 PROFOUND trial, DDR alterations from a predefined 15-gene panel were found in 778 of 2792 (28%) patients.²⁸ However, as exploratory analyses of PROFOUND and TRITON2 have shown, not all DDR mutations are

TABLE 2. Pivotal Clinic Trials of PARP Inhibitors in mCRPC

Trial	Setting	Treatment arms	Genes evaluated	Primary end point
Olaparib				
TOPARP-A, phase 2²⁵	Unselected, after 1-2 lines of chemotherapy	Olaparib (n = 49)	113-gene panel	Composite response ^a : 33% in all patients, 88% of 16 patients with DDR mutations
TOPARP-B, phase 2²⁶	≥1 predefined DDR mutations, after 1 or 2 lines of taxanes	1:1 randomization to olaparib 300 mg BID (n = 49) vs 400 mg BID (n = 49)	Tumor-based NGS used in genes related to DDR or PARP sensitivity	Composite response ^a : 54.3% in 400-mg cohort vs 39.1% in 300-mg cohort
PROFOUND, phase 3²⁸	≥1 predefined DDR mutations, after enzalutamide or abiraterone; prior taxane chemotherapy allowed	2:1 randomization to olaparib vs enzalutamide or abiraterone	Cohort A: <i>BRCA1</i> , <i>BRCA2</i> , <i>ATM</i> Cohort B: <i>BRIP1</i> , <i>BARD1</i> , <i>CDK12</i> , <i>CHEK1</i> , <i>CHEK2</i> , <i>FANCL</i> , <i>PALB2</i> , <i>PPP2R2A</i> , <i>RAD51B</i> , <i>RAD51C</i> , <i>RAD51D</i> , <i>RAD54L</i>	Cohort A, median PFS: olaparib (n = 162) at 7.4 months vs control (n = 83) at 3.6 months (HR, 0.34, 95% CI, 0.25-0.47; <i>P</i> < .001)
Rucaparib				
TRITON2, phase 2³⁰	Germline or somatic <i>BRCA1</i> or <i>BRCA2</i> mutation after 1-2 lines of NHT and 1 prior taxane-based chemotherapy for CRPC	Rucaparib (n = 115)	<i>BRCA1</i> (n = 13), <i>BRCA2</i> (n = 102)	ORR, ^b 43.5% (95% CI, 31.0%-56.7%) Median DOR: not reached (95% CI, 6.4 months to not reached) Response duration ≥6 months: 15/27 (56%)
TRITON2, phase 2³¹	Germline or somatic prespecified, non- <i>BRCA</i> DDR mutations after 1-2 lines of NHT and 1 prior taxane-based chemotherapy for CRPC	Rucaparib (n = 78)	<i>ATM</i> , <i>BARD1</i> , <i>BRIP1</i> , <i>CDK12</i> , <i>CHEK2</i> , <i>FANCA</i> , <i>NBN</i> , <i>PALB2</i> , <i>RAD51</i> , <i>RAD51B</i> , <i>RAD51C</i> , <i>RAD51D</i> , <i>RAD54</i>	ORR, ^b 10.5% (2/19) <i>ATM</i> , 0% (0/10) <i>CDK12</i> , 11.1% (1/9) <i>CHEK2</i> , 28.6% (4/14) Other DDR mutations: <i>FANCA</i> (1/4), <i>NBN</i> (0/4), <i>BRIP1</i> (1/2), <i>PALB2</i> (1/2), <i>RAD51</i> (0/1), <i>RAD51B</i> (1/1), <i>RAD54L</i> (0/1)
Talazoparib				
TALAPRO-1, phase 2³²	Prespecified DDR mutation after ≥1 taxane-based chemotherapy and ≥1 line of NHT	Talazoparib (n = 75)	<i>ATM</i> , <i>ATR</i> , <i>BRCA1/2</i> , <i>CHEK2</i> , <i>FANCA</i> , <i>MLH1</i> , <i>MRE11A</i> , <i>NBN</i> , <i>PALB2</i> , <i>RAD51C</i>	ORR by specific alteration: <i>BRCA1/2</i> , 43.9% (18/41); <i>PALB2</i> , 33.3% (1/3); <i>ATM</i> , 11.8% (2/17)
Niraparib				
GALAHAD, phase 2³³	Prespecified DDR mutation after ≥1 taxane-based chemotherapy and ≥1 line of NHT	Niraparib (n = 81)	<i>BRCA1/2</i> , <i>ATM</i> , <i>FANCA</i> , <i>PALB2</i> , <i>CHEK2</i> , <i>BRIP1</i> , <i>HDAC2</i>	ORR by specific alteration: <i>BRCA1/2</i> , 41% (12/29); non- <i>BRCA</i> , 9% (2/22)

^aConfirmed composite response defined as radiographic response according to RECIST 1.1, reduction in PSA level ≥50% from baseline, and/or conversion of circulating tumor cell count (from ≥5 cells per 7.5 mL blood at baseline to <5 cells per 7.5 mL blood).

^bModified RECIST v1.1 and Prostate Cancer Clinical Trials Working Group 3 criteria.

BID, twice daily; CRPC, castrate-resistant prostate cancer; DDR, DNA damage repair; DOR, duration of response; mCRPC, metastatic CRPC; NGS, next-generation sequencing; NHT, novel hormonal therapy; ORR, overall response rate; PFS, progression-free survival.

equal in eliciting response to PARP inhibitors in mCRPC. Exploratory gene-level analyses in PROFOUND showed that in the intention-to-treat population, HRs for death for the comparison of olaparib versus the control were 0.42 and 0.59 for patients who had alterations only in *BRCA1* and *BRCA2*, respectively, while the HR for those with non-*BRCA* genes was 0.95 (95% CI, 0.68-1.34).²⁹ There was an improved median OS of 17.4 months with olaparib vs 12.6

months with control (HR, 0.64; 95% CI, 0.39-1.08) after prior taxane therapy in patients with only *BRCA1* or *BRCA2* alterations. A more pronounced effect of previous taxane use was seen in those with only *ATM* mutations, however; for them, median OS was improved with olaparib (17.6 months) compared with control (12.4 months; HR, 0.45; 95% CI, 0.22-0.95). It should be noted that these subgroup analyses were not powered to detect a treatment effect across

these subgroups, so these results should be interpreted with caution.

A similar theme was observed in the TRITON2 study, as no radiographic or PSA responses were seen in 11 patients with confirmed biallelic *ATM* loss or 11 patients with *ATM* germline mutations.³¹ Instead, the bulk of responses to rucaparib was observed in patients with *BRCA1* or *BRCA2* mutations, while in patients with mCRPC having non-*BRCA* DDR mutations, responses were seen only in

those with *PALB2*, *FANCA*, *BRIP1*, and *RAD51B* mutations.^{30,31} Higher PSA responses have also been seen in those with *BRCA2* vs *BRCA1* mutations and biallelic vs monoallelic loss, but the number of patients with *BRCA1* mutations and monoallelic loss was small.³⁰ One can argue, based on the constellation of these findings, that the approved indications for olaparib and rucaparib should be limited to those with mCRPC harboring *BRCA1* or *BRCA2* mutations, with perhaps the potential to benefit those with select non-*ATM* DDR gene mutations. Of note, the rucaparib label is restricted to those with deleterious *BRCA* mutations only (germline and/or somatic) while the olaparib label applies to the DDR genes prespecified in PROFOUND (Table 2).^{37,38} In both PROFOUND and TRITON2, deleterious DDR alterations were identified with tumor-based NGS of archival or recent biopsy tissues (Foundation Medicine) from primary or metastatic disease, while TRITON2 permitted plasma-based NGS as well.^{28,30} The FDA also approved the FoundationOne CDx (Foundation Medicine, Inc) assay for selection of patients with mCRPC carrying DDR gene alterations and the BRACAnalysis CDx test (Myriad Genetic Laboratories, Inc) for *BRCA1/2* alterations as companion diagnostics for olaparib treatment.

Choosing the Right PARP Inhibitor

Unlike olaparib and rucaparib, talazoparib and niraparib, although under active investigation, have not been FDA approved for mCRPC. Of the 2 PARP inhibitors approved for mCRPC harboring select DDR mutations, olaparib is approved for those with mCRPC who have progressed on the NHTs enzalutamide or abiraterone,²⁸ while rucaparib is approved in patients with mCRPC who have been treated with an NHT and a taxane-based chemotherapy.³⁰ Therefore, olaparib offers earlier access to a PARP inhibitor along the mCRPC treatment continuum (ie, if taxanes have

not been used), but it has still shown benefit, on subgroup analysis, in those previously treated with taxanes—45% of patients treated with olaparib in PROFOUND had received prior docetaxel.²⁸ In TRITON2, 36.5% of patients treated with rucaparib had previously received ≥ 2 AR-directed therapies; 93.9% had received prior docetaxel in the castrate-resistant setting; 10.4% had received sipuleucel-T; and 12.2% had received radium-223, therefore showing efficacy in a heavily pretreated population.³⁰

Ultimately, olaparib was granted regular FDA approval, based on its higher level of evidence (phase 3 PROFOUND trial), while rucaparib was granted accelerated FDA approval—meaning that clinical trial data (TRITON2) strongly suggest benefit, but level of proof is not yet available. One could also argue that rucaparib is approved in mCRPC patients with *BRCA* mutations only, while olaparib is approved for a more expanded DDR gene panel beyond *BRCA* mutations; as discussed earlier, however, the majority of responses to PARP inhibitors in this setting have been observed in those with *BRCA1/2* only.^{37,38} When separating these groups, only 12% of mCRPC cases have defects in *BRCA1* or *BRCA2* and only 8% to 18% have defects in non-*BRCA* DDR genes.^{25,28,30} A head-to-head comparison of the efficacy of PARP inhibitors in prostate cancer does not exist. The choice of PARP inhibitor in routine clinical practice therefore depends on not only the DDR alterations detected but also the treatment setting of the patient with mCRPC; the receipt of specific prior lines of systemic therapy as per FDA labeled indications must be taken into account. With the development of other PARP inhibitors in this arena, debate will continue regarding the ideal agent to use in prostate cancer. Such decisions would need to incorporate level of evidence, safety and tolerability, quality-of-life metrics, cost effectiveness, and discussions of provider and patient preferences that should underlie the

physician-patient relationship.

Toxicities

In the updated survival analysis of the phase 3 PROFOUND trial, the median duration of olaparib therapy was 7.6 months vs 3.9 months with control.²⁹ Of 256 patients randomized to the olaparib group, 46% of patients had interruptions of olaparib due to AEs (vs 19% in control), 23% required dose reductions due to AEs (vs 5% in control), and 20% discontinued treatment due to AEs (vs 8% in control). Grade ≥ 3 AEs were seen in 52% of patients, with anemia (23%) and fatigue (3%) the most common. Median duration of rucaparib therapy was 6.5 months in TRITON2, with treatment interruptions due to AEs occurring in 56.5% (most commonly due to anemia, thrombocytopenia, or fatigue), dose reductions occurring in 40.9%, and treatment discontinuations occurring in 7.8%.³⁰ Grade ≥ 3 AEs due to rucaparib occurred in 60.9% of patients, with the most common being anemia (25.2%), thrombocytopenia (9.6%), and fatigue (8.7%). Although no new cancers, pneumonitis, myelodysplastic syndrome, or acute myeloid leukemia were observed in the 30-day safety follow-up with olaparib in PROFOUND, 1 case of fatal acute myeloid leukemia occurred in a patient with mCRPC who had germline *BRCA2* deficiency diagnosed 54 days after the discontinuation of olaparib (15.7 months duration of olaparib exposure).²⁹

In short, anemia and fatigue are the most common and significant AEs, or class effect, of PARP inhibitors in patients with mCRPC. Toxicity profiles appear to be similar between the 2 FDA-approved PARP inhibitors, with nearly half of men treated with these drugs requiring either treatment interruptions or dose reductions. Of note in PROFOUND, men without surgical castration were required to continue luteinizing hormone–releasing hormone analogue therapy with olaparib; while in TRITON2, men were required to receive a concomitant gonadotropin-

releasing hormone analogue, or to have had prior bilateral orchiectomy facilitated by rucaparib. Therefore, PARP inhibitor therapy should not be considered a way to spare patients from undergoing hormonal therapy.^{29,30}

Conclusions

PARP inhibitors have demonstrated promising efficacy and manageable toxicities in pretreated patients with mCRPC: a high-risk group in desperate need of additional treatment options. With continued development of this class of agents in advanced prostate cancer, more work should be focused on the subgroup of patients with non-*BRCA* DDR mutations

who could benefit from PARP inhibition. Also, ongoing trials seek to establish PARP inhibitors in earlier treatment settings (eg, first-line metastatic prostate cancer and nonmetastatic prostate cancer). Lastly, with greater clinical implementation of and familiarity with PARP inhibitors in prostate cancer, development of rational combination strategies with this drug class would be warranted to further exploit its anticancer potential. ■

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CIN CAN STRIKE AT ANY MOMENT

It's time to take a critical fresh look at chemotherapy-induced neutropenia (CIN), and how the COVID-19 pandemic is changing the standard-of-care guidelines.

Cancer plus COVID-19—and the threat patients everywhere are now facing

Infection has always been a concern in patients who may be at risk of neutropenia associated with chemotherapy. And now, with the onset of the global COVID-19 pandemic, they are facing an even higher mortality rate. While cancer-associated risk factors with COVID-19 are not yet fully understood, individuals with active hematologic or lung malignancies, lymphopenia, or baseline neutropenia show worse outcomes when also diagnosed with COVID-19.¹ The result? A revisiting of practice guidelines, the expansion of prophylactic granulocyte-colony stimulating factor (G-CSF) for patients who are at intermediate risk for neutropenia, and a renewed urgency to address the high unmet need of preventing CIN.²

When ANC drops, so do your patient's defenses

During chemotherapy, the absolute neutrophil count (ANC) drops until it reaches its lowest point (nadir). The timely detection and diagnosis of CIN make it possible to administer the appropriate G-CSF.³ Otherwise, severe (Grade 4) neutropenia may cause dose reductions in therapy regimens and compromise the chemotherapy's efficacy, potentially reducing a patient's survival.⁴ Fever and systemic infections from neutropenia are also serious complications (Figure 1), as they may lead to

hospitalizations, which place substantial economic costs and strains on the healthcare system.⁵⁻⁸

FIGURE 1: GRADE 4 NEUTROPENIA DROPS ANC LEVELS—AND LEADS TO FEVER, INFECTION, OR BACTEREMIA⁸

Republished with permission of [WILEY], from Buckley, S.A., Othus, M., Vainstein, V., Abkowitz, J.L., Estey, E.H. and Walter, R.B. (2014), Prediction of adverse events during intensive induction chemotherapy for acute myeloid leukemia or high-grade myelodysplastic syndromes. *Am. J. Hematol.*, 89: 423-428. <https://doi.org/10.1002/ajh.23661>; permission conveyed through Copyright Clearance Center, Inc.

There is a direct association between baseline blood counts and the likelihood of developing a fever or being diagnosed with a documented infection or bacteremia.⁸

Once regimens are disrupted due to low ANC levels, the eruption of complications begins

CIN remains the most common serious toxicity of current chemotherapeutic regimens. Despite advances in therapy, it continues to put patients at risk of immune-compromising infections.⁹ These repeated infections and subsequent lower ANC levels may result in treatment delays and dose reductions³—as well as costly extended or repeated hospitalizations and eventually decreased survival.^{10,11}

CIN's devastating impact on your patient's treatment regimen

CIN can not only compromise your patient's immune system and make them vulnerable to long-term infection, but it may also wreak havoc on the regimen you prescribed, **making them face the devastating "4 Ds":**

DECREASE

their recommended treatment dose

DELAY

their treatment cycles

DOWNGRADE

their prescribed regimen

DISCONTINUE

their recommended treatment dose

DAYS 1-10: THE GREATEST RISK

G-CSFs leave patients vulnerable

- It takes up to 8 days for G-CSFs to accelerate the maturation and proliferation of neutrophil precursors in bone marrow¹
- G-CSF benefits are not seen until the eighth day following chemotherapy¹²
- Patients treated with various chemotherapies may still experience Grade 4 neutropenia between Days 6-8, even with the use of G-CSF¹²

Cycle 1 of chemotherapy may put patients at risk

- In Cycle 1, the ANC nadir takes place between Days 7-10¹³
- CIN episodes are the highest in Cycle 1 in patients with breast cancer⁹
- Most initial neutropenic events and infection events occur in Cycle 1¹⁴
- The risk of initial hospitalization spikes by Day 10, particularly in high-risk patients with febrile neutropenia (FN)¹⁵ (Figure 2)
- Chemotherapy-related death rates have been observed in certain study populations to be as high as 13%, with 37% of these deaths occurring during Cycle 1¹⁶

FIGURE 2: CUMULATIVE PROBABILITY OF INITIAL HOSPITALIZATION FOR FN BY RISK COMPOSITE SCORE¹⁵

Lyman, G.H. and Delgado, D.J. (2003), Risk and timing of hospitalization for febrile neutropenia in patients receiving CHOP, CHOP-R, or CNOP chemotherapy for intermediate-grade non-Hodgkin lymphoma. *Cancer*, 98: 2402-2409. <https://doi.org/10.1002/cncr.11827> Copyright ©2003 American Cancer Society

Patients go unprotected as early as Week 1

G-CSFs may leave patients vulnerable to CIN as early as Week 1 of Cycle 1.^{12,17} Should their ANC drop and approach 1.0 (or below), they run the risk of encountering life-threatening consequences, including infection, FN, hospitalization, and death.¹⁸

THE RISK IS REAL

Although infections may linger in the healthcare setting, it's critical to reduce exposure and protect patients with cancer during the COVID-19 pandemic. This is precisely why prophylactic prevention therapy is now being recommended to include patients who may also be at intermediate risk of developing FN.¹⁹

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A 65-Year-Old Man With Back Pain and Imaging Findings of Spinal Cord Compression

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ABSTRACT: Spinal cord compression is a potentially devastating consequence of cancer. Early recognition of the signs and symptoms permit diagnosis prior to the development of irreversible neurological damage. This complication occurs in 5% to 10% of patients with malignancy, often at the end stages of the patient's illness; however, it can be the presenting manifestation of malignancy in up to 23% of patients. With the advances in surgical, radiation, and medical oncology approaches, the outcomes of patients with malignant spinal cord compression continue to improve. We discuss the case of a previously healthy man, aged 65 years, who presented with back pain and a large T8 spinal mass, leading to a diagnosis of multiple myeloma with spinal cord compromise.

Introduction

Spinal vertebral bone involvement with or without neurological deterioration can occur as a skeletal-related event in various cancers. The true incidence of malignant spinal cord compression is not known, but the estimate is about 15% in patients with advanced cancer.¹ Metastases to the spine occur most commonly in patients with breast, prostate, and lung cancer, followed by those with renal, gastrointestinal, and thyroid cancer and malignant melanoma.² Multiple myeloma is among the most common hematological malignancies leading to this complication. The spinal cord compression may present as a primary tumor (solitary plasmacytoma) or as part of the systemic involvement of multiple myeloma.³⁻⁵ Direct tumor extension into the vertebral column or the collapse of a vertebral body that contains metastatic disease can lead to the compression of the

spinal cord. Initially, this causes reversible edema, venous congestion, and demyelination, followed by vascular injury and cord necrosis. With prolonged compression, permanent neurological damage occurs. Appropriate treatment of malignant spinal cord compression is complex and requires a multidisciplinary team approach.

Regardless of the tumor histology causing the spinal cord compression, the 3 most widely utilized treatment modalities have been surgery, radiation therapy (RT), and the administration of glucocorticoids, with or without systemic anticancer therapy. The introduction of new spinal instrumentations and surgical approaches, along with advances in radiation and medical oncology treatments, has considerably improved the extent of therapeutic options, resulting in better outcomes. Identifying the patients who would most benefit from what initial approach—surgical, radiation,

or medical treatment—is the most crucial part of appropriate management.

Case

A man aged 65 years presented with right-sided lower thoracic back pain of 1-month duration; it was brought upon by pushing a sliding door in his garage. While it was initially a sharp pain, it transformed into a dull continuous ache radiating to his right rib and right hemithorax. He thought he pulled a muscle and saw a chiropractor, but he received no relief despite 5 chiropractic treatment sessions. During all this time he did not notice any extremity weakness or bladder or bowel incontinence, but he eighth area. He next saw his primary care provider, and a CT scan of his chest revealed a soft-tissue mass measuring 6.2 × 3.5 × 2.8 cm in the posterior mediastinum/posterior chest wall with involvement of the posterior eighth rib and adjacent T8 vertebral

body, with extension into the right aspect of the spinal canal (**Figure 1**). Further evaluation with an MRI of the thoracic spine confirmed the T8 compression and associated soft-tissue mass causing moderate-to-severe central spinal stenosis (**Figure 2**). A CT-guided biopsy of this large destructive mass revealed sheets of plasma cells (**Figures 3 and 4**). Further work-up revealed abnormal serum protein electrophoresis with a 3.53 g/dL monoclonal serum paraprotein, abnormal serum immunoglobulins (Ig; 5365 mg/dL; IgA, 23 mg/dL; IgM, 11 mg/dL), abnormal free light chains (λ free light chain, 14.6 mg/L; λ free light chain, 146.2 mg/L; ratio, 0.1), and abnormal λ -2 microglobulin of 4.9 mg/L. Bone marrow aspiration and biopsy revealed plasma cell myeloma comprising 40% of marrow cellularity (**Figures 5 and 6**). Staging work-up was completed with a PET-CT, confirming large osseous destructive mass at T8 level (**Figure 7**).

Discussion

Malignant spinal cord and/or cauda equina compression is a relatively common complication of malignancy. While it is most common in the late stages of cancer, it can be the first manifestation of malignant disease. Depending on the extent and location of the spinal cord involvement, patients may present with various symptoms and signs, ranging from pain and motor and/or sensory loss to paraplegia and urinary or fecal incontinence. Long-term neurological functioning closely correlates with the patient's mobility at the time of initial presentation. Patients with established spinal cord compression classically exhibit bilateral upper motor neuron findings below the level of the compression, but unilateral findings can also be seen. A circumferential sensory level below which sensation is reduced or altered may be noted. Bowel or bladder dysfunction can be present. In some cases, loss of balance may be the main presenting symptom due to compression of the posterior spinal cord.^{6,7}

Choice of Initial Treatment Modality

The goals of treatment for spinal cord compression are adequate pain control, relief of spinal cord or cauda equina compression, and maintenance of spinal stability, while preserving or improving neurologic function. After the immediate administration of glucocorticoids in nearly all patients, the choice of initial treatment modality depends on several factors, including the presence or absence of spinal instability, the degree of compression of the spinal cord, and the relative radiological and/or chemotherapeutic sensitivity of the tumor.^{8,9}

An expert opinion consensus classification system for spinal instability has been developed based on the available evidence about patient symptoms and radiographic criteria.¹⁰ This classification uses 6 individual components of spinal instability: spinal location of the tumor, presence and character of the pain, nature of bone metastases, radiographic spinal alignment, extent of vertebral body involvement, and extent of posterior spinal element involvement. All of these are scored to create a final composite Spine Instability Neoplastic Score (SINS) (**Table 1**).¹¹ In guiding the operative vs nonoperative management of patients with neoplastic spinal cord compression, SINS has been shown to be useful, with very good interobserver agreement among radiologists and radiation oncologists.^{12,13} According to this classification system, patients with a score of 7 or higher are considered to be at risk for spinal instability. The most appropriate treatment modality for an unstable spine is stabilization either by surgery with fixation¹⁴ or by percutaneous vertebral repair.¹⁵ RT and spinal bracing have not been shown to be effective for this group of patients.^{16,17}

Surgery

A life expectancy of at least 3 months and neurologic function compromise of less than 24 hours have been utilized as indicators for surgical candidacy.¹⁸ Patients with hematologic malignancies should be

TABLE 1. The Spine Instability Neoplastic Score

Spine location of tumor	Score
Junctional (C1-C2, C7-T2, T11-L1, L5-S1)	3
Mobile spine (C3-C6, L2-L4)	2
Semirigid spine (T3-T10)	1
Rigid spine (S2-S5)	0
Presence and nature of pain	
Mechanical or postural	3
Occasional pain, not mechanical	1
No pain	0
Nature of bone metastases	
Lytic	2
Mixed lytic/blastic	1
Blastic	0
Radiographic spinal alignment	
Subluxation/translation present	4
De novo deformity (kyphosis/scoliosis)	2
Normal alignment	0
Vertebral body involvement	
>50% collapse	3
<50% collapse	2
No collapse, with >50% of the body involved	1
None of the above	0
Extent of posterior involvement	
Bilateral	3
Unilateral	1
No involvement	0

excluded, as they are best managed by RT or chemotherapy. Surgical intervention is performed to accomplish mechanical stabilization, pain relief, preservation of neurological function, and local tumor reduction. Although various surgical approaches can be used, the majority of cases have historically been managed by decompressive posterior laminectomy. However, without instrumentation, decompressive laminectomy has been associated with a failure to resolve anterior compression as well as to cause or exacerbate spinal instability. A stand-alone laminectomy is

considered only for metastatic involvement of the epidural space and lamina.

Additionally, the choice of surgical approach—anterior, posterior, or circumferential—is determined by the affected region of the spine. Metastatic spine lesions occurring ventrally in the subaxial cervical spine are best approached anteriorly. For thoracic spine lesions, transpedicular approaches are preferred, because an anterior approach can be challenging due to mediastinal contents. The transpedicular corpectomy and costotransversectomy can provide the added benefit of ventrally decompressing the spinal cord or thecal sac. Costotransversectomy involves more extensive resection and bone removal by providing better access to the anterior spinal column from a more lateral route.¹⁹⁻²¹ Modern surgical techniques and the development of spinal implants composed of high-quality materials, such as titanium, have significantly improved outcomes.

Prospective evaluations of RT plus laminectomy without instrumentation have not shown any benefit for this combination compared with RT alone.²² Data from prospective cohorts demonstrate that laminectomy combined with instrumentation for stabilization could improve neurological outcomes and pain.^{23,24} However, these prospective studies do not have control groups, so conclusions are limited. In a select group of patients, surgery followed by RT is a beneficial treatment when compared with RT alone. In a randomized trial, patients with single-level disease, good performance status, and an onset of symptoms within 24 hours were treated with either circumferential decompressive surgery followed by RT (30 Gy in 10 fractions) or RT alone. Analysis showed a clear difference in the number of patients who were able to walk 4 steps post treatment, as well as higher rates of continence and better muscle strength and functional ability, with less need for opioid analgesics and corticosteroids.²⁵ Patients who are not candidates for radical surgery but who have an unstable spine may benefit from minimally invasive techniques such as

Figure 1. Axial contrasted image shows a right spinal soft-tissue mass invading the vertebral body, pedicle, lamina, transverse process, rib, and adjacent pleura. There may be some lung invasion. The mass also extends into the spinal canal, causing significant stenosis.

Figure 2. T2 MRI sequence of the mass more easily differentiates the mass from the central canal contents. The interface between the tumor and thecal sac is identified with significant mass effect, severe neural foramen compromise, and moderate-to-severe spinal stenosis. Again seen are the areas of bony invasion as seen on the CT image.

■ **Figure 3 and 4.** Spinal mass biopsy showing sheets of plasma cells (hematoxylin and eosin stain, 400× magnification) (**left**). Spinal-mass biopsy showing λ light chain restriction (in situ hybridization for lambda; 400× magnification) (**right**).

■ **Figure 5 and 6.** Bone marrow aspirate showing sheets and clusters of plasma cells (hematoxylin and eosin stain; 400× magnification) (**left**); Bone marrow aspirate showing lambda light chain restriction (in situ hybridization for lambda; 400× magnification) (**right**).

vertebroplasty and kyphoplasty. Percutaneous vertebroplasty is performed by the percutaneous placement of 1 or 2 trocars into the vertebral bodies through the pedicles, or by the extrapedicular approach and the injection of methylmethacrylate under fluoroscopic guidance. Balloon kyphoplasty is a modified version of percutaneous vertebroplasty; it utilizes an inflatable balloon in a fractured vertebra to create a cavity into which the cement can be injected.^{26,27}

Radiation Therapy

In the absence of compression fracture or instability, external beam RT (EBRT) is also an effective treatment option for patients with significant comorbidities and limited life expectancy. RT is an indispensable part of adjuvant treatment following spine surgery when it was not possible to obtain wide surgical margins. To avoid adversely affecting wound healing, RT should be given 1 to 3 weeks after surgery.²⁸ RT schedules need to be individ-

ualized, and efficacy is highly dependent on histology. In general, patients with solid tumors, such as breast and prostate cancers, are moderately radiosensitive, while patients who are mostly radioresistant include those with cancers such as melanoma, osteosarcoma, and thyroid, colon, and renal cancers. RT alone is frequently utilized in patients with such hematological malignancies as lymphoma or myeloma due to the sensitivity of these tumors to RT.²⁹ In a systematic review involving

TABLE 2. Results From Glucocorticoid Therapy, Radiation Therapy, and Surgical Therapy Trials

Results from glucocorticoid therapy + RT trials	Baseline ambulation rate %	Posttreatment ambulation rate %	Median survival	Reference
10 mg dexamethasone IV bolus followed by 4 mg q6h plus RT 21-30 Gy	47	40	NR	Vecht et al ⁴⁸
100 mg dexamethasone IV bolus followed by 4 mg q6h plus RT 21-30 Gy	53	64	NR	Vecht et al ⁴⁸
96 mg dexamethasone IV bolus followed by 24 mg q6h plus RT 28 Gy	63	81	6 months	Sorensen et al ⁴⁹
16 mg dexamethasone IV bolus followed by 4 mg q6h plus RT 30 Gy	82	60-90	2.4 months	Graham et al ⁵⁰
96 mg dexamethasone IV bolus followed by 24 mg q6h plus RT 30 Gy	67	33-50	2.1 months	Graham et al ⁵⁰
Results from glucocorticoid therapy + RT trials				
30 Gy in 10 fractions	31	69	3.5 months	Aas et al ⁵¹
36 Gy	60	78	NR	Zaidat et al ⁵²
16 Gy in 2 fractions	47	63	5 months	Maranzano et al ⁵³
28 Gy in 4 fractions	52	61	3.6 months	Helweg-Larsen et al ⁵⁴
30 Gy in 10 fractions	100	100	14 months	Maranzano et al ⁵⁵
30 Gy in 10 fractions	45	74	NR	Latini et al ⁵⁶
Results from surgical therapy trials				
En bloc excision, palliative debulking	73	85	12	Ibrahim et al ⁵⁷
Single-stage posterolateral vertebrectomy	85	100	NR	Street et al ⁵⁸
Decompressive surgery	68	89	13 months	Mannion et al ⁵⁹
Single-stage posterolateral transpedicular and vertebral stabilization	99	99	7.7	Wang et al ⁶⁰
Vertebral body resection with anterior approach	26	80	NR	Siegal et al ⁶¹

IV, intravenous; NR, not reached; q6h, every 6 hours; RT, radiation therapy.

7 retrospective studies with 885 patients, RT provided a mean local disease control rate of 77%.²⁹ In a meta-analysis involving 543 patients, a pain control rate of 54% to 83% was reported with the use of RT.³⁰

No standard RT regimen exists for the treatment of malignant spinal cord compression. For patients with painful bone metastases, 1 to 5 low-fraction regimens with high single doses (4 to 10 Gy) have been shown to provide similar clinical outcomes to those of more protracted regimens.³¹⁻³⁵ In a prospective, randomized, phase 3 trial, Maranzano et al randomized 300 patients to either a short-course (8 Gy × 2 days) or split-course (5 Gy × 3 days or 3 Gy × 5 days) schedule. At a median follow up of 33 months (range, 4-61), both regimens of hypofractionated RT were effective, with no severe adverse effects. Considering the convenience of the short-course regimen, the authors concluded that the short-course

therapy could be the hypofractionated RT regimen of choice for patients with malignant spinal cord compression.³⁶

With the advances in stereotactic RT techniques, this approach has been utilized to allow precise high-dose targeting in 1 or 2 fractions while minimizing exposure to the healthy surrounding spinal cord tissue.³⁷ A systematic review involving 59 studies with 5655 patients treated with stereotactic RT for spinal metastases showed local control rates of 80% to 90% for patients with newly diagnosed disease, 80% for postsurgical patients, and 65% for previously radiated patients.³⁸ Results from glucocorticoid therapy, RT, and surgical therapy trials of malignant spinal cord compression are summarized in **Table 2**.

Spinal Cord Compression in Multiple Myeloma

Multiple myeloma is a clonal B-cell disorder

characterized by malignant transformation and the proliferation and accumulation of postgerminal center plasma cells in the bone marrow and occasionally at extramedullary sites. The reported incidence of extramedullary disease in newly diagnosed multiple myeloma ranges from 7% to 18%, while 6% to 20% of patients may develop extramedullary disease later in their disease course.³⁹ The outcomes of patients with multiple myeloma have significantly improved due to the widespread use of autologous stem cell transplantation (ASCT) and novel therapies targeting both the myeloma clone and its microenvironment. Control of bone disease in myeloma patients still represents a therapeutic challenge, however. At some time during their disease course, more than two-thirds of these patients present with osteopenia, osteoporosis, or pathological fractures, which frequently involve the spine and

■ **Figure 7.** Large osseous destructive mass posterior right hemithorax with prominent destruction of the right posterior eighth rib and adjacent T8 vertebral body. There is likely encroachment into the spinal canal with mass effect upon the thoracic spinal cord.

■ **Figure 8.** T2 MRI sequence shows significant decrease in size compared with prior image, with a soft-tissue mass at the right T8 level involving the posterior elements, the neural foramen, and the right lateral epidural space of the spinal canal.

cause spinal cord compression.⁴⁰

Treatment of spinal lesions in multiple myeloma requires a multidisciplinary approach. Prompt diagnosis and immediate treatment are critically important. Systemic therapy, including such modalities as chemotherapy agents, steroids, proteasome inhibitors, and immunomodulatory drugs, can be used in select patients with minimal

risk of neurologic deficit. Surgical management of multiple myeloma–related vertebral lesions is seldom utilized due to this disease’s sensitivity to chemotherapy and RT. The rare indications for surgical intervention may include unstable fractures and spinal cord compression caused by bone fragments protruding from a vertebral fracture.⁴¹

The combination of EBRT and

glucocorticoids is usually the treatment of choice for multiple myeloma patients who have impending vertebral fracture or spinal cord compression; it also provides pain control. EBRT also represents the treatment of choice for solitary plasmacytomas.^{42,43} Early studies that were conducted in small patient cohorts demonstrated that pain relief, quality of life, and motor function were improved in a sizable proportion of treated patients.^{44,45} No differences in general efficacy or in the extent and rapidity of pain relief have been observed using a fractionated 2-week course of 30 Gy vs a single fraction of 8 to 10 Gy.⁴⁶ The radiation field should be large enough to compensate patient motion but as limited as possible to preserve marrow function. This is especially true for patients who are candidates for ASCT, because peripheral blood stem cell collection can be impaired when RT is applied in large fields.⁴⁷

Outcome of the Case

The patient was evaluated by neurosurgery, medical oncology, radiation oncology, and interventional radiology specialties in a multidisciplinary fashion. The SINS was calculated to be 4. He was started on oral dexamethasone along with EBRT to his spinal disease. He received a total of 20 Gy (5 daily fractions of 4 Gy each). Upon completion of his EBRT, he was started on a lenalidomide, bortezomib, and dexamethasone (RVD) regimen. Within the first week of his radiation treatment, he reported a 90% decrease in spinal pain. Five weeks after the start of EBRT, a repeat MRI of the spine showed a significant decrease in spinal mass (**Figure 8**). Following 2 cycles of RVD, a very good partial response was achieved. After the completion of 4 cycles of RVD, he will be undergoing ASCT with high-dose melphalan chemotherapy. ■

FINANCIAL DISCLOSURE: The 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 full reference list, visit:**
cancernetwork.com/Case_Study_3.21

CONTINUING MEDICAL EDUCATION (CME)

Leveraging Evolving Data Sets on PARP Inhibitors in Ovarian Cancer to Inform Treatment Decision-making

FACULTY

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LEARNING OBJECTIVES

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

- Analyze evidence related to molecular testing and its application in selection of therapy for patients with ovarian cancer
- Understand and apply key findings from clinical trials to specific clinical cases reflective of ovarian cancer cases encountered in clinical practice
- Evaluate emerging therapeutic approaches, including combination approaches, and their appropriateness for specific populations of patients with ovarian cancer
- Summarize strategies for recognition and management of adverse events associated with specific treatments for ovarian cancer

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ACTIVITY OVERVIEW: Ovarian cancer is the most lethal gynecologic malignancy, accounting for 5% of all cancer deaths. Despite high rates of an initial response to debulking surgery followed by platinum-containing chemotherapy, rates of disease recurrence are high, occurring in 70% to 80% of patients. Poly (ADP-ribose) polymerase (PARP) inhibitors provide a treatment option for patients with recurrent advanced ovarian cancer following prior treatment. This therapy now demonstrates a prolonged progression-free survival benefit in women, who are newly diagnosed with advanced ovarian cancer, and provides hope for improved long-term outcomes. This continuing medical education activity provides an overview of the clinical impact of recent and emerging trial data for PARP inhibitors in ovarian cancer treatment and is intended to illuminate frontline, later-line, and maintenance therapies that are used in the ovarian cancer treatment paradigm. Adverse events and management will also be discussed.

Current Approaches for the Treatment of Ovarian Cancer

The standard of care for advanced ovarian cancer consists of debulking surgery, followed by a platinum-containing chemotherapy regimen. Recurrence rates are high and relapsed tumors often develop resistance to carboplatin/cisplatin.¹ The 5-year survival rate for patients with late-stage ovarian cancer is a dismal 29.2%.^{2,3}

Deficiencies in homologous recombination repair are associated with ovarian cancer, and these deficiencies stem from a variety of genomic aberrations, including mutations in *BRCA1*, *BRCA2*, *CDK12*,

RAD, and *FA*.⁴ The PARP inhibitors prevent the repair of DNA single-strand breaks and encourage their conversion to double-strand breaks, leading to tumor cell death. This is particularly efficient in patients who have homologous recombination deficient ovarian cancer, such as those who harbor a *BRCA1* or *BRCA2* mutation.⁵

The National Comprehensive Cancer Network (NCCN) testing guidelines recommend that genetic counseling and testing be considered for women with a history of ovarian carcinoma, fallopian tube, or primary peritoneal cancer.^{6,7} The Society of Gynecologic Oncology and the American Society of Clinical

Oncology guidelines provide similar recommendations to those of the NCCN and additionally recommend testing irrespective of family history.⁸

PARP Inhibitors in Recurrent Ovarian Cancer

These agents have been investigated in several studies as treatment for recurrent ovarian cancer and are listed in **Table 1**.

Several studies have also investigated PARP inhibitors as maintenance therapy in recurrent ovarian cancer, as outlined below in **Table 2**.

PARP Inhibitors in Primary Ovarian Cancer

A critical need for treatment options exists for newly diagnosed patients with advanced-stage ovarian cancer, particularly given the lack of screening options and nondescript symptoms at early stages. In several studies outlined in **Table 3**, PARP inhibition has been investigated as a therapeutic strategy in primary ovarian cancer.

Owing to the success of these trials, PARP inhibitors have now been approved in both recurrent and frontline maintenance settings for patients with advanced ovarian cancer. **Table 4** below highlights selected PARP inhibitors and corresponding indications. Currently, there are 3 PARP inhibitors that have indications for the treatment of ovarian cancer.⁷ Mechanistically, each PARP inhibitor exhibits its own nuances. The PARP trapping ability, platinum responsiveness, *BRCA* mutation status, and number of prior therapies all influence responsiveness to PARP inhibitors.

The most common hematologic toxicities associated with PARP inhibitors are anemia, thrombocytopenia, and neutropenia.⁸ Gastrointestinal toxicities are also common for

TABLE 1. PARP Inhibitors as Treatment in Recurrent Ovarian Cancer⁹⁻¹¹

Study	Study 1 gBRCAm	ARIEL2/ Study 10 BRCAm	ARIEL2/Study 10 BRCAwt	QUADRA gBRCAm	QUADRA HRD+	SOLO3 gBRCAm	AVANOVA ITT	CLIO gBRCAm	CLIO gBRCAwt
Agent	Olaparib	Rucaparib	Rucaparib	Niraparib	Niraparib	Olaparib	Niraparib + bevacizumab	Olaparib	Olaparib
ORR	34% (26%-42%)	53.8% (44%-64%)	29% (LOH high) 10% (LOH low)	29%	27%	72%	60%	28.6%	7.5%
DOR (months)	7.9 (5.6-9.6)	9.2 (6.6-11.6)	10.8 (5.7-NR) LOH high 5.6 (4.6-8.5) LOH low	8.3 (6.6-NR)	9.2 (5.9-15.2)	PFS, mos 12.4 vs 9.2	PFS, mos 11.9 vs 5.5	—	—
LOT	≥ 3	≥ 2	≥ 2	4-5	4-5	≥ 2	≥ 1	No limit	No limit

BRCAwt, *BRCA* wild type; gBRCAm, germline *BRCA* mutated; DOR, duration of response; HRD, homologous recombination deficiency; ITT, intention to treat; LOH, loss of heterozygosity (high or low); LOT, lines of therapy; NR, not reached; ORR, overall response rate; PARP, poly (ADP-ribose) polymerase; PFS, progression-free survival.

PARP inhibitors, with nausea and vomiting being the most prevalent. Fatigue is commonly seen with all PARP inhibitors and is generally managed with nonpharmacological treatments. Neurological (eg, headache, insomnia); respiratory (eg, dyspnea, cough); and cutaneous (eg, pruritis, photophobia) toxicities are much less common;

however, they should not be overlooked. Adverse event rates seen with PARP inhibitors in 3 recently published clinical trials are listed in **Table 5**.²⁰⁻²²

PARP Inhibitors in Combination Therapy

While the use of PARP inhibitors as single agents has demonstrated effectiveness in

terms of antitumor activity in platinum-sensitive disease, there is a need to move beyond monotherapy approaches to avoid resistance. Ongoing trials are investigating PARP inhibitors in combination with various agents, including immunotherapy, PI3K inhibitors, and antiangiogenic agents. In recent years, immune checkpoint

inhibitors have demonstrated positive outcomes when used in combination with PARP inhibitors.

The PARP inhibitors act via multiple mechanisms of action, including PARP trapping and catalytic inhibition, which need to be considered when selecting appropriate combination therapies. Other challenges associated with combining PARP inhibitors with other agents include the unmet need for biomarkers that would inform therapy, and dose-limiting toxicities caused by combination therapy that have not been observed in single-agent trials. Despite these challenges, important opportunities exist to target PARP-inhibitor resistance mechanisms and enhance the mutational load and immunogenicity of the tumor.²³

Combining PARP inhibitors with antiangiogenic agents is of interest because it may

TABLE 2. PARP Inhibitors as Maintenance Therapy in Recurrent Ovarian Cancer¹²⁻¹⁵

Study	Study 19	SOLO-2 gBRCAm	NOVA gBRCAm	NOVA Non-gBRCAm	ARIEL-3 BRCAm	ARIEL-3 ITT
Agent	Olaparib	Olaparib	Niraparib	Niraparib	Rucaparib	Rucaparib
Difference in PFS (months)	8.4 vs 4.8	19.1 vs 5.5	21.0 vs 5.5	9.3 vs 3.9	16.6 vs 5.4	10.8 vs 5.4
PFS HR (investigator assessed)	0.35 (95% CI, 0.25-0.49; <i>P</i> < .001)	0.30 (95% CI, 0.22-0.41; <i>P</i> < .0001)	0.27 (95% CI, 0.18-0.40)	0.53 (95% CI, 0.41-0.68)	0.23 (95% CI, 0.16-0.34; <i>P</i> < .0001)	0.36 (95% CI, 0.30-0.45; <i>P</i> < .0001)
PFS HR (BICR)	0.39 (95% CI, 0.27-0.55; <i>P</i> < .001)	0.25 (95% CI, 0.18-0.35; <i>P</i> < .0001)	0.27 (95% CI, 0.17-0.41; <i>P</i> < .0001)	0.45 (95% CI, 0.34-0.61; <i>P</i> < .0001)	0.20 (95% CI, 0.13-0.32; <i>P</i> < .0001)	0.35 (95% CI, 0.28-0.45; <i>P</i> < .0001)

BICR, blinded independent central review; gBRCAm, germline BRCA mutated; ITT, intention to treat; PARP, poly (ADP-ribose) polymerase; PFS, progression-free survival.

TABLE 3. PARP Inhibitor Trials in Primary Ovarian Cancer¹⁶⁻¹⁹

Study	Histology	BRCA status	Surgical status	Randomization/start of PARPi	Experimental arm	Control arm	All patients	BRCAm [HR] median PFS (months)	BRCAwt HRD positive	HRD negative
SOLO1	HGS/HGE	Mut	All-comers	Maintenance therapy	Olaparib	Placebo	NT	HR, 0.30 (0.23-0.41); PFS, NR vs 13.8	NT	NT
PRIMA	HGS/HGE	All-comers	PDS: IV or RD IDS: all	Maintenance therapy	Niraparib	Placebo	HR, 0.62 (0.50-0.76); PFS, 13.8 vs 8.2	HR, 0.43 (0.31-0.59); PFS, 21.9 vs 10.4	HR, 0.50 (0.31-0.83); PFS, NR	HR, 0.68 (0.49-0.94); PFS, NR
VELIA	HGS	All-comers	All-comers	Up front	Veliparib	Placebo	HR, 0.68 (0.56-0.83); PFS, 23.5 vs 17.3	HR, 0.44 (0.28-0.68); PFS: 34.7 vs 22.0	HR, 0.74 (0.52-1.06); PFS, 22.9 vs 19.8	HR, 0.81 (0.60-1.09); PFS, 15.0 vs 11.5
PAOLA-1	HGS/HGE/nonmuc BRCA positive	All-comers	All-comers	Maintenance therapy	Olaparib + bev	Bev + placebo	HR, 0.59 (0.49-0.72); PFS, 22.1 vs 16.6	HR, 0.33 (0.25-0.45); PFS: 37.2 vs 17.7	HR, 0.43 (0.28-0.66); PFS, 28.1 vs 16.6	HR, 0.92 (0.72-1.17); PFS, 16.6 vs 16.0

Bev, bevacizumab; BRCAwt, BRCA wild type; BRCAm, BRCA mutated; HGE, high-grade endometrioid; HGS, high-grade serous; HRD, homologous recombination deficiency; IDS, interval debulking surgery; ITT, intention to treat; IV, intravenous; Mut, mutated; NT, not tested; PARP, poly (ADP-ribose) polymerase; PARPi, PARP inhibitor; PDS, primary-debulking surgery; PFS, progression-free survival; RD, residual disease.

circumvent adverse effects of chemotherapy, such as myelosuppression. Currently, the NCCN guidelines list bevacizumab, an anti-vascular endothelial growth factor (VEGF) therapy, as a preferred agent in both combination therapy and monotherapy in the treatment of recurrent disease.⁷ Current PARP + antiangiogenic trials in ovarian cancer are outlined in **Table 6**.

Immune checkpoint inhibitors are also being evaluated in combination with PARP inhibitors, as they can promote error-prone repair, leading to increased point mutations and a potential increase in neoantigens. The PARP inhibitors can also lead to an immune-activating environment through the promotion of DNA damage and release of cytosolic DNA, which results in the activation of the STING pathway and upregulation of an interferon response. Moreover, DNA damage and activation of the ATM/ATR/CHK1 pathways can lead to PD-L1 upregulation, which, in the presence of an immune checkpoint blockade can then lead to potential synergy.

The combination of pembrolizumab and niraparib has shown promise in the TOPACIO study of patients with platinum-resistant ovarian cancer. The combination of niraparib and pembrolizumab yielded an objective response rate of 25% among patients with platinum-resistant ovarian cancer.²⁴ Pembrolizumab has shown activity in advanced recurrent ovarian cancer (AOC), with an 8% response rate and median progression-free survival (PFS) of 2.1 months, as reported in the

TABLE 4. FDA Approvals of PARP Inhibitors in Ovarian Cancer⁷

	Olaparib	Rucaparib	Niraparib	Talazoparib	Veliparib
Maintenance, frontline	Germline or somatic <i>BRCA1/2</i> mutation	—	Platinum-sensitive maintenance after CR/PR	—	—
Maintenance, recurrent	Platinum-sensitive maintenance after CR/PR	Platinum-sensitive maintenance	Platinum-sensitive maintenance after CR/PR	—	—
Treatment, recurrent	Germline <i>BRCA1/2</i> mutation; 3 prior treatments	Germline or somatic <i>BRCA1/2</i> mutation; 2 prior treatments	—	—	—
Nonovarian indications	Breast cancer (<i>BRCA1/2</i> mutation, previously treated with chemotherapy)	—	—	Breast cancer; germline <i>BRCA1/2</i> mutation	Under investigation; no indications at this time
Monotherapy dose	Tablet: 300 mg bid Capsule: 400 mg bid	600 mg bid	300 mg daily	1 mg daily	300 mg bid

Bid, indicated twice a day; CR, complete response; PARP, poly (ADP-ribose) polymerase; PR, partial response.

TABLE 5. Adverse Event Rates of PARP Inhibitors in Selected Clinical Trials²⁰⁻²²

Grade 3/4 AEs	Olaparib SOLO2 (NCT01874353) N = 195	Rucaparib ARIEL3 (NCT01968213) N = 372	Niraparib NOVA (NCT01847274) N = 376
Anemia (%)	19	19	25.3
Neutropenia (%)	5	7	19.6
Thrombocytopenia (%)	1	5	33.8
Fatigue/asthenia (%)	4	7	8.2
Nausea (%)	3	4	3.0
Vomiting (%)	3	4	1.9

AE, adverse effect; PARP, poly (ADP-ribose) polymerase.

KEYNOTE-100 trial. Because platinum chemotherapies also induce T cell proliferation and enhance tumor cell recognition through PD-1/PD-L1, the combination of pembrolizumab and carboplatin has also been evaluated in platinum-resistant AOC in a phase 1/2 study. In that study, 30.4% of the patients had archival tumor tissue with modified percent scoring ≥ 5 for PD-L1 and all achieved partial response (42.8%) or stable disease (57.2%). Overall median PFS was 4.6 months (95% CI, 2.7-6.2). Rate of

PFS at 6 months was 40.4% (95% CI, 25.5-65.5). In the same study, the combination of pembrolizumab with low-dose carboplatin was well tolerated and showed activity in heavily pretreated platinum-resistant AOC. Survival and biomarker analyses are currently ongoing.²⁵ **Table 7** outlines ongoing studies of PARP inhibitor and checkpoint inhibitor combination therapies. ■

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For full reference list, visit
gotoper.com/go/ovc-parp21lovarian

TABLE 6. Ongoing Trials Exploring the Combination of Antiangiogenic Agents and PARP Inhibitors

Active comparator	Experimental therapy	Study	Estimated enrollment	Patient population	Prior therapies	Primary outcomes
Platinum-sensitive ovarian cancer						
Maintenance niraparib	Maintenance niraparib + bevacizumab	AVANOVA (NCT02354131)	108	Platinum-sensitive, recurrent epithelial ovarian, fallopian tube, or peritoneal cancer	Must have received platinum-containing therapy for primary disease	PFS
Platinum-based chemotherapy	Olaparib or olaparib + cediranib	NRG-GY004 (NCT02446600)	549	Platinum-sensitive, recurrent HGS or HGE ovarian, primary peritoneal, or fallopian tube cancers; also, high-risk histologies with documented <i>BRCA1/2</i> mutations	Must have included a first-line platinum-based regimen	PFS
Maintenance olaparib	Maintenance olaparib + cediranib	ICON9 (NCT03278717)	618	Relapsed, platinum-sensitive ovarian, fallopian tube, or peritoneal cancer	Must have received 4-6 cycles of second-line platinum-based chemotherapy	PFS, OS
Platinum-resistant ovarian cancer						
Study	Arms	Estimated enrollment	Patient population			
NCI GY005(COCOS)	Olaparib alone	680	Platinum-resistant or refractory, HGS ovarian cancer			
NCT02502266	Cediranib alone Olaparib + cediranib Physician choice	—	Germline <i>BRCA1/2</i>			
OCTOVA NCT03117933	Paclitaxel alone Olaparib alone Olaparib + cediranib	138	Platinum-resistant ovarian cancer Stratification for prior PARP, prior antiangiogenic and <i>BRCA</i> status			
CONCERTO NCT02889900	Olaparib + cediranib	62	Relapsed, platinum-resistant ovarian, fallopian tube, or peritoneal cancer No germline <i>BRCA</i> mutation			
NCT02681237	Single arm cediranib + olaparib	34	Relapsed HGS ovarian cancer/HGE ovarian cancer with progression on prior PARPi Platinum-sensitive and platinum-resistant cohort			

HGE, high-grade endometrioid; HGS, high-grade serous; PARPi, PARP inhibitor; PFS, progression-free survival; OS, overall survival.

TABLE 7. Checkpoint Inhibitors + PARPi Combination Trials

Recurrent ovarian cancer				
Author/trial	N	Population	ORR (%)	DCR (%)
MEDIOLA (durvalumab + olaparib)	32	g <i>BRCA</i> Plat sensitive	72%	81
TOPACIO (pembrolizumab + niraparib)	60	t <i>BRCA</i> wt, 77% t <i>BRCA</i> m, 19% Plat-R, 50% Plat-Refr, 29% Plat ineligible, 21%	18% (5% CR/13% PR) Plat-R, 21% Plat-Refr, 13%	67 Median DOR, 9.3 months
Lee et al. NCT02484404 (durvalumab + olaparib)	35	Plat-R 83%	14% (all PR)	37
Newly diagnosed ovarian cancer				
Trial	Agents	Patient population	Arms	
DUO-O (AGO-OVAR23/ENGOT OV46) (NCT03737643)	Olaparib Durvalumab	t <i>BRCA</i> nonmutated LGSOC excluded	CP/bev/placebo/placebo CP/bev/durvalumab/placebo CP/bev/durvalumab/olaparib	
FIRST (ENGOT OV44) (NCT03602859)	Niraparib Dostarlimab Bev optional	Mucinous excluded t <i>BRCA</i> m guaranteed niraparib arm	CP/placebo/placebo CP/placebo/niraparib CP/dostarlimab/niraparib	
KEYLYNK-001 (ENGOT OV43) (NCT03740165)	Olaparib Pembrolizumab Bev optional	t <i>BRCA</i> nonmutated All histologies	CP/placebo/placebo CP/pembrolizumab/placebo CP/pembrolizumab/olaparib	
ATHENA (GOG3020/ENGOT OV45) (NCT03522246)	Rucaparib Nivolumab	Maintenance after chemo Stage III/IV, high grade Response to Plat	Placebo/placebo Placebo/nivolumab Placebo/rucaparib Nivolumab/rucaparib	

Bev, bevacizumab; *BRCA*m, *BRCA* mutated; *BRCA*wt, *BRCA* wild type; chemo, chemotherapy; CP, paclitaxel and carboplatin; CR, complete response; DCR, disease control rate; DOR, duration of response; g*BRCA*, germline *BRCA*; HGE, high-grade endometrioid; HGS, high-grade serous; LGSOC, low-grade serous carcinoma of the ovary; ORR, overall response rate; PARPi, PARP inhibitor; Plat, platinum; Plat ineligible, platinum ineligible; Plat-R, platinum-resistant; Plat-Refr, platinum refractory; PR, partial response; t*BRCA*, tumor *BRCA*.

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The Role of Postmastectomy Radiotherapy in Locally Advanced Breast Cancer After Pathological Complete Response to Neoadjuvant Chemotherapy

Christian Haydeé Flores-Balcázar, MD, MSc; Francisco Javier Castro-Alonso, MD; Tania Patricia Hernández-Barragán, MD, MSc; Jesús Delgado-de la Mora, MD; Antonino Daidone, MD, MSc; and Guadalupe Elizabeth Trejo-Durán, MD, MSc

THE CASE

A previously healthy woman, aged 32 years, presented to the oncology clinic with a 6-month history of left-breast tumor, mastalgia, and swollen axillary nodes. Physical examination was relevant for a 6-cm palpable mass in the upper outer quadrant of the left breast and an ipsilateral 2-cm, nonfixed axillary lymph node. Mammography showed a 1-cm mass in the upper outer quadrant, a 5.2-cm mass in the lower outer quadrant, and enlarged pathologic lymph nodes (BI-RADS category 5 disease). Breast ultrasound revealed 3 axillary lymph nodes with cortical thickening and loss of normal morphology (the largest with a 2.6-cm length in the long axis) (**Figure 1A-B**). The breast's core biopsy revealed a grade 3 apocrine invasive carcinoma with lymphovascular invasion; immunohistochemistry testing showed HER2-negative, hormone receptor-negative disease (estrogen receptor, 0%; progesterone receptor, 0%; HER2-negative, Ki67, 50%) (**Figure 2A-B**). A fine-needle aspiration biopsy of the axillary lymph nodes showed invasive breast carcinoma as well. Bone scintigraphy and a chest/abdomen CT scan ruled out metastatic disease. Upon initial diagnosis, clinical stage was deemed as cT3N1M0 (American Joint Committee on Cancer 8th edition: anatomic stage IIIA, clinical prognostic stage IIIC).

After a multidisciplinary tumor board discussion, the patient underwent neoadjuvant chemotherapy with weekly paclitaxel, followed by 4 cycles of dose-dense doxorubicin plus cyclophosphamide. After completing neoadjuvant treatment, clinical examination was relevant for a residual 1-cm palpable left breast mass and no palpable axillary nodes. Mammography and breast ultrasound showed a 77% partial response in the primary tumors, and axillary nodes with normal morphology and size (**Figure 1C-D**). Due to multicentric tumor disease, breast-conserving surgery would not confer satisfactory cosmetic results on her, and a modified radical mastectomy with intraoperative sentinel lymph node biopsy (and second-stage breast reconstruction) was planned. However, during surgery, the surgeons failed to identify the mapped lymph node, and level I-III axillary lymph node dissection was performed. The pathology report described complete pathological response: Miller and Payne criteria grade 5 response with the absence of malignant cells within the mastectomy specimen and in 24 lymph nodes (**Figure 2C-E**). Pathological staging after neoadjuvant treatment concluded ypT0N0M0 disease. Subsequent treatment for this patient was discussed in another tumor board.

Considering the complete pathological response achieved, what is the best treatment option for this patient after neoadjuvant chemotherapy and surgery?

- A. Surveillance only
- B. Adjuvant chemotherapy with capecitabine
- C. Adjuvant radiotherapy to the chest wall and regional lymph nodes
- D. Adjuvant radiotherapy to the chest wall only

➤ **TURN TO PAGE 140** for the answer and a discussion of this case by experts.

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CORRECT ANSWER: C. Adjuvant radiotherapy to the chest wall and regional lymph nodes

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Discussion

Worldwide, breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death in women¹; regional and distant recurrences occur even when appropriate breast and axillary surgery is performed, thus compromising survival.² In patients with a high risk of recurrence after mastectomy (involvement of axillary lymph nodes, tumor size >5 cm, invasion to the skin, or pectoral fascia), radiation therapy is indicated.³ Following upfront surgery and adjuvant chemotherapy, postmastectomy radiation therapy (PMRT; radiation to the chest wall and regional lymph nodes) decreases the rate of locoregional recurrence (LRR) and increases long-term disease-free survival (DFS), cancer-specific survival (CSS), and overall survival (OS).⁴ These benefits have been reported in multiple trials and meta-analyses.⁵⁻⁹

The benefits mentioned above have not been consistently demonstrated when neoadjuvant chemotherapy (NACT) is used.¹⁰ The primary goal

of NACT is to induce tumor response before surgery and enable breast conservation.¹¹ NACT results in long-term distant metastasis-free survival (DMFS) and OS similar to those achieved with primary surgery followed by adjuvant systemic therapy.^{12,13} Pathologic complete response (pCR) after NACT is associated with improved OS in breast cancer patients¹⁴; this association persists even when pCR is limited to either the breast (ypT0) or nodal (ypN0) compartments.^{15,16} When analyzing by breast cancer subtypes, patients with triple-negative and HER2-positive, hormone receptor-negative disease consistently achieve significant OS benefit, while this does not hold true for hormone receptor-positive tumors (whether they are HER2-positive or negative).^{14,15} To date, it is unclear how the response to NACT should be incorporated into decisions regarding locoregional adjuvant therapy.¹⁷ Data from ongoing NACT trials are still pending (NCT01872975; NCT01901094).^{18,19}

None of the prospective phase 3

trials yet conducted have investigated the impact of omitting PMRT in patients who received NACT and develop certain tumor response (ypN0 or pCR). The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 and B-27 NACT trials were performed when PMRT benefit was unknown and thus prohibited; these studies are a unique way to study the pattern of recurrence following NACT.^{20,21} A combined analysis of such trials reported that the axillary nodal response to NACT (ypN0) yielded low LRR rates without the use of PMRT, even in initially involved cases (cN+), thus supporting the hypothesis that a NACT response selects a lower-risk group that does not receive benefit from the addition of PMRT.²² Therefore, ypN0 (vs ypN+) is the usual way in which NACT studies report their findings.

Retrospective studies show discordant results of PMRT in the NACT setting. Data from MD Anderson Cancer Center showed that clinical stage II-III patients had a lower rate of LRR when PMRT was used (10-year LRR, 11% vs 22%; $P = .0001$), despite the fact that more advanced disease was present in the PMRT group; patients with clinical stage III-IV disease with complete response still had benefited from PMRT.²³

Figure 1. Imaging findings before (superior) and after (inferior) neoadjuvant chemotherapy. **(A)** Left mediolateral oblique projection of baseline mammography showing heterogeneous calcifications; 5.2-cm and 1-cm masses located 4 cm and 5 cm from the nipple, respectively (yellow arrows). **(B)** Left axilla basal ultrasound revealing enlarged pathologic lymph nodes (red arrows). **(C)** Left mediolateral oblique projection of follow-up mammography showing partial response in breast masses. **(D)** Left axilla follow-up ultrasound showing a lymph node with preserved morphology and size (red arrow).

TABLE. Contemporary Studies Analyzing PMRT Data in Patients With NACT

Author	N	Initial clinical stage	Patients with pCR	LRR (PMRT vs no PMRT)	DFS (PMRT vs no PMRT)	OS (PMRT vs no PMRT)
McGuire et al (2020) ²⁹	106	I: 2% II: 31% IIIA: 30% IIIB: 25% IIIC: 11%	100%	10-year: Stage I-II, 0% vs 0% Stage III, 7.3% vs 33.3%*	10-year: Stage I-II, NR Stage III, 87.9% vs 40.7%*	10-year: Stage I-II, NR Stage III, 77.3% vs 33.0%*
Shim et al (2014) ²⁶	151	IIA: 4.6% IIB: 55.6% IIIA: 31.1% IIIB: 8.6%	23.8%	5-year: 1.9% vs 6.5%	5-year: 91.2% vs 83.0%	5-year: 93.3% vs 89.9%
Wang et al (2020) ⁴¹	142	IIA: 22.5% IIB: 77.5%	33.8%	6-year: 5.5% vs 12.5%	5-year: 88.7% vs 72.4%*	5-year: 96.1% vs 95.0%

DFS, disease-free survival; LRR, locoregional recurrence; NACT, neoadjuvant chemotherapy; NR, not reported; OS, overall survival; pCR, pathologic complete response; PMRT, postmastectomy radiation therapy.

*Statistically significant difference ($P < .05$).

An analysis of 3 prospective German trials showed that PMRT was associated with a lower risk of LRR, especially in patients with cT3/T4 and cN+ tumors; patients who converted from cN+ to ypN0 had significantly lower LRR risk with PMRT (HR, 0.19; 95% CI, 0.04-0.97; $P = .05$). No benefit in DFS was noted in patients who were clinically node positive at diagnosis and received RT.²⁴ A French study investigated the outcomes of 134 women with clinical stage II-III disease treated with NACT and ypN0 disease evidenced in axillary dissection specimens. PMRT was not associated with significant differences in LRR-free survival or OS.²⁵ A multicenter study of 417 similar patients in Korea also failed to show benefit from PMRT in LRR, DFS, or OS.²⁶

National database studies also have divergent conclusions. A study based on data from the Japanese Breast Cancer Registry examined 3226 patients with cT1-4 cN0-2 tumors with NACT and mastectomy and the association between PMRT and LRR and OS based on ypN status. PMRT was not associated with significant differences in 5-year LRR-free survival or 5-year OS for ypN0 and ypN1 patients; only the ypN2-3 cohort showed benefit in the aforementioned outcomes.²⁷ A similar analysis of data from the United States' National Clinical Data Base

(NCDB) examined the outcomes of 15,315 cT1-3 cN1 patients with NACT and either mastectomy or breast-conserving surgery. For the mastectomy patients ($N = 10,283$), PMRT was independently associated with improved OS for both the ypN0 (HR, 0.729; 95% CI, 0.566-0.939; $P = .015$) and ypN1 (HR, 0.772; 95% CI, 0.689-0.866; $P < .001$) groups.²⁸

The benefit of PMRT when achieving pCR is more difficult to ascertain, as most of the studies are underpowered to show significant differences in this subgroup with relatively good prognoses. The only retrospective study that analyzed this population comes from MD Anderson Cancer Center, in which the outcome of 226 stage I-III patients and a pCR to NACT was examined: While PMRT did not affect the 10-year LRR of patients with stage I-II disease, patients with stage III disease saw a significant decrease in the 10-year LRR (7.3% vs 33.3%; $P = .04$), and significant increases in DMFS (87.9% vs 40.7%; $P = .0006$), CSS (87% vs 40%; $P = .0014$), and OS (77.3% vs 33.3%; $P = .0016$) were achieved by PMRT.²⁹ In an analysis of patients with pCR ($N = 275$) in the Taiwan Cancer Registry, PMRT was associated with improved LRR-free survival but not with DMFS or OS.³⁰ Further data from these and other relevant studies are listed in the **Table**.

Two ongoing phase 3 studies, NSABP B-51 and Alliance A011202, are investigating the role of adjuvant radiotherapy in ypN0 and ypN+ patients, respectively.^{18,19} Results from these trials will help clarify if adjuvant radiotherapy can be safely omitted in these subsets of patients after NACT, and they are highly anticipated. However, while results from the aforementioned trials are not yet available, the 2021 National Comprehensive Cancer Network (NCCN) clinical guidelines state that in patients with NACT, adjuvant radiotherapy should be based on the maximal disease stage irrespective of tumor response to NACT.³¹ Therefore, based on the current NCCN guidelines, answer (a) is incorrect: Patients with locally advanced disease at diagnosis should receive adjuvant radiotherapy even with an excellent response to NACT. Surveillance omits potential benefits in LRR, DMFS, and OS.³¹ Regarding adjuvant capecitabine, available data support its use only when residual invasive disease is present after NACT, as it offers an improvement in OS. Such benefit is independent of the one provided by radiotherapy.³² Currently, no data support adjuvant capecitabine in patients who achieve a pCR. Therefore, answer (b) is incorrect.

Most recently, tumor biology has been evaluated as an essential factor to consider when thinking about the omis-

■ **Figure 2.** Histological sections stained with hematoxylin and eosin. **(A)** Initial breast biopsy identifies apocrine adenocarcinoma characterized by solid growth [4x]. **(B)** Breast tumor is composed of cells with pleomorphism and extensive eosinophilic cytoplasm [40x]. In the mastectomy specimen, **(C)** extensive areas of fibrosis [4x], **(D)** dystrophic calcifications [10x], **(E)** and macrophage clusters [10x] were identified; no invasive or in situ carcinoma was detected.

sion of PMRT. Hormone receptor-positive tumors are associated with lesser LRR and better OS; the relationship between HER2 positivity and different cancer outcomes has not consistently been demonstrated.^{23,24,30} In a post hoc analysis of the ACOSOG Z1071 NACT trial, the omission of PMRT was associated with a higher rate of LRR in cT0-T4cN1-2 patients. Patients with triple-negative tumors had higher LRR rates than hormone receptor-positive patients (HR, 3.46; 95% CI, 1.68-7.13). Among this subgroup, patients with PMRT had numerically greater LRR-free rates compared with no PMRT (91.0% vs 77.9%); the difference was not statistically significant likely due to the small sample.³³ In another analysis from the NCDB, patients with cN1 disease and ypN0 tumors did not have an OS benefit with PMRT; however, among the hormone receptor-negative

subgroup, patients had an OS improvement (HR, 0.65; $P < .01$).³⁴

Even in triple-negative disease, several other prognostic factors must be taken into account. In a study of 390 patients in China with triple-negative, stage I-III disease without PMRT, predictive factors for any LRR were studied. On multivariate analysis, 4 risk factors were associated with increased risk of recurrence: aged <50 years, lymphovascular invasion, high-grade tumor, and 3 or more involved lymph nodes. The 5-year LRR rate for patients who had 0 or 1, 2, and 3 or 4 risk factors were 4.2%, 25.2%, and 81.0%, respectively ($P < .0001$).³⁵ The patient from the present case had 3 of those risk factors. It is worth mentioning that the adverse outcome of triple-negative disease can potentially be mitigated by PMRT. In a prospective controlled trial, patients with triple-

negative, stage I-II disease who had modified radical mastectomy were randomized to chemotherapy or chemotherapy followed by PMRT. The addition of PMRT significantly increased the 5-year DFS (88.3% vs 74.6%; $P = .02$) and OS (90.4% vs 78.7%; $P = .03$).³⁶ Notably, the 2 above-mentioned trials were not specific to patients receiving NACT.

The value of adding regional node irradiation (RNI) to chest wall irradiation with up-front surgery and adjuvant chemotherapy has been addressed by several randomized trials, demonstrating consistent benefit in LRR, DFS, and CSS. No improvement in OS has been shown on a single-study basis.^{37,38} A meta-analysis of these and other studies ($N = 10,620$ patients) showed that adding radiation therapy to supraclavicular and internal mammary lymph nodes (vs radiation to the chest wall only) improves LRR, DMFS, and OS.³⁹

Information about RNI in addition to chest wall radiotherapy when using NACT is scarce. Most of the previously described studies used radiotherapy to the chest wall and "regional nodes at risk" without properly describing which regions were irradiated.^{23-27,29,30,33,34} A retrospective study from MD Anderson Cancer Center explored the benefit of RNI in addition to radiation to the chest wall/breast in node-positive breast cancer treated with NACT. RNI was defined as radiation therapy to at least 1 of the regional draining lymphatic basins at the radiation oncologist's discretion. On multivariate analysis, RNI significantly reduced the risk of LRR (HR, 0.497; 95% CI, 0.279-0.884; $P = .02$); no benefit to CSS or OS was seen.⁴⁰

NCCN guidelines state that in patients with N1 disease, radiation therapy to chest wall, infraclavicular and supraclavicular regions, internal mammary chain plus any part of the axillary bed at risk should be strongly considered.³¹ In the last Saint Gallen consensus, 85% of participants agreed that radiation to the chest wall plus regional

nodes would be the optimal choice for patients with N1 disease when adverse features are present (ie, triple-negative disease).⁴¹ Therefore answer (d) is incorrect: Radiation fields in locally advanced, high-risk disease should include regional lymph nodes in addition to the chest wall. Thus, (c) is the correct answer.

Outcome of This Case

The patient received PMRT (50 Gy in 25 fractions) to the chest wall and regional lymph nodes (axillary levels I-III, supraclavicular, and internal mammary) because of the high-risk factors of her disease. The patient has been under follow-up during the past 16 months without evidence of locoregional recurrence or distant metastases; her breast reconstruction surgery is being planned.

Note: Due to the absence of randomized controlled trials that determine the effect of PMRT in patients with NACT who achieve pCR, the authors highlight the necessity of multidisciplinary team evaluation for each patient. This case represents the authors' opinion of how this particular patient should be treated

off-trial. The ongoing randomized studies will elucidate whether this is ultimately the correct approach. ■

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Detecting Cancer Earlier Using Circulating Tumor DNA

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

- Summarize the scientific rationale for using circulating tumor DNA (ctDNA) as a biomarker for detecting cancer
- Describe the clinical implications of effectively measuring ctDNA for the detection of cancer
- Explain the most recent data surrounding the use of ctDNA for early cancer detection

RELEASE DATE: March 1, 2021

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Significant advancements are being made in the use of circulating tumor DNA (ctDNA) for the noninvasive assessment of cancer.^{1,2} ctDNA consists of fragmented segments of DNA that are shed from tumor cells into adjacent body fluids and the circulatory system. Important features of ctDNA analysis include ctDNA fragment length, DNA copy number, and phenotypic information.

ctDNA analysis is often used as an alternative to tissue biopsy for tumor genotyping and for guiding therapy in patients with metastatic cancer.^{1,3} It is also used to detect minimal residual disease after treatment.^{4,5} It can be used to assess prognosis and potential resistance to treatment and to help monitor response to treatment. Moreover, there is increasing evidence that ctDNA has a potential role in the early detection of many types of cancer.^{1-3,6,7}

The value of ctDNA analysis can be enhanced by combining it with the assessment of other biomarkers, including certain proteins, epigenetic markers, circulating tumor RNA, nucleosomes, exosomes, and immune markers.^{1,8-10} Methylation status, one of the most widely studied epigenetic markers in this setting, has been shown to be particularly valuable.⁸

Several companies are developing ctDNA tests for early cancer detection, and the results are promising.^{1,9} However, barriers to the clinical application of early detection tests include the following:^{1,9-11}

- An early detection test should be able to identify multiple cancer types with-

out prior knowledge of a specific cancer mutation.

- Clonal hematopoiesis can complicate the results of ctDNA analysis.
- Because of the lower disease burden in early disease, tumors may not shed enough ctDNA for detection.

Despite these obstacles, the promise of ctDNA analysis in the early detection of cancer continues to grow, with the expectation that advances in early detection and intervention will result in significantly reduced morbidity and mortality.

Tanios Bekaii-Saab, MD, FACP reviews recent advances in the use of ctDNA analysis and its potential role in the early detection of cancer.

Q: Could you briefly describe the distinction between circulating tumor DNA and cell-free DNA?

BEKAI-SAAB: There is quite a bit of confusion between the terms. Circulating tumor DNA (ctDNA) depicts the DNA that belongs to the tumor. It is a valuable marker in cancer. Cell-free DNA (cfDNA) is a broader term that describes DNA that is freely circulating in the bloodstream but is not necessarily of tumor origin. cfDNA is not a new term; it was identified in the 1940s.¹ cfDNA is released from normal cells as a result of normal cellular turnover and as a result of tissue injury or inflammation. If someone exercises quite a bit or has surgery, the cfDNA levels go up. It is important to understand that people who do not have cancer have cfDNA levels that

are very fluctuant.

In patients who have cancer, ctDNA is a fraction of the overall cfDNA. In very early cancer, it can be as low as 0.05% to 0.1% of the cfDNA. In those with significant tumor load, it can go up to 90%. This is important to keep in mind because it has been the crux of the challenge of the detection and analysis of ctDNA.

Q: What is the scientific rationale for using ctDNA as a biomarker for early cancer detection?

BEKAI-SAAB: First, cancer is a significant health care problem. It remains the second leading cause of death worldwide.¹² ctDNA can be used as a marker for early-stage cancer, and it has the advantage of being able to identify alterations that are specific to the cancer cell. The problem is that the earlier the cancer, the lower the yield of the ctDNA. As assay sensitivity improves, it will almost be like capturing a needle in a haystack. The good news is that our assays seem quite sensitive.¹ As the understanding of tumor-specific alterations and the events that precede these alterations has improved, the markers have reached a higher sensitivity and can be developed for screening for early-stage cancer.

Q: What are the major clinical implications of effectively measuring ctDNA as a biomarker for early cancer detection?

BEKAI-SAAB: The motivation for early detection of tumors is clear. We know that earlier detection of malignancy results in a significant decrease in can-

cer-specific mortality. For breast cancer screening we had mammography. For cervical cancer screening we had Pap smears. For colorectal cancer we had colonoscopy, and now we have the stool-based assay that uses DNA and methylation DNA markers for early screening.

We also know that many of the protein biomarkers, such as cancer antigen (CA) 19-9 and CA 125, are not always very useful. Even alpha-fetoprotein and prostate-specific antigen (PSA), which are useful in liver cancer and prostate cancer, respectively, do not have very high sensitivity or specificity. With PSA, many patients unnecessarily go down that diagnostic path with no given diagnosis. So these tools are good, but not great, and they are not easy. Colonoscopy, Pap smears, and mammography are invasive and do not have a high level of sensitivity or specificity in some cases.

We do not have generalizable biomarkers that detect cancer early across the board. We do the best we can in the absence of more sensitive and specific biomarkers. Most cancers are not screened for because their prevalence in the general population is too low to justify screening on an individual cancer basis. This has limited the capacity to mass screen patients.

It would be great if we could develop ctDNA tests for early cancer detection and make them widely available as multi-cancer tests. Certainly that has health implications, since detecting cancer early is the best option for providing a cure or at least longer remissions. It also has economic implications. Cancer

treatment is very expensive and it is draining the system. There is substantial lost time because patients have to take off work or go on disability. There are significant financial burdens on families with cancer. We often hear about patients having lost their life savings. They go into bankruptcy because of cancer and its treatment.

It makes sense to be able to screen cancers across the board with a multi-cancer early detection test that can simultaneously identify many of the cancers, essentially using one blood tube to screen for the more common and the less common cancers. This would significantly lessen the burden of cancer. But it is important that the test minimizes false-positive results, which is a big concern in terms of cost-effectiveness.

Q: Which patient populations would have the greatest benefit from early cancer detection using ctDNA?

BEKAI-SAAB: That has yet to be defined. We could start with patients who are older than 50, where we know the risk of cancer is increasing. But in specific settings, such as breast cancer and colon cancer, we are seeing cancer being diagnosed in younger and younger patients. So the age keeps falling, from 50 to perhaps 40 or 45. I would also add high-risk patients, such as those with a strong family history. We have to consider multiple stratifiers, including certain exposures, to identify patients who are at the highest risk. At some point we might start considering everyone for screening, but for now it would

be important to identify the patients who are older and at higher risk.

Q: Which cancer types do you think are least likely to benefit from the use of ctDNA for early cancer detection?

BEKAI-SAAB: That is a tough question because it depends on whether we will have a multi-cancer screening test or will just be focusing on screening for the more common cancers. That question will have to be answered in terms of the health care value of the test versus cost. Initially, one of the challenges will be in patients with cancers that shed very low levels of ctDNA. Pancreatic cancer, for example, will be very challenging. The good news is that research is trying to identify how to use methylation markers and DNA markers to identify those cancers early.⁸ I hope that eventually there will be no limitation on the cancer type, if we have the right test for early detection.

But for now we have to prioritize. We should start with the cancers that are more common and that we have screening modalities for. With colon cancer, for example, ctDNA testing can be compared to screening with colonoscopy, sigmoidoscopy, or fecal occult blood testing. For breast cancer it can be compared to mammography. For cervical cancer it can be compared to Pap smears. ctDNA screening would make sense in lung cancer, where it could be compared to low-dose CT in high-risk patients, meaning those who are smokers. We should focus on patients that we consider high

risk rather than the younger and low-risk patients.

Q: What challenges are there for effectively using ctDNA as a biomarker for early cancer detection?

BEKAI-SAAB: There are multiple obstacles. Foremost is that ctDNA levels in patients with early-stage cancers are much lower than those with advanced and metastatic disease. As our tests become more sensitive, this will become less of an issue. Another challenge is that the proportion of patients with early-stage cancer who have detectable ctDNA using the current technology is lower than we would want. The current technology is missing 30% or more of those patients. For example, if we screen 100 patients with early-stage cancer, we are likely to identify 50% to 70%, not 100%. That is not bad to start with, but the goal would be to get as close as possible to 100%.

Another challenge is identifying the right patient populations to start with. Are we going to screen everyone from the day they are born? Probably not. Are we going to start screening at age 30, 40, 50? We think we know where the age cutoff is for many cancers that we typically screen for, but will we start screening earlier and earlier? These challenges will probably be resolved in the near future, so I think that the future is looking quite bright. But we do have a long way to go with respect to refining the practice of screening patients across the board.

Q: What are the key emerging ctDNA assays for early cancer

detection that are being evaluated in clinical studies?

BEKAI-SAAB: There are several emerging assays (**Table**).^{1,9,13-18} GRAIL has been one of the leaders with the Circulating Cell-free Genome Atlas, STRIVE, and SUMMIT studies.^{9,16} CancerSEEK is another platform that uses a unique, noninvasive test to analyze mutations, as well as protein biomarkers in the blood.¹³ Guardant Health is leading the ECLIPSE trial of about 10,000-plus patients. In this trial, the LUNAR-2 blood test is being used to screen for colorectal cancer in average-risk adults.¹⁷ This test will be compared with colonoscopy screening to see if specificity can be increased from less than 90% to more than 90%.

Freenome is conducting the AI-EMERGE study for detection of early-stage colorectal cancer.^{9,14} This platform uses machine learning and artificial intelligence to assess the performance of a blood test that assesses cfDNA epigenetic and protein biomarkers. They are hoping to increase significantly the sensitivity and specificity of testing from less than 90% to close to 95%. *[Editor's note: preliminary data indicate a sensitivity of 92% for early disease.¹⁴]*

Exact Sciences has Cologuard[®], which is FDA-approved for colorectal cancer screening and has a high level of sensitivity and specificity.¹⁸ Exact Sciences also has developed a blood-based test for early detection of hepatocellular carcinoma (HCC). Data suggest that the combination of methylated DNA and protein biomarkers

TABLE. Examples of ctDNA/cfDNA Assays for Early Cancer Detection*

Company	Assays/Studies	Results
GRAIL	Next-generation sequencing blood tests are being evaluated in the Circulating Cell-free Genome Atlas Study, SUMMIT, and STRIVE.	In 2019, FDA granted breakthrough device status for early detection of multiple cancer types in patients 50 years and older. ¹⁶
Guardant Health	LUNAR-2 liquid biopsy test for colorectal cancer is being evaluated in the ECLIPSE study.	LUNAR-2 was reported to have sensitivity of 90.3% and specificity of 96.6% for early detection of colorectal cancer. ¹⁷
Freemove	AI-EMERGE is a platform using artificial intelligence and machine learning for early detection of colorectal cancer.	Putcha et al reported preliminary data indicating that the test had a sensitivity of 92% for early disease. ¹⁴
Exact Sciences/Thrive	CancerSeek is a blood test designed to detect multiple cancer types as early as possible. It assesses protein biomarkers and tumor-specific mutations in circulating DNA. ¹³	The test identified 8 common cancers (ovary, liver, stomach, pancreas, esophagus, colorectal, lung, and breast). In ovarian, liver, stomach, pancreatic, and esophageal cancers, sensitivity ranged from 69% to 98%. Specificity was greater than 99%. ¹³
Exact Sciences	Cologuard® is used for colorectal cancer screening.	FDA-approved for colorectal cancer. ¹⁸
Exact Sciences	An assay is being studied for early detection of HCC.	In 2019, FDA granted breakthrough device status for early detection of HCC. Data reported by Chalasani et al suggest that the combination of methylated DNA and protein biomarkers can detect early-stage HCC at a higher sensitivity rate than traditional methods, such as alpha-fetoprotein. ¹⁵

* This Table is not comprehensive; other assays are being studied.

cfDNA, cell-free DNA; ctDNA, circulating tumor DNA; FDA, Food and Drug Administration; HCC, hepatocellular carcinoma.

can detect early-stage HCC at a higher sensitivity rate than traditional methods, such as alpha-fetoprotein.¹⁵

Q: In what ways do you anticipate that the use of ctDNA for early cancer detection will be integrated into clinical practice?

BEKAI-SAAB: I foresee that initially we will have a primary use for ctDNA for early cancer detection to enhance our current modalities in breast, lung, colon, and prostate cancers, and perhaps others such as HCC. It may enhance the detection of gastric cancer, which is one of the most common cancers worldwide. In the next few years, as we establish the routine use of ctDNA for early detection, the testing will be integrated primarily in settings in which we know screening makes a difference, and then gradually expanded

so that we have multi-cancer tests for the detection of any cancer.

Q: Finally, what do you think the value and the potential role of integrating methylating DNA biomarkers with ctDNA analysis will be?

BEKAI-SAAB: It is important to understand that cancer formation is accompanied by widespread DNA methylation changes within the cell. DNA methylation is a very early event in cancer, so its utility comes in early screening. These changes are typically characterized by a globally hypomethylated genome with some focal hypermethylation of tumor-suppressor genes, and these aberrant DNA methylation patterns often occur in the promoter regions.⁸ Many of these epigenetic changes occur early in tumor formation and are highly pervasive across all

tumor types. This is essentially where we want to be. We want to have multi-cancer detection.

DNA methylation changes are important to cancer biomarker testing. We already have a proof of principle in colon cancer, where Cologuard® uses this technology and is widely used and has enhanced significantly the early detection of cancer.¹⁸ The DNA methylation changes can be detected with accuracy in the cfDNA in the blood, not just with high sensitivity but also with high specificity. The changes can be detected in different biosamples, such as stool, urine, and brushings for esophageal cancer, so it is not limited to the blood. It is important to have biomarkers that are easy to detect across multiple biosamples because in other parts of the world, where blood samples are difficult to manipulate and store, it may be easier to use stool or urine

or other biosamples. I think that these tests can be economical, too. They are easier to use and are highly specific. Ultimately, these tests may be suitable for worldwide population screening, but that is looking way into the future. ■

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For full reference list, visit <https://www.gotoper.com/go/onc-circulating-tumor-dna2021>

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