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MAY 2020 | Vol 34 • No 5

LUNG CANCER

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Forging Ahead in a Time of Crisis

Continuing the fight against lung
cancer in the COVID-19 era

GU Cancer Managing Prostate Cancer Surgical Patients During the COVID-19 Pandemic

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Andrew A. Davis, MD; William J. Gradishar, MD

GI Cancer Current Knowledge and New Directions in Cholangiocarcinoma

Milind Javle, MD

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patient care during this time,

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ONCOLOGY[®] (ISSN 0890-9091) is published monthly by MultiMedia Healthcare LLC, 2 Clarke Drive, Suite 100 Cranbury, NJ 08512. Annual subscription rates: US, \$199 and Canada, \$219; students and nurses, \$96; international, \$249. Single copies: \$20 each. Institutional US, \$299; Canada, \$329; international, \$375. Periodicals postage paid at Trenton, NJ and at additional mailing offices. POSTMASTER: Please send address changes to *ONCOLOGY* PO Box 457, Cranbury NJ 08512-0457, USA. Publications Mail Agreement No 40612608. Return Undeliverable Canadian Addresses to: IMEX Global Solutions, PO Box 25542 London ON N6C 6B2. Canadian G.S.T. number: R-124213133R001. Printed in U.S.A.

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Navigating Uncharted Waters

While so much of the medical community has focused its attention on treating and caring for patients with the coronavirus disease 2019 (COVID-19), the unfortunate truth is that the need for quality and compassionate cancer care continues.

In this issue of *ONCOLOGY*[®], we spoke with David R. Gandara, MD, director of the thoracic oncology program and senior adviser to the director of the University of California Davis Comprehensive Cancer Center, about the impact of the pandemic on the current management and treatment of patients with lung cancer, as well as the future of patient care in a post-COVID-19 world.

"What has happened has dramatically changed how we practice, how we interact with lung cancer patients," says Gandara. "But it hasn't altered the basic premise that lung cancer is now a highly treatable disease."

Gandara also looks ahead at how the current state of virtual interactions in medical education might persist once the pandemic has passed. "I actually hope some long-term changes will occur in both cancer care and education," says Gandara. "Attendees, virtual attendees, will be able to select what sessions they tune into and which they don't. I think this will change the face of [continuing medical education]."

Also in this issue, you will read about how Judd W.

Moul, MD, and his colleagues at the Duke Cancer Institute are managing their care of surgical patients with prostate cancer in the face of the COVID-19 pandemic. Moul's report, along with expert commentary from Eric A. Klein, MD, regarding his experience at the Cleveland Clinic, attests to the ability of oncologists, and the medical community at large, to adapt and continue to provide expert care in the face of unprecedented challenges.

For this month's clinical quandary, you will read about the case of a 56-year-old man with immune-mediated adverse events involving multiple organ sites. How do we resolve this? Read on to find out.

Within these pages, you will also find a review of novel neoadjuvant treatment strategies for triple-negative breast cancer, a roundup of some of the recently released abstracts from the Society of Gynecologic Oncology 2020 Annual Meeting on Women's Cancer, and an Image IQ to test your knowledge of hematological malignancies.

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

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Fighting 2 Enemies: Cancer and COVID-19

Julie M. Vose, MD, MBA
Editor-in-Chief of ONCOLOGY®

The coronavirus disease 2019 (COVID-19) pandemic is affecting every aspect of medical care worldwide. Our patients with an oncologic diagnosis are among the most vulnerable populations. In addition, oncology patients often have other known risk factors, such as advanced age and other comorbidities, that put them at the greatest risk for COVID-19 complications should they become infected. Although few data are published yet, results from the experience in Wuhan, China, demonstrated that patients with cancer who were infected with COVID-19 had increased complications and mortality.¹ In this study population, 28 patients with COVID-19 infection had a median age of 65 years (range, 56-70 years) and lung cancer was the most frequent diagnosis (25%). A total of 15 (53.6%) patients had severe events and the death rate was 28.6%. The risk of developing severe events was even greater if the last antitumor treatment was given within 14 days of hospitalization.

Given this information, most cancer centers have taken drastic steps to modify the risk of COVID-19 infection in our oncology patients and medical staff. As a result, many nonurgent visits in medical, surgical, and radiation oncology subspecialties are being conducted by telehealth. It is estimated that up

to 60% to 70% of physician visits are not being performed in person during this time of the pandemic. In addition, chemotherapy sessions or oncologic surgery that require inpatient hospital care are also being evaluated carefully to decrease volume and create hospital capacity for symptomatic patients with COVID-19 infection. We have now become very familiar with online meetings, which work surprisingly well, and in some ways allow increased participation from health-care workers who may be at several different sites or at home. At many centers, basic research laboratories are closed and clinical research is reduced to include only critical protocols open for our patients with cancer.

Some areas of the country, such as New York City, have gone through a peak time of infection and the incidence of cases and hospitalizations are decreasing. However, other areas of the country, such as the less-populated areas and rural areas, are still experiencing a slow increase in the number of cases and hospitalizations. Each area should be considered separately with respect to oncology preparations and needs. Another concern for all oncology providers is that we may experience secondary peaks of COVID-19 activity over the upcoming weeks to months following the first peak of infection. It will be

very difficult for patients who need oncologic care to wait much longer, and oncology practices need to keep financially solvent.

Are there any positive outcomes from this pandemic? We can hope that the use of telehealth will continue for appropriate patients even after this crisis passes. Telehealth visits can be a viable option for some patients as long as the amount of revenue for these visits continues to be the same for in-person visits. Another positive aspect of this pandemic is that health care providers are able to cross state lines to help bolster health care workers in another state. We are certainly learning a great deal about working efficiently and trying to maximize the tests and treatments we have available. This pandemic has also brought out the importance of sharing information worldwide to assist each other against a common enemy.

As oncology health care providers, we must all work together to help our patients get the treatment and active follow-up they need. Perhaps we can use this time to improve and focus oncology care and research for the benefit of our patients. ■

REFERENCE

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Managing Prostate Cancer Surgical Patients during the COVID-19 Pandemic: A Brief Report of the Duke Cancer Institute's Initial Experience

Judd W. Moul, MD, FACS*; Andrew Chang, MD; Brant A. Inman, MD

Division of Urology, Department of Surgery, Duke Cancer Institute, Duke University, Durham, NC 27710

**Correspondence: Judd Moul, MD, 3707 DUMC, Durham, NC 27710; judd.moul@duke.edu.*

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has rapidly placed tremendous stress on health systems around the world. In response, multiple health systems have postponed elective surgeries in order to conserve hospital beds and personal protective equipment, minimize patient traffic, and prevent unnecessary utilization and exposure of health care workers.¹ The American College of Surgeons released the following statement on March 13, 2020: "Each hospital, health system and surgeon should thoughtfully review all scheduled elective procedures with a plan to minimize, postpone, or cancel electively scheduled operations, endoscopies or other invasive procedures until we have passed the predicted inflection point in the exposure graph and can be confident that our health care infrastructure can support a potentially rapid and overwhelming uptick in critical patient care needs."² In our state, North Carolina, Governor Roy Cooper requested that all hospitals postpone elective and nonurgent procedures and surgeries effective March 23, 2020.

Aside from clear-cut examples of immediately life-threatening versus truly elective cases, most procedures exist on a continuum of potential harm that may result from postponing surgical

PERSPECTIVE

E. David Crawford, MD, reflects on current triage challenges on [page 160](#) and **Eric A. Klein, MD**, shares the Cleveland Clinic experience on [page 163](#)

treatment. This is particularly germane to surgeries for cancer, in which long-term outcomes are often dependent on timely intervention. In urology, considerations regarding case stratification have been published to help guide our review processes.³⁻⁵ However, ultimately, this process needs to be customized to the level of COVID-19 severity in each region. The goal is to remain vigilant and prepared for the population-level risk of COVID-19, but to reasonably ration available resources to treat non-COVID-19 diseases that threaten our patients.

In North Carolina, testing-confirmed COVID-19 case numbers and hospital resources are illustrated in the **Figure**. At this point (as of April 9, 2020), case numbers in North Carolina are rising but lag behind those of the main US epicenters; hospital resources remain relatively well preserved.

Within this current COVID-19 environment, we outline our approach

to stratifying surgical management of prostate cancer here at Duke University Hospital.

Prostate Cancer

The diagnosis and management of adenocarcinoma of the prostate, or prostate cancer (PC), have been and remain controversial during the best of times, but the COVID-19 pandemic certainly adds fuel to the fire. Providing safe and appropriate care requires a nuanced approach. Fortunately, risk stratification of the severity of localized and advanced PC has been in practice for many years and is being used now to its full extent to triage prostate cancer patients for surgical care.

Traditionally, PC had been placed into 3 risk groups as defined by D'Amico et al: low, intermediate, and high risk. These were later adopted by major professional organizations, including the American Urological Association, National Comprehensive Cancer Network, and American Society of Clinical Oncology.

gy.⁶⁻⁹ These organizations have relied on American Joint Committee for Cancer for the backbone stage groups¹⁰ In 2020, most experts use a classification of 5 risk groups for localized prostate cancer (Table 1). The boxed areas are the two highest categories of high and very high risk disease. Men in these two groups at our center have been considered to move forward with scheduled surgery during the COVID-19 pandemic subject to local hospital considerations regarding the severity of COVID and would be the first patients to be rescheduled for surgery once the COVID pandemic subsides. In our risk schema, we have reverted to the traditional 3 risk group system collapsing very low and low risk and combining high and very high risk.

The staffs of the Duke Cancer Institute Center for Prostate and Urologic Cancers, working with the Duke Cancer Center's surgeon-in-chief and his office, developed a COVID-19 triage table (Table 2) to help our teams make prudent and consistent decisions about prostate cancer surgeries during the pandemic surge for as long as local conditions dictate. This schema also stratifies patients for clinic visits and procedures. Currently, our timelines for care are:

- Priority 3: See/do now
- Priority 2: Delay 6-12 weeks
- Priority 1: Delay 3-6 months

Importantly, when this is communicated to patients, it must be made clear that these timelines are approximate and likely will change. If COVID-19 worsens, the timelines will shift to incorporate significantly longer delays.

To further illustrate the process for triage of localized prostate cancer at our center, we offer several specific surgery case examples. With these, we hope to help practicing urologic oncologists to make triage and treatment recommendations for their patients.

Cases

CASE 1. involves a high-risk 62-year-old African American man with a pros-

FIGURE COVID-19 data obtained online via the North Carolina Electronic Disease Surveillance System

Source: North Carolina Center for Health Statistics (2020). (<https://www.ncdhs.gov/>), last updated April 8, 2020; **KEY:** COVID-19, the coronavirus 2019; PPE, personal protection equipment.

TABLE 1. Risk Groups- Five Current Groups for Localized Prostate Cancer

Risk Group ¹ : Clinically Localized	
Very low risk	T1c: Gleason score ≤ 6 ; PSA < 10 ng/mL; Fewer than 3 prostate biopsy cores positive, $\leq 50\%$ cancer in each core; PSA density < 0.15 ng/mL/g
Low risk	T1-T2a; Gleason score ≤ 6 ; PSA < 10 ng/mL
Intermediate risk	T2b-T2c or Gleason score 7 or PSA 10-20 ng/mL
High risk	T3a or Gleason score 8-10 or PSA > 20 ng/mL
Very high risk	T3b-T4 or Primary Gleason pattern 5 or > 4 cores with Gleason score 8-10
Risk Group ¹ : Metastatic	
Any T, N1, M0; Any T, Any N, M1	

CASE 1 High Risk: Postpone due to COVID-19; Placed on ADT **62 y AA M- Gleason 4+3 PC. +PNI bilaterally. PSA 28. cT2a.**

- AUA-SS 23, BI 5, IIEF 17
- **IMAGING:** MRI 111 cc, PI-RADS 4 lesion involving bilateral posterior medial apex; BS negative
- **PMH:** BMI 29, HTN
- **PSH:** bladder repair, open right hernia repair with right orchiectomy
- **FH:** None pertinent

KEY: AA, African American; ADT, androgen deprivation therapy; AUA-SS, American Urological Association Symptom Score; BI, bother index; BMI, body mass index; BS, bone scintigraphy; COVID-19, coronavirus 2019; cT2a, clinical stage T2a; FH, family history; IIEF, International Index of Erectile Dysfunction; HTN, hypertension; M, male; PC, prostate cancer; PI-RADS, Prostate Imaging Reporting and Data System; PMH, past medical history; PNI, perineural invasion; PSA, prostate-specific antigen; PSH, past surgical history; y, years.

CASE 2 High Risk: Postponed Due to COVID-19; Placed on ADT **62 y AA M- Gleason 4+3 PC. +PNI bilaterally. PSA 44. cT3a.**

- AUA-SS 7, BI 2, IIEF 6
- **IMAGING:** TRUSS 39 cc. CT, BS negative
- **PMH:** BMI 24, HLD, NIDDM
- **PSH:** Lab umbilical hernia repair
- **FH:** None pertinent

KEY: AA, African American; ADT, androgen deprivation therapy; AUA-SS, American Urological Association Symptom Score; BI, bother index; BMI, body mass index; BS, bone scintigraphy; COVID-19, coronavirus 2019; cT3a, clinical stage T3a; FH, family history; HLD, hyperlipidemia; IIEF, International Index of Erectile Dysfunction; M, man; NIDDM, non-insulin-dependent diabetes mellitus; PC, prostate cancer; PMH, past medical history; PNI, perineural invasion; PSA, prostate-specific antigen; PSH, past surgical history; TRUS, transrectal ultrasonography; y, years.

tate-specific antigen (PSA) measurement higher than 20. We contemplated moving forward with his case but instead decided to postpone surgery and start androgen deprivation therapy (ADT) with leuprolide at a 45-mg 6-month depot dose. This decision was due to several factors, including his very large prostate gland (measuring more than 100 cc), the possibility of a narrow pelvis due to his ethnicity, and prior pelvic surgery. We surmised that his case, as treated at our center, could be more difficult as compared with an average overnight admission for open or robotic radical prostatectomy (RP), with potentially more bleeding and more use of health care resources. Based on the literature about the use of neoadjuvant ADT, we felt that this course of action would have a low probability of harm and would also decrease his prostate size, making future surgery potentially less morbid. Based on work from Gleave et al in a Canadian randomized controlled trial, we will continue the ADT for at least 3 months and reevaluate him for RP at that time.¹¹

Under normal conditions, we generally do not administer neoadjuvant ADT to RP patients because of the lack of a proven survival benefit.^{12,13} However, during COVID-19, we are trying to alleviate harm from delaying surgery, and prior trials did show that taking the time to prescribe hormonal therapy did not lessen survival versus proceeding directly to surgery.

CASE 2. Here, an African American male aged 64 years has high-volume grade group 2 and 3 PC, a PSA of 44, and clinical stage T2a disease. As such, he is classified as high risk. We elected to postpone his surgery in part because he also has uncontrolled diabetes, and we had concern that proceeding to RP during this pandemic could have led to excess hospitalization and use of excess health care resources. We also elected to start neoadjuvant ADT, a more controversial decision in this case because the hormonal therapy could make diabetes control more challenging. In the

TABLE 2. Duke University Triage of Prostate Cancer During COVID-19 Outbreak (Version 1 April 6, 2020)

Priority Level (CMS and ACS)				
		3 (highest priority)	2 (intermediate priority)	1 (low priority)
Prostate	New consults	High risk (Gleason 8+, T3, PSA >20) Bad histology (eg small cell)	Intermediate risk (Gleason 7, T2, PSA 10-20)	Low risk (Gleason 1, T1c, PSA <10)
	Follow-ups	Postop complications RP high risk, <3 m	RP high risk, 3-12m	RP high risk, >1y; RP intermediate or low risk
	Biopsy	High risk	Intermediate risk	Low risk; Active surveillance
	Surgery	High risk and >6-month wait Small cell	High risk and <6-month wait; Intermediate risk and >6-month wait	Intermediate risk and <6-month wait; low risk

KEY: COVID-19, coronavirus disease 2019; PSA, prostate specific antigen; RP, radical prostatectomy

end, however, we felt that the high-volume cancer should be controlled without delay; we also took into consideration that the patient might ultimately favor radiation over surgery. Some experts could argue that we should postpone this case for only 30 days and hold off on use of ADT. However, the current uncertainty of the COVID-19 peak and the potential need to use excess health care resources in the perioperative period for this patient prompted us to make the case management decisions described above.

CASE 3. This case involves a very healthy African American man, aged 61 years, with Gleason 4+4=8 in only 2 cores but with a PSA higher than 30. Because he was in excellent health and had high-risk disease, he was deemed appropriate for surgery based on day-to-day conditions at our center. He was negative for COVID-19 based on a test performed 72 hours before surgery at our drive-through testing site. (As of early April 2020, our health system requires preoperative COVID-19 testing for all scheduled surgery patients, performed at our center; we currently do not allow testing outside of our own health system.)

To not overutilize health care resources, we performed only a unilateral right-side

CASE 3 High Risk: Recommended to Proceed to RP

61 y AA M- Gleason 4+4 PC. +PNI. PSA 36. cT1c.

- AUA-SS 3, BI 1, IIEF 20
- **IMAGING:** TRUS 31 cc. CT, BS negative
- **PMH:** BMI 29, kidney cancer, NIDDM
- **PSH:** Right nephrectomy
- **FH:** None pertinent

KEY: AA, African American; AUA-SS, American Urological Association Symptom Score; BI, bother index; BMI, body mass index; BS, bone scintigraphy; COVID-19, coronavirus 2019; cT1c, clinical stage T1c; FH, family history; Hx, history; IIEF, International Index of Erectile Dysfunction; M, male; PC, prostate cancer; PMH, past medical history; PNI, perineural invasion; PSA, prostate-specific antigen; PSH, past surgical history; RP, radical prostatectomy; TRUS, transrectal ultrasonography; y, years.

CASE 4 High Risk: Recommended to Proceed to RP

58 y Caucasian M- Gleason 4+4 PC. PSA 22. cT2c.

- AUA-SS 2, BI 1, IIEF 20
- **IMAGING:** TRUS 70 cc. MRI with PI-RADS 5 at right apex. BS negative.
- **PMH:** BMI 27, nephrolithiasis
- **PSH:** None
- **FH:** Bladder cancer (father)

KEY: AUA-SS, American Urological Association Symptom Score; BI, bother index; BMI, body mass index; BS, bone scintigraphy; cT2c, clinical stage T2c; FH, family history; IIEF, International Index of Erectile Dysfunction; M, male; PC, prostate cancer; PMH, past medical history; PI-RADS, Prostate Imaging Reporting and Data System; PSA, prostate-specific antigen; PSH, past surgical history; RP, radical prostatectomy; TRUS, transrectal ultrasonography; y, years.

PERSPECTIVE BY

E. David Crawford, MD**Challenges of Surgical and Radiotherapy Triage**

Judd Moul, MD, FACS harnesses his prior military experience and uses this knowledge in concert with his colleagues at Duke to provide risk stratification in order to triage the care of men with prostate cancer during this current pandemic. As he points out the treatment of all stages of prostate cancer, particularly early prostate cancer remains controversial. The current challenges and limitations of care posed by the COVID-19 pandemic has further highlighted these controversies.

There are a number of different stratifications for prostate cancer including those from the American Urological Association, NCCN, ASCO and American joint committee for cancer. Moul and colleagues developed a triage table as described in this manuscript and then

prioritized based on reducing the risk to patients and caregivers. They then focus on the process of triaging men with localized prostate cancer and provide specific case examples which are thoughtful and minimize the risk to all concerned. While the main focus of this presentation is on surgical management, radiation oncologists who also treat men with localized prostate cancer have a similar challenges. There is no question that they want to continue to provide high-level care and at the same time protect patients and healthcare providers. We are seeing a resurgence of interest higher dose shorter course methodologies such as tomotherapy and CyberKnife. In addition there is currently a tremendous interest in using brachytherapy because of recent publications

substantiated the survival benefits and minimal side effects. Couple this with the ease of delivery and limited exposure to a healthcare workers.^{1,2}

I applaud Moul and his associates for educating us in this very difficult time.

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Crawford is Chairman, Prostate Conditions Education Council; Editor in Chief, Grand Rounds in Urology; and Professor of Urology, University of California San Diego, La Jolla, California.

pelvic lymphadenectomy in association with the radical retropubic prostatectomy; we did not perform an extended lymph node dissection. Our reasoning was that we did not want to risk a lymphocele that would possibly increase utilization of health care resources during our upcoming COVID-19 peak.

Our enhanced recovery after surgery protocol for RP dictates the use of bupivacaine liposome injectable suspension (Exparel 266 mg/20 cc mixed with 20 cc 0.25% standard bupivacaine) in the incision on closure and use of enoxaparin sodium (Lovenox 0.4 ml/40 mg subcutaneous, daily). The upivacaine increases the probability of discharge from the hospital on postoperative day 1, which is always

desirable but is even more so during the COVID-19 pandemic. The enoxaparin is for deep venous thrombosis prophylaxis, but this might also increase the risk of a lymphocele. This was our reasoning for the unilateral standard lymphadenectomy.

CASE 4. This healthy 58-year-old healthy Caucasian man with lower volume Gleason 8 prostate cancer but with a PSA level of over 20. This gentleman is a commercial pilot and was originally contacted and asked to postpone his surgery and initiate short term ADT (this was very early in our hospital preparedness where any surgery was being subject to postpone-ment). The patient was, understandably, not keen for preoperative ADT and was

concerned that use of ADT may lengthen his return to flight status with the Federal Aviation Administration (FAA). Ultimately, he was deemed high risk and was approved to move forward with radical retropubic prostatectomy and unilateral pelvic lymphadenectomy after negative COVID-19 testing.

CASE 5. This Caucasian male business executive, aged 75 years, was recommended by his community urologist to undergo external beam radiotherapy and neoadjuvant hormonal therapy due to his age and morbid obesity (body mass index = 38). However, the patient was keen to have surgery instead and presented to our center for a second opinion soon before

COVID-19 arrived in our area. He was scheduled for radical retropubic prostatectomy but was very strongly encouraged to see a radiation oncologist for proper multidisciplinary education and counseling. When the COVID-19 crisis emerged, he and his local urologist were contacted by our team with our recommendation that he start leuprolide neoadjuvant hormonal therapy and then strongly consider external beam radiotherapy and not proceed to RP. The patient refused and is currently on the surgical schedule for fall 2020. This case illustrates that, even in a pandemic, we cannot force therapy decisions on patients. As of now (early April 2020), it remains unclear what management this patient will ultimately elect.

CASE 6. Prior to the pandemic, this individual with male hypogonadism and obesity, aged 62 years, was diagnosed with low-risk localized prostate cancer. He initially elected RP because he has low testosterone which, arguably, might lessen the long-term success of active surveillance and increase his risk for recurrence and unfavorable pathology. Under normal circumstances, low-risk men are asked to choose between active treatment and active surveillance, and this patient chose surgery. When COVID-19 worsened in our region and our COVID-19 surgical guidelines were announced, we contacted him to say that his surgery could be postponed up to 6 months. At that point, he agreed to active surveillance. He will have a follow-up PSA measurement and prostate examination 6 months after his biopsy date, and he may ultimately have a prostate MRI and/or repeat prostate biopsy before being reconsidered for surgery. Low-risk men, most of whom should probably be placed on active surveillance anyway, are “low-hanging fruit” during COVID-19, those in whom surgery can be postponed or avoided to help prevent overburdening the health care system during the surge.

CASE 7. A healthy Caucasian man, aged

CASE 5 High Risk: Surgery postponed; Recommended to Start DT and Consider EBRT (not RP)

75 y Caucasian M- Gleason 4+4 PC. +PNI. PSA 14. cT1c.

- AUA-SS 10, BI 0, IIEF 17
- **IMAGING:** DRE 30 cc. CT, BS negative
- **PMH:** BMI 38, HTN, HLD, ex-smoker
- **PSH:** None
- **FH:** None pertinent

KEY: ADT, androgen deprivation therapy; AUA-SS, American Urological Association Symptom Score; BI, bother index; BMI, body mass index; BS, bone scintigraphy; cT1c, clinical stage T1c; DRE, xxx; EBRT, external beam radiation therapy; FH, family history; HLD, hyperlipidemia; HTN, hypertension; IIEF, International Index of Erectile Dysfunction; M, male; PC, prostate cancer; PMH, past medical history; PNI, perineural invasion; PSA, prostate-specific antigen; PSH, past surgical history; RP, radical prostatectomy; y, years.

CASE 6 Low Risk: Postpone RP up to 6 months or Consider Active Surveillance

62 y Caucasian M- Gleason 3+3 PC. PSA 2. cT2a.

- AUA-SS 11, BI 4, IIEF 23
- **IMAGING:** TRUS 44 cc
- **PMH:** BMI 35, GERD, hypogonadism (on T)
- **PSH:** Lap right orchiectomy and hernia repair, cholecystectomy
- **FH:** None pertinent

KEY: AUA-SS, American Urological Association Symptom Score; BI, bother index; BMI, body mass index; cT2a, clinical stage T2a; FH, family history; GERD, gastroesophageal reflux disease; IIEF, International Index of Erectile Dysfunction; lap, laparoscopic; M, male; PC, prostate cancer; PMH, past medical history; PSA, prostate-specific antigen; PSH, past surgical history; RP, radical prostatectomy; TRUS, transrectal ultrasonography; y, years.

CASE 7 Intermediate Risk: Postpone RP up to 3 months

70 y Caucasian M- Gleason 3+4 PC. PSA 7.5. cT1c.

- AUA-SS 3, BI 1, IIEF 5
- **IMAGING:** TRUS 19 cc. CT, BS negative
- **PMH:** BMI 25, NIDDM, HLD, hypothyroidism, OA
- **PSH:** None
- **FH:** None pertinent

KEY: AUA-SS, American Urological Association Symptom Score; BI, bother index; BMI, body mass index; BS, bone scintigraphy; cT1c, clinical stage T1c; FH, family history; HLD, hyperlipidemia; IIEF, International Index of Erectile Dysfunction; M, male; NIDDM, non-insulin-dependent diabetes mellitus; OA, osteoarthritis; PC, prostate cancer; PMH, past medical history; PSA, prostate-specific antigen; PSH, past surgical history; RP, radical prostatectomy; TRUS, transrectal ultrasonography; y, years.

70 years, presented to our center with Gleason 8 in 4 of 12 cores, a PSA of 7.5, and clinical stage T1c disease. He had been scheduled for RP, with a surgery date several weeks out. This date proved to coincide with the start of the COVID-19 pandemic in our area. At the time of the COVID-19 surgery postponement process for this patient, we realized that a pathology review had not yet been completed in accordance with our policy of having outside pathology slides reviewed at our center for accuracy. Interestingly, after the pathology review, the patient was downgraded to Gleason 3 + 4 = 7 in the 4 involved cores, reclassifying his risk group from high to intermediate; surgery was postponed for up to 3 months. Before the pathology review, the patient had been offered neoadjuvant ADT but declined. In retrospect, in light of the subsequent pathology downgrading, this was a wise move.

Summary

The COVID-19 pandemic scenario continues to change and vary throughout the United States and the world. Our process at Duke will undoubtedly evolve. Nevertheless, we wanted to share our initial experience with COVID-19 surgical triage with some specific examples.

Overall, healthy men with high- and very high-risk localized prostate cancer are currently proceeding to surgery, while low- and intermediate-risk men are being postponed. We have also elected to employ neoadjuvant ADT selectively in less-healthy men who may require more health care resources at a critical time when our health system is at or nearing peak COVID-19 capacity.

FINANCIAL DISCLOSURE: The authors have

The COVID-19 pandemic continues to change and the crisis varies throughout the US and the world. Our process will undoubtedly evolve.

no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

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Mouli is urologic oncologist at the Duke Cancer Institute in Durham, NC.

Chang is a resident urologist at the Duke Cancer Institute and Duke University Medical Center in Durham, NC.

Inman is a urologist and surgical oncologist at the Duke Cancer Institute in Durham, NC.

PERSPECTIVE BY

Eric A. Klein, MD**A Rational Approach to Managing Prostate Cancer in an Irrational Time**

The authors have nicely outlined the challenges that virtually all developed countries are facing during the onslaught of SARS-CoV-2. Most states have enacted temporary bans against all but essential surgeries; they have left local physicians to use their judgment to determine the meaning of “essential,” considering individual threats to life, limb, and vital organ systems and progression in stage or metastasis for cancers, while ensuring the safety of patients and caregivers with respect to maintaining an adequate supply of intensive care unit (ICU) beds, ventilators, and personal protective equipment (PPE). Thus, in large measure, the definition of “essential” depends on local conditions: the incidence of infection, the capacity of the regional hospital system, the number of affected caregivers who may be temporarily out of the workforce, the daily burn rate of PPE use, and so on.

For the management of cancer in general, there are other factors to consider in deciding what is “essential,” including increased potential exposure to coronavirus infection in immunocompromised patients needing to go to a treatment center for chemo- or immunotherapy; patient anxiety related to delaying initiation of or ongoing therapy; and concerns about whether delaying therapy could influence the chance for cure.

Fortunately for patients with prostate cancer, a substantial amount of evidence from vast

experience with active surveillance indicates that those with very low-, low-, and intermediate-risk disease do not compromise their chance for cure by delaying curative treatment.¹ Although fewer data are available for those with high-risk (HR) and very high-risk (VHR) disease, in a recently published retrospective pooled analysis from 3 high-volume tertiary centers, we found no difference in rates of biochemical failure, metastasis, prostate-cancer-specific mortality, or all-cause mortality in those with HR or VHR disease treated <8, within 8-12, or >12 weeks after diagnosis.² In our observation and experience, a delay of up to 90 days for locally advanced or high-grade prostate cancer does not seem to have an adverse effect on short-term outcomes, although 1 prior report found that for HR disease, biochemical failure rates were worse for those with a delay of >90 days.³ An alternative strategy is the use of androgen deprivation therapy as a delaying tactic, which presumably can delay the risk of tumor progression indefinitely. This is also likely safe, at least for a few months, but it's not clear if the extra cost and toxicity are worth the presumed safety margin, and there is a risk that use for as little as 24 weeks can induce genomic changes characteristic of metastatic castrate-resistant disease, which could compromise cure.⁴

At Cleveland Clinic, we have considered cancer-related and

non-cancer-related factors and devised a tiered approach to performing urological surgery and office procedures (**Figure**).⁵ At the initial stage of the crisis, when the magnitude of the number and severity of SARS-CoV-2 cases was unknown, we worked with institutional leadership and the decision was made to put all tier 3 and 4 surgeries on hold. As events evolved, and it became clear that early stay-at-home orders and social distancing were effective in flattening the incidence curve in northeast Ohio and that our hospital and caregiver resources would not be overwhelmed with cases, we began (starting the week of April 20) doing tier 3 cases on a limited basis as our system ramps up again, based on availability of operating rooms and nursing and anesthesia personnel, and on patient preference. We have followed a similar process for office-based and nursing procedures. System-wide real-time information with daily monitoring of resources has allowed us to do this safely: The creation of dashboards to monitor system-wide hospitalization and ICU usage for COVID-19-related and non-COVID-19-related care and PPE usage/stock availability, along with our tiered approach to procedures, allows for a rational, measured, and real-time approach that can be dialed back or ramped up as dictated by events related to SARS-CoV-2.

Perspective continued on page 164

Klein is chairman at Glickman Urological & Kidney Institute Cleveland Clinic

Eric A. Klein, MD

PERSPECTIVE CONTINUED FROM PAGE 163

TABLE. Cleveland Clinic Department of Urology: Recommended Surgical Priority Tiers (COVID-19)

0 Emergency	1	2	3	4 nonessential
Obstructed kidney/infection	Cystectomy – high risk cancer	CAP GG3-5 or GG2 with more than 2 cores or tumor length > 5 mm or Gleason 3+3 w >50% core positivity in number of cores or any PSA >10	Cystectomy – not high risk	CAP GG1 or GG2 with 2 or fewer cores of max length <5 mm
Urologic abscess/wound washout	Nephrectomy – IVC thrombus	RPLND	Partial Nx >4 cm	Partial Nx SRM
Torsion	TURBT high risk	Radical Nx	TURBT low risk	Adrenalectomy (CA not suspected) and asymptomatic
Clot retention	Stage 2 sacral neuromodulation	Adrenalectomy (cancer suspected) or symptomatic	Neurogenic cysto/Botox	Asymptomatic non-obstructing renal stone
Hemorrhage	Orchiectomy – cancer	Urogenital/colovesical fistulas	Ureterscopy for presumed low risk upper tract UC	Slings
Pregnant with obstruction	Nephroureterectomy	Adult ureteral reimplant or pyeloplasty	Stone with stent/neph tube or symptomatic	Pelvic organ prolapse
Cadaveric renal tx	Penile cancer	BPH requiring indwelling catheter	Urethral diverticula	Sacral neuromodulation stage 1 or total
Urinary retention unable to place catheter	Ureteral stone	Stent change	Mesh removal/ sling incision	Artificial urethral sphincter
Penile fracture	Urethral Stricture with imminent obstruction		Ureterolysis	Penile prosthesis
Infected prosthesis/device	Recto/pubo urethral fistula		SNM IPG change	Infertility/non cancer scrotal surgery
Priapism	Ureterscopy for suspected high risk upper tract UC			Pediatric: reimplant, penile and benign testicular cases
				Living donor renal tx
				Vasectomy/circumcision
				BPH on self cath or safely voiding
				Urethral stricture no imminent obstruction
				Buried penis
				Peyronies

Source: Recommendations for tiered stratification of urologic surgery urgency in the COVID-19 era. *J Urol*. Published online April, 21, 2020. **KEY:** IVC, inferior vena cava; tx, transplant

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MEET OUR EXPERT

Gandara is the director of the thoracic oncology program and senior advisor to the director of the University of California Davis Comprehensive Cancer Center.

Forging Ahead in a Time of Crisis

Continuing the fight against lung cancer in the COVID-19 era

The coronavirus disease 2019 (COVID-19) pandemic has greatly impacted all areas of the medical world. While nurses and physicians on the front lines search for answers on how to treat this novel disease, oncologists and cancer care providers around the world search for answers of their own. Should treatments be continued or halted? Should surgeries be postponed? And how can the same standard of care in be delivered in a socially distanced world?

ONCOLOGY® recently sat down with David R. Gandara, MD, director of the thoracic oncology program and senior advisor to the director of the University of California (UC) Davis Comprehensive Cancer Center, to discuss the impact of the pandemic on the current management and treatment of patients with lung cancer, as well as the future of education and patient care in a post-COVID-19 world. While the crisis may have “dramatically changed how we practice,” Gandara says, “it hasn’t altered the basic premise that lung cancer is now a highly treatable disease.”

Q: COVID-19, a respiratory pandemic, is obviously the biggest news in the world right now. How has that changed the way you practice as a lung

cancer physician and the way you research?

GANDARA: Well, what has happened has dramatically changed how we practice, how we interact with lung cancer patients. But it hasn’t altered the basic premise that lung cancer is now a highly treatable disease, that it is both genomically and immunologically complex, and that we want to offer our patients their best therapeutic options.

That being said, right now at UC Davis and most other community and academic cancer centers around the United States—including the National Cancer Institute, which has allowed this for patients on clinical trials—we have converted all of our routine follow-up to virtual or video virtual visits. I just had my first series of those in the past 2 weeks. I can visually see the patient and they can see me. I can see their scans and their laboratory results and talk and interact with them. This is now a forum for seeing patients that is accepted by insurers, including CMS for Medicare. Although virtual visits don’t have, of course, the ability to do a physical exam on the patient, for routine care of cancer patients, even those receiving cancer chemotherapy, it’s a way to have those interval or interim visits without exposing them to the risk of coming to our

office and possible exposure to COVID-19.

At UC Davis Cancer Center, everyone entering the door has their temperature taken and [is administered] questions regarding possible symptoms that could be associated with COVID-19. If they have either an elevated temperature or symptoms, they don’t come into the cancer center and are referred instead to a COVID-19 center at UC Davis. There, we would engage them and work them up for COVID-19, depending on what the situation was.

So, this is a huge change. Of course, a lot of our cancer drugs now are oral, so the patient doesn’t have to come into the infusion center. But a lot of them, including the checkpoint immunotherapeutics, are intravenous. In that case, the patient comes into the cancer center after they’ve been checked, and they get their cancer treatment through the infusion center in a very safe manner—as safe as possible. But if they didn’t need to see the physician in a separate visit, then they don’t face-to-face. That’s done virtually.

Q: Obviously, patients with lung cancer are a uniquely vulnerable patient population. Have you had to change treatment plans at all in light of the virus?

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How will all the other needed care be provided during the pandemic?

Timothy Hoff, PhD

As our health care system and others around the world gear up to deal with the largest public health crisis of the past 100 years, an important question to ask is: How will all the other needed health care delivery occur during the pandemic?

This needed healthcare includes elective surgeries that may still be important to help an individual function or manage other healthcare conditions; primary care services like chronic disease management that patients must get to avoid having their conditions worsen or cause other health problems; and preventive care that may help reduce the possibility of getting COVID-19 or mitigate its severity once contracted.

Given the healthcare system's current inability to properly address the pandemic, it is fair to wonder how much other important healthcare will be neglected during the outbreak, and what additional negative impact this will have on the health status of Americans.

Already, my family and I have received emails from our providers telling us that their offices are closing to all but emergency care, for time periods that may last a while. We have been told by a couple providers that we may be able to conduct telehealth visits with them for certain issues. It is difficult to understand how telehealth

can be used quickly or in a high-quality manner for services like orthopedics, cardiology, or dermatology; or any care that requires lab work, imaging, procedures, or an actual physical examination.

Regarding virtual care, the reality is we are simply nowhere close to having the technology or expertise to do it right, regardless of payment being available. In addition, some health care professional still has to be involved in telehealth provision,

There is no doubt that our health system must gear up first and foremost for the crisis at hand. The need to keep people at home and away from public spaces is a short-term imperative to blunting COVID-19's spread.

so in a system with no capacity, it is hard to imagine telehealth making much short-term difference.

There is no doubt that our health system must gear up first and foremost for the crisis at hand. The need to keep people at home and away from public spaces is a short-term imperative to blunting COVID-19's spread. But over the longer term, if we

make patients significantly delay or cancel important care, they require to stay healthy and function independently, or provide it in a low-quality way, we risk making the effects of this pandemic much worse.

Blood sugars and high blood pressure that cannot be monitored or controlled properly; unperformed surgical procedures that would enhance patients' ability to care for themselves or others; mental health issues that will impact people's ability to think and behave proactively with respect to staying healthy, and being able to work and earn a paycheck—left neglected, these realities will amplify how COVID-19 affects local populations and leave many more Americans in worse health once this pandemic is over.

There are no easy solutions to these problems. Nations have spent years underinvesting in primary care systems almost everywhere—Italy, the United Kingdom, and the United States, to name a few. Here in the US we have encouraged an expensive, fragmented, and mostly hospital-based system of specialty care.

And because hospitals are having to care for the sickest COVID-19 patients, it is difficult to get other needed forms of care out to the places where many live and work. Many hospitals have to almost shut

down and focus solely on patients with COVID-19, both because of the highly communicable aspects of the illness and their lack of capacity to do anything else while dealing with patient demand from the illness.

How soon they are able to go back to business as usual once the current crisis ends is an open question. It may not be easy for them.

Even when we have enough COVID-19 tests available, we will have difficulty getting the tests out to individual patients, in part because there are many communities without enough care providers, and because many medical practices are closing for extended periods of time.

What is left of the primary care system in the US will need to step up in trying to handle a good chunk of this other needed care delivery once the current crisis eases.

Bringing physicians and nurses out of retirement in local communities to work in primary care offices and urgent care centers is one needed step.

Moving whatever basic primary care we can to the virtual space, whether via phone or computer, is a second step. Making some primary and urgent care offices in local communities remain open 24 hours a day, with certain hours allocated for specific types of care delivery, and staffed accordingly, is a third step. Redesigning workflows in these offices to improve care efficiency is a fourth step. Providing added financial support to these offices, in the form of enhanced reimbursement, underlies it all. These steps may require many months to be implemented. When the time is right, we have to try.

The COVID-19 pandemic is like nothing we have seen in our lifetimes. We must do

everything possible to lessen its potential destructiveness. That includes making sure we do not forget about the other important care patients require to stay healthy and function. If we do, we risk emerging from this crisis with a population and workforce much less able to contribute in making our society and economy strong again.

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.

Hoff is professor of management, healthcare systems, and health policy at Northeastern University in

Boston; a visiting associate fellow at the University of Oxford, and author of *Next in Line: Lowered Care Expectations in the Age of Retail- and Value-Based Health*.

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KEY QUESTION

In the long term, do you see expect to see lasting changes to treatment or practice management based on what we're experiencing right now with COVID-19?

GANDARA: I do. I actually hope some long-term changes will occur in both cancer care and education, including continuing medical education (CME), because of our ability to use video, virtual visits for cancer patients, and also WebEx and other forms of virtual CME. One big hurdle up until now was whether a video visit for a patient with cancer could be considered a legal document as their face-to-face visit would. That hurdle has now been passed; [for] every insurer, these video visits are considered equivalent to face-to-face, and they are billable. In other words, an oncologist can see a patient virtually and still be reimbursed for the time and effort that they put in.

Similarly, I think this experience with COVID-19 will change the face of CME in the future. American Association for Cancer Research this year, American Society of Clinical Oncology (ASCO) this year, are going to be entirely virtual, and yet the same content is being presented. The same sort of discussants will be discussing the material, just in a different format. Attendees, virtual attendees, will be able to select what sessions they tune into and which they don't. I think this will change the face of CME. I think probably our own meetings, going forward, once this COVID-19 situation is over—and I'm hoping we have a good outcome within a few months—will likely have both virtual and face-to-face components.

GANDARA: We're dealing with a population who has a cancer which either started or is still present in their lung. Many of them, if they were smokers, have chronic obstructive pulmonary disease. They are older patients in general, although, of course, as everyone knows, we do have a cohort of patients who are young, never smokers, women. But most are older and previous smokers, so they are

at higher risk. There is a considerable debate, not only in lung cancer, but around the United States for all types of cancers, about whether we should alter our therapy, whether we should withhold chemotherapy or immunotherapy, or whether should we give it on schedule.

I did a social media poll last week and asked practicing oncologists whether they would arbitrarily hold either

chemotherapy or immunotherapy or neither or both in a lung cancer patient. Of 357 people who responded, almost 70% said no, they would treat patients on schedule, assuming that they don't have active COVID-19 infection. A small percentage, about 10%, said they would hold chemotherapy, 5% said they would hold immunotherapy, and about 5% said they would hold both. But the great majority would treat patients on schedule. In this social media poll, I also had a number of patients who independently responded with their views, and every single one of them said, in effect, "I know that COVID-19 may kill me, but lung cancer untreated will kill me, so please treat us like you are treating us every week." So, although there is considerable debate about this, and some institutions are holding therapy, my own belief, and that of our institution, is that we should treat patients if we can do it safely.

Q: It seems like this is where medicine was headed in the first place, but the COVID-19 experience has supercharged the move toward more virtual medicine and doing more things online rather than face-to-face.

GANDARA: Yes, I think we were moving in this direction already, and this accelerated the pace. Obviously, we have regularly scheduled WebEx CME, grand rounds, and a variety of other [presentations] that we do, and there is good uptake by attendees. It has very often been difficult for physicians,

except on an occasional basis, to take off from a practice or from their academic research to attend a meeting face-to-face. But attending virtually is easier, and also, if there is enduring material from it, then that physician could, for example, view it at night, after they have dinner and have some free time. So, yes, we're moving more quickly in that direction.

Q: At the upcoming International Lung Cancer Congress® (ILCC), what events and discussions are you most excited to attend?

GANDARA: I think I should start with saying that our ILCC is a unique CME experience, because it's purposely placed about 6 weeks after the annual ASCO meeting. Faculty and attendees will have heard the news and the advances that are presented there, and then at ILCC, they'll be able to listen to expert faculty and interact with them about the new information. I've always referred to our meeting as a think tank, because it's much more like that than like a regular meeting. It has not only classic lectures, but it has a number of panel discussions with experts, multidisciplinary, including all the disciplines that are involved in lung cancer or thoracic malignancy care. The new and important things this year—we're still early in the year—or I would maybe say for 2019-2020 so far, are new drug approvals. We have quite a variety of those. We [also] have new guidelines about how to use liquid biopsy. [Plus,] we

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Q&A: Forging Ahead in a Time of Crisis

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have increasing information about lung cancer screening; we believe lives have been saved because we're finding patients with earlier-stage disease. So, a whole variety of things are new, that are educational opportunities, that will be presented at ILCC 2020.

Q: Are you especially looking forward to certain sessions?

GANDARA: At ILCC each year, we have a session on new drugs that are coming out and new classes of drugs that are available. That will be a highlight of this meeting. In particular, although new findings have occurred in several drug classes, one that is brand new is the development of drugs for *KRAS* G12C mutation. *KRAS* has been an undruggable target—I've always said this myself—because of the difficulty in developing a drug that could inhibit that mutation. But now we [do] have drugs, and 5 of them are in development and we'll be hearing about them at ILCC. That will clearly be a highlight.

Q: How does the virtual nature of the meeting change things?

GANDARA: It's not the same as a face-to-face meeting, obviously, but an advantage is that you can incorporate attendees who are not able to physically travel to Huntington Beach for ILCC. You're also able to broaden the scope of the faculty, because some faculty, for instance, will be coming from Europe

or Asia, and as COVID-19 evolves, they and we may still have travel restrictions. So even if there's a face-to-face component, having a virtual component will be important. We also will be able to have enduring material, which is developed in a more comprehensive way because the entire meeting, of course, will be audio- and videotaped. So not only attendees, but sponsors as well, will be able to have this information available for educational purposes of their own.

Q: Jumping to a broader clinical question, we've seen so many advances in lung cancer over the past 10 years. What major trends or developments do you anticipate seeing in the near future?

GANDARA: So many rapid advances have occurred in the therapeutic options for lung cancer, and also in diagnostics, that it's hard to believe that they could continue to come at such a fast rate over the next year or two. But already we have a number of challenges and opportunities which have [evolved from] these advances. I'll just give you 1 example: We now have 8 oncogene-driven lung cancers, non-small cell lung cancers (NSCLCs), that are recognized in guidelines. You should test a patient's tumor for these oncogenes before offering therapy, and we soon will have number 9 because I'm sure the *KRAS* G12C will soon be FDA approved. With

that, it's even more important for practicing oncologists to realize that even a patient who is a previous smoker might have 1 of these 8 or 9 oncogenes. [In fact,] *KRAS* G12C is associated with smoking, and the best treatment for [patients with a *KRAS* G12C mutation] is a targeted therapy rather than chemotherapy or immunotherapy or even a combination of the 2.

Another example, related to diagnostics and molecular testing: We already know that patients with *EGFR*-mutated lung cancer, patients with *ALK*-translocated lung cancer, don't fare well with checkpoint immunotherapy. They do much better when treated with targeted drugs. So how does a practicing oncologist then test for all of these oncogenes in a time-efficient manner, with good sensitivity, good specificity, and have a turnaround time of 1 to 2 weeks, so that they can treat the patient with a personalized or precision medicine approach rather than empiric? We now have that ability, and liquid biopsy is bringing us that, so that it can all be done simultaneously, rather than testing for one gene right after the other, sequentially, which takes a long time, and if it's a tissue, would use up all the tissue. That's another example of where we have opportunities to move the field forward.

Q: Have you noticed any sort of overarching theme or clinical development, especially one that will be reflected

at ILCC?

GANDARA: The theme of personalized medicine, of course, has been present for several years, and it continues to grow. I'll give you a perspective on this. With the recognition that in advanced-stage NSCLC, checkpoint immunotherapy plus platinum-based chemotherapy is very effective, there has been some divergence of opinion about what that means. Some people say, "This makes things simpler, because I can just treat everybody who comes in the door with advanced NSCLC with this regimen." But many other people, including myself, say, "No, this actually makes things more complex, because even with the efficacy of the combination of checkpoint immunotherapy and platinum-based chemotherapy, we need to make sure the patient who comes in doesn't have one of the oncogenes and would [in fact] be better served by a targeted therapy."

So, at ILCC this year, we will continue to define that personalized medicine approach. One component of this is a special part of the meeting, a molecular tumor board, with case presentations, and the audience is asked, with audience-response devices, "What would you do in this case? Would you empirically treat the patient? Would you wait until the testing comes back?" [Another component] of the meeting is the Addario Lectureship, named after Bonnie Addario from the Addario Lung Cancer Foundation, which has a precision medicine team. Each year, a world-recognized lung cancer oncologist

is chosen for that award. Last year, the awardee was Solange Peters from Switzerland, and she is the president-elect for the European Society for Medical Oncology. We have already made our selection for this year, which would be July 2020 when ILCC occurs, but of course I cannot tell you who the awardee is yet because it is secret until close to the meeting. But I will tell you that as part of this award, the awardee is featured on a big billboard at Times Square in New York City. Their picture is there for an entire day, the same day as the presentation. So, assuming we're through COVID-19 by the end of July, all of this will happen in real time.

Q: Can you discuss some study results that have been published in the past year or so that might be considered transformative or practice-changing?

GANDARA: I think one [transformation] would be in regard to RET fusions. We have had some nonspecific drugs—and when I say nonspecific, they're multitargeted—which had activity against RET before. But now we have multiple drugs which are either just approved or have breakthrough designation for RET; these are much more targeted against the gene and much more active. One of those drugs is called LOXO 292, and the response rate in patients with these fusions is 75% or above. That sort of thing is happening in many areas of lung cancer oncology.

Another example would be in extensive-stage small cell

lung cancer (SCLC), where we literally have had no major advance in more than 20 years. Platinum chemotherapy, at least in the United States, remains the standard of care. Now, that being said, in this past year we have seen 2 new regimens based on adding a checkpoint inhibitor to that same platinum-etoposide chemotherapy base, and in two phase 3 studies, that combination regimen showed superior response and progression-free survival, and also overall survival was better with the combination compared with the platinum chemotherapy alone. So now 2 drugs—2 checkpoint inhibitors, atezolizumab and durvalumab—are approved for extensive-stage SCLC.

These advances are not just in one area or the other: They're in multiple areas. Again, what that means is that a practicing oncologist has to stay on top of the field, [which can be] increasingly difficult, and the best way to do that is by CME such as we're providing in our meeting.

Q: Looking forward, what other studies do you anticipate coming out in the next year or so?

GANDARA: One opportunity that comes up is that if a checkpoint inhibitor plus platinum chemotherapy is more effective than chemotherapy alone in extensive SCLC, [can we see what happens] if we move it to the one-third of patients who have limited-stage SCLC? Here, we know already we can cure a percentage, but it's probably no better than 25%. Could the addition of

checkpoint immunotherapy actually increase the cure rate in limited-stage disease?

Moving back to the oncogene sphere, another opportunity would be in an EGFR tyrosine kinase inhibitor (TKI)-resistant lung cancer, or even in initial therapy where we have 5 drugs—all very good drugs, TKIs—to treat *EGFR*-mutated lung cancer. But, invariably, even with what could be considered the best of these drugs, osimertinib (Tagrisso), acquired resistance occurs. So, a multitude of trials are ongoing, to try to see if we can enhance the activity of these already very good TKIs in the management of *EGFR*-mutated lung cancer. Some are combinations of TKIs, and some are combinations of a drug like osimertinib with an EGFR monoclonal antibody such as necitumumab (Portrazza). Some of these are adding chemotherapy, platinum chemotherapy, to the TKI, and others are adding antiangiogenic agents. Not all of these will be superior, and some will also be associated with more toxicity. So, we'll have to look at the risk and benefit that come out of these trials. But these trials are clearly important to do, and we're looking forward to the results.

Q: Let's discuss your research a bit: You've been very involved with the Lung-MAP protocol, correct?

GANDARA: Lung-MAP is a huge, one-of-a-kind undertaking. It is the only master protocol which has regulatory intent in all the substudies. It is also the

only master protocol which is a public-private partnership among the National Cancer Institute with its cooperative groups, the Foundation of the National Institutes of Health (NIH), the Friends of Cancer Research, and now more than 15 pharmaceutical companies who have partnered to develop their drugs within this paradigm.

The other thing that's unique about it is that we have next-generation sequencing as the foundation for determining whether oncogenes are present or not. That partnership is with Foundation Medicine. We have enrolled more than 2000 patients to date, and we have completed about 10 or 12 substudies so far. So, this is meant to be self-sustaining. We continually have new studies opening and other studies closing. It's a new way of developing drugs for lung cancer, hopefully ruling out drugs or drug combinations that are not active and doing it very promptly. On the other hand, we are able to screen large numbers of patients—we're screening 1500 patients per year with lung cancer—so we can test drugs even in rare genotypes. That means [a lot] if, say, a gene [is present in] only 4% of all lung cancers, and there's a good new drug that we think will work in it. Unless you have a broad-based screening trial like this, and you have multiple studies, you can't achieve that goal, because no one wants to screen 100 patients to find only 4 who are eligible for a trial. And, a patient doesn't want to be told, "Oh, you have a rare genotype;

you have only a 1-in-a-100 or 4-in-a-100 chance of having it.” So, Lung-MAP is proving to be very successful, and I think it will continue for the longer-term future.

Q: When you say ‘very successful,’ what do you think are the most noteworthy results to come out of this project?

GANDARA: When Lung-MAP was developed 5 years ago, it was really forward-thinking, I would say. Our goal was [to determine if] we could screen lung cancer patients for a variety of genomic mutations and alterations, in a fast, efficient manner, and then place them on to substudies where they would get a drug against that target—and the answer was yes, we could. Our average turnaround time for the FoundationOne test is 10 days. Clearly, that’s within the window of someone in the community using a test like this to screen their patient, unless, of course, it’s an emergency. We’ve shown that it’s feasible; we can screen, and we can do it in a timely fashion. The other thing is, we’ve already completed a dozen trials. Now, some of these were negative, but these are all drugs and mutations that are FDA approved in other cancers. What we showed in a very timely fashion was that the same mutation in a lung cancer patient wasn’t sensitive to the drug, even if it was, let’s say, in breast cancer or chronic lymphocytic leukemia or another malignancy, where these same drugs and targets led to FDA approvals. So, for all of these reasons, we can say that

■ A 3D rendered illustration of lung cancer.

Lung-MAP has been successful.

It was also successful because we wanted to see if we could we engage all of the cooperative groups under the National Cancer Institute in Lung-MAP. And the answer was yes, with people from all the various groups leading various trials, leading various committees. We also said, Can we engage the community? And the answer again is yes. We have 650 sites throughout the United States. The majority are in the community, and the majority of accrual of patients to the trial has come from the community. So, another success story.

But we’ve had many challenges along the way. We’re writing a book. I’m just kidding. But we’re writing a book called *Lessons Learned*. When you try to put something together like this, it seems, of course, simpler on the surface than it actually is. Over the period of time we’ve been

running Lung-MAP, we found that we had to make multiple adjustments, so we had to be flexible, nimble. For instance, after 1 year of the Lung-MAP, we had the approval of checkpoint immunotherapy in second-line treatment, and that changed everything. But it then gave us more opportunities to develop components of Lung-MAP, to say, “Well, what if a patient doesn’t respond to checkpoint immunotherapy, or what if they respond and then they fail?” So, we have an entire arm of Lung-MAP composed of trials for patients with immunotherapy-refractory disease.

Q: Let’s switch gears and talk a little bit about you and your career. Which of your investigative accomplishments are you most proud of?

GANDARA: Well, I can start by saying that my particular interest has been in drug de-

velopment, where I’ve had grants from the National Cancer Institute for 25 years for early therapeutics. One accomplishment I’m proud of is being a founding co-chair of the National Cancer Institute Investigational Drug Steering Committee, of which I am still a member. In addition, my interest in particular tumor types is lung cancer. I’m very proud to have led the lung cancer committee for the Southwest Oncology Group for 15 years, and in that regard, [to have had] many accomplishments associated with more than 100 clinical trials being accomplished through that group and through our association with the National Cancer Institute during that time.

I’ve also always considered myself to be an educator. So, I’m very proud that our ILCC is now in its 21st year. It is always among the highest-rated cancer conferences in terms of attendee ratings for the

meeting, and that is quite an accomplishment. Additionally, we have a one-of-a-kind association in lung cancer, the International Association for the Study of Lung Cancer, and I am very proud to have not only led its world conference in San Francisco, but also to have served as the president of the organization.

I think, lastly, I've always valued mentorship. When I had mentorship early in my career, that it was incredibly important to me, so I have tried to be a good mentor as well. At this point, I've mentored more than 50 young oncologists as well as PhD students and medical students, and I'm a mentor now to 5 different people on their grant submissions. A very important thing to me is being able to provide my expertise and my experience to help others.

Q: Are you particularly proud of working on specific drugs that have been brought to market?

GANDARA: Well, I think probably the accomplishment I'm most proud of in terms of what I have developed is not a specific drug, but rather a test. A year and a half ago, I published for the first time an assay which could assess tumor mutational burden (TMB) from blood. This was in collaboration with Foundation Medicine and Roche Genentech, where we used a study on which I'm the senior author. The OAK trial, a positive trial for survival of atezolizumab versus docetaxel, is among my major accomplishments.

We went back to that trial

and used blood specimens that had been collected to see if we could duplicate the predictive value that had been seen with tissue analysis of TMB, and, in fact, we could. That diagnostic test has now completed its phase 3 evaluation in a trial called BFAST. We don't know the results yet, but it is a trial where atezolizumab or platinum chemotherapy were the 2 arms, and the patients were selected by blood TMB. So, I would say that is one of my greatest accomplishments, but I don't know if we will have a companion diagnostic yet. It depends on the results of the trial.

Q: You're pretty active on Twitter. How did that come about, and why?

GANDARA: My interest in Twitter comes from 2 areas, I think. One is being an educator: If you've seen my tweets on Twitter, you know most of them are talking about breakthroughs or controversies, where I'm either providing information like the link to a publication, or I'm saying I thought this was quite impressive, what do you think, and engaging not only oncologists who are on Twitter, but patients and patient advocates. There is [also] so much bad information on the internet, I feel like it is part of my moral obligation to do what I can to speak on a factual basis, and to point it out misinformation. Communication with patients and patient advocates has been another aspect of my career that I have concentrated on. Some physicians have the skill to be able to break down complex information regarding ge-

nomics of cancer or treatment and describe it to patients in a way that they can understand. I've always worked on that skill, to the point where now I think I do a good job of it.

I've taken this into many venues. For example, the Addario Lung Cancer Foundation, now known as GO2 after their recent merger, has a monthly session called the Living Room. In their headquarters in the San Francisco Bay area, they have a big room with couches set up like a living room, and once a month they serve dinner and it is filled with patients, patient advocates, their families, and their friends—but it is also webcast live to 140 countries around the world. I have spoken there probably yearly, and among the things I've tried to do is to communicate to patients in ways that they can understand. I use a lot of analogies. For example, when you talk about genetic testing of cancer, and how many mutations there could be and why every lung cancer patient is different, I will hold up my finger and I will say, "You know that your fingerprint is different from essentially everyone else's," and everybody says yes. Then I tell them that when we're talking about this molecular testing, this next-generation sequencing for hundreds of genes, that is the molecular fingerprint of your cancer. Then they say, oh, yeah, that makes total sense now, I understand this. Or I will talk about why a TKI against EGFR mutation works initially, and then it stops and there's drug resistance. I will talk about the driver. I'll say, "Pretend you're

on a bus, and you're driving, and you stop at an intermediate stop and the driver gets off, and the person in the row behind him becomes the new driver. That's what's happening in your cancer. That's acquired resistance. You have a new driver for your cancer, so we have to test and find out what it is and treat it appropriately." So that is another communication skill that I feel is very important, and I try to share it when I can.

Q: I've read that you've always had an interest in writing. It's somewhat unusual to see someone who combines a passion for science with the ability to write. How have you found that you can marry those 2 interests?

GANDARA: I'll give you a little background story here. When I graduated from high school, I said that I wanted to be a writer. I was going to be the next Hemingway. Once I got into college, I said, oh, Journalism 101, this doesn't interest me so much—maybe I should look at something else. So, I decided to go into medicine. But I have always kept my interest in writing, and I think I actually have a fairly good writing skill. So, whereas other people sometimes struggle with putting their clinical studies or their research into manuscripts, I actually love to do it. I edit manuscripts for many, many other people. So, I have been able to blend my writing skills into my medical career. I've published almost 400 peer-reviewed articles and hope to do more. ■

SERIES EDITORS

E. David Crawford, MD

Maria T. Bourlon, MD

Immune-Related Adverse Events Involving Multiple Organ Sites in a Patient Treated With Nivolumab Plus Ipilimumab

Yuly A. Remolina-Bonilla, MD¹; Brenda Jiménez-Franco, MD²; Elaine T. Lam, MD, FACP³; and Maria T. Bourlon, MD, MSc⁴

¹Clinical Researcher, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. Mexico City, Mexico.; ²Internal Medicine Resident, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. Mexico City, Mexico.; ³Associate Professor, Department of Medicine, Division of Medical Oncology. University of Colorado Anschutz Medical Campus. Aurora, Colorado.; ⁴Associate Professor, Hematology and Medical Oncology Department. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. Mexico City, Mexico.

THE CASE

A 56-year-old white man with a 74 pack-year smoking history presented with macroscopic hematuria

and a significant weight loss of 45 pounds in 6 months. His clinical laboratory tests indicated iron deficiency anemia and a computed tomography (CT) scan showed a left kidney tumor, mediastinal lymph nodes, and multiple lung metastases. A percutaneous CT-guided kidney biopsy revealed grade 3 clear cell renal carcinoma based on World Health Organization/International Society of Urologic Pathology classification.

The patient started first-line systemic treatment for intermediate-risk metastatic renal cell carcinoma (mRCC) with combination immunotherapy with nivolumab plus ipilimumab.¹ After 10 days of the first cycle, he presented with a pruritic maculopapular rash covering 20% of his body surface (**Figure 1A**). In consensus with the Dermatology Department, we considered this to be a grade 2 cutaneous immune-related adverse event (irAE) based on the Common Terminology Criteria for Adverse Events (CTCAE).² He received topical steroids and an oral antihistamine for 1 week; however, due to lack of clinical improvement, the patient was reevaluated and clinical laboratory tests were performed. Results showed a creatinine increase of grade 2 per CTCAE (his

FIGURE 1. Rash Before (**A**) and After a Systemic Steroid Course (**B**)

Which of the following are true about irAEs with ICIs?

- A.** irAEs are more common when an ICI combination is given
- B.** The incidence of irAEs at multiple sites is at least 10%
- C.** irAEs usually develop within weeks to 3 months after initiation of ICIs
- D.** irAEs may be associated with better clinical outcomes
- E.** All of the Above

➔ **TURN TO PAGE 172** for the answer and a discussion of this case by experts.

CORRECT ANSWER: E. All of the Above

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baseline creatinine was 1.1 mg/dL, which increased 2.3 times) (**Figure 2**). Nephrology was consulted for work-up of this acute kidney injury. Urinary tract infection and urinary tract obstruction were ruled out and a bland urinary sediment was found. The patient was diagnosed with tubulointerstitial nephritis related to immune checkpoint inhibitors (ICIs).

Our patient had irAEs involving multiple organ sites; therefore, systemic steroids (prednisone 40 mg once daily) were initiated for the grade 2 irAE and ICIs were held. Ten days later, the grade 2 rash resolved (**Figure 1B**), and renal failure improved to grade 1 with decreased creatinine levels. He started a slow steroid taper over 4 weeks.²

Discussion

ICIs are associated with a distinctive class of adverse events (AEs), denominated irAEs. The management of these events remains challenging, and most recommendations are based on expert opinion and guidelines for the management of irAEs from several oncology societies.²⁻⁵

irAEs could be explained by T-cell function disinhibition; however, the exact mechanisms remain unknown. Some

studies suggest that these events are due to a combination of autoreactive T cells, autoantibodies, and cytokine secretion.⁶⁻⁹

The frequency of irAEs varies according to tumor type, disease stage, and agent or agents prescribed. The incidence of irAEs is estimated to be lower with anti-programmed cell death protein 1 (PD-1) or anti-programmed death-ligand 1 (PD-L1) monotherapy (any grade, 58%-85%; grades 3-4, 7%-20%)^{4,10,11} compared with anti-cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) monotherapy (any grade, 60%-85%; grades 3-4, 10%-27%).^{12,13} The highest rates of irAEs have been observed with anti-PD-L1 and anti-CTLA-4 combinations (any grade, 93%-95%; grades 3-, 40%-55%).^{4,14,15} Fatal irAEs are relatively uncommon, with an incidence of 0.3% to 1.3%.^{11,16,17} Therefore, answer A is true.

Currently, ICIs are the preferred first-line therapy for mRCC,¹⁸ either in combination with tyrosine kinase inhibitors^{19,20} or another ICI.^{1,21} The phase 3 CheckMate 214 study evaluated nivolumab plus ipilimumab versus sunitinib in patients with untreated mRCC. Among the 550 patients who received nivolumab plus ipilimumab, 46% experienced grade 3 to 4 AEs, 35%

required high-dose systemic steroids (≥ 40 mg of prednisone per day), and 22% of patients developed treatment-related AEs leading to discontinuation. The most common irAEs were increased liver enzymes (2%-3%) and diarrhea (3%).^{1,21}

Although it is generally accepted that patients receiving ICIs and combination ICIs may experience irAEs affecting multiple organ sites, the exact incidence of concurrent or sequential irAEs in the same patient has not been reported in the kidney cancer population. However, in a retrospective study of 559 patients with non-small cell lung cancer (NSCLC) given nivolumab or pembrolizumab, 231 (41%) developed irAEs, and 40 (17.4%) presented multiple-site irAEs. These were defined as immune-related events occurring in different systems/organs in the same patient. The most frequent irAEs of any grade were classified as endocrine, cutaneous, and gastrointestinal (GI). In contrast, the most common grades 3 to 4 irAEs were GI and pulmonary. In the multivariate analysis, no factor was associated with the development of single- or multiple-site irAEs. Overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) were higher among patients with AEs compared with those who did not experience AEs ($P < .0001$), but no significant differences were observed among those who presented multiple-site events compared with those who had single-site irAEs. Among patients with irAEs, 32 (6.1%) discontinued treatment due AEs, and no statistical differences were found in ORR, PFS, and OS when compared in those who did not discontinue treatment.²²

The data regarding the incidence of multiple irAEs in the same patient is very scarce. It comes from heterogeneous populations (ie, different tumor types and stages) and retrospective studies. The **Table** includes data from studies that report the frequency of multiple-site irAEs, which varies from 13% to 53%.²²⁻³⁰ Therefore, answer B is a correct statement.

Similar to incidence, the onset of irAEs highly depends of the type of ICI and

Figure 2. Evolution of Serum Creatinine Values

TABLE. Studies Reporting the Frequency of Multiple-Site irAEs in Cancer Patients Treated With ICIs²²⁻³⁰

Study	Tumor type(s)	ICI	Organ/system involved	irAE frequency	
				Single site	Multiple site
Dupont et al²³ (N = 311)	Melanoma, NSCLC	Single agent: ▪ nivolumab ▪ pembrolizumab	Skin, gastrointestinal, endocrine, rheumatic, pulmonary, and renal	116/311 (37%)	43/311 (13.8%) 2 irAEs: 38/43 3 irAEs: 3/43 4 irAEs: 2/43
Kartolo et al²⁴ (N = 78)	Melanoma, NSCLC, and RCC	Single agent: ▪ ipilimumab ▪ pembrolizumab ▪ nivolumab	Skin, gastrointestinal, endocrine, pulmonary, and renal	41/78 (52%)	12/78 (15%)
Cortellini et al²² (N = 599)	NSCLC	Single agent: ▪ nivolumab ▪ pembrolizumab	Endocrine, skin, gastrointestinal, other, pulmonary, and hepatic	231/599 (41.3%)	40/231 (17.4%)
Nigro et al²⁵ (N = 318)	Advanced cancer (any histology)	Anti-PD-1/PD-L1 monotherapy	Not reported	285/318 (89%)	80/285 (28%)
Okada et al²⁶ (N = 15)	Melanoma	Nivolumab	Skin, endocrine (hypothyroidism), gastrointestinal (diarrhea), and hepatic	8/15 (53%)	5/15 (33%)
Singh et al²⁷ (N = 65)	Lung, head, and neck	Single agent: ▪ pembrolizumab Combination: ▪ ICIs + non-checkpoint inhibitor ▪ Concurrent radiation therapy	Gastrointestinal, pulmonary, and hepatic	51/65 (78%)	17/51 (33%)
Abu-Sbeih et al²⁸ (N = 427)	Melanoma; genitourinary; head, neck, and chest; hematological neoplasms; and other solid tumors	Single agent: ▪ ipilimumab ▪ nivolumab ▪ pembrolizumab ▪ atezolizumab Combination: ▪ ipilimumab + nivolumab	Gastrointestinal, pulmonary, endocrine, skin, and hepatic	202/427 (47.3%)	76/202 (37.6%)
Ricciuti et al²⁹ (N = 195)	NSCLC	Nivolumab	Endocrine, gastrointestinal, and skin	85/195 (43%)	37/85 (43%)
Le Burel et al³⁰ (N = 30)	Several tumor types	Single agent: ▪ nivolumab ▪ pembrolizumab ▪ atezolizumab ▪ durvalumab Combination: ▪ ipilimumab + nivolumab	Only hematologic and rheumatic irAEs reported	30/30 (100%)	16/30 (53%) Hematologic and rheumatic irAEs involve multiple sites more frequently

ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; RCC, renal cell carcinoma.

whether the ICI is used as monotherapy or in combination. The toxicities associated with ipilimumab appear within the first 2 to 12 weeks of treatment, usually during the induction phase. The onset of AEs with anti-PD-1 drugs is slightly longer, occurring 5 to 15 weeks after the first dose of treatment. Finally, with ICI combinations, toxicities occur earlier and over a more prolonged period of time.^{4,11,31} Concern-

ing the development of multiple-site irAEs, the mean time since ICI initiation to their development was similar to single-site irAEs (62 vs 78 days, $P = .414$).²⁸ Answer C is also correct.

Steroids are the mainstay management strategy for irAEs and can be used in conjunction with other immunosuppressive agents according to the evolution and severity of the event. For grade 2 toxicities,

ICIs are held, and corticosteroids are initiated at an initial dose of 0.5 to 1 mg/kg per day (prednisone or equivalent). For grade 3 toxicities, ICIs are held, and high-dose corticosteroids are initiated at an initial dose of 1 to 2 mg/kg day (prednisone or equivalent). For grade 4 toxicities, ICIs are permanently discontinued, and high-dose corticosteroids are initiated. Upon response to treatment, cortico-

steroids are tapered over 4 to 6 weeks. If there is no response, corticosteroids are used in conjunction with other immunosuppressive agents, such as infliximab or mycophenolate, depending on site of irAE and severity.² irAEs may affect more than 1 organ simultaneously (as in our case) or sequentially. Therefore, immunosuppressive treatment may require a longer duration or to be given at different periods of time. In the case of multiple-site AEs, the MD Anderson Cancer Center experience indicates that treatment type, its duration, and associated complications were comparable between patients with single and multiple irAEs.²⁸

In 2 retrospective studies in patients with mRCC treated with nivolumab after receiving a prior tyrosine kinase inhibitor, OS and PFS were significantly longer in those with irAEs than in those without irAEs. Multivariable analyses revealed a protective association with irAEs in both outcomes in each study.^{32,33} In addition, an Italian study analyzed patients with NSCLC treated with nivolumab and found that individuals who developed at least 2 irAEs (43%) had longer median PFS and OS compared with those with a single or no irAEs ($P < .0001$). Among patients with irAEs, 14% ($n = 12$) discontinued immunotherapy because of AEs, and at the time of analysis, 11 were alive without disease progression or subsequent treatment.²⁹ In lieu of this evidence, there is some suggestion that irAEs may be associated with better clinical outcomes. Therefore, answer D is a correct statement.

Data from the CheckMate 214 study of mRCC treatment in the first-line setting revealed that in the ICI arm, 25% of patients discontinued treatment due to irAEs (median duration of treatment 2.1 months). These patients generally had higher ORRs, complete response rates, and 24-month OS compared with sunitinib. These efficacy outcomes were also similar to the intention-to-treat population in the nivolumab plus ipilimumab arm. The latter suggests that oncological outcomes remain comparable with immu-

notherapy despite the need for treatment suspension due to toxicity.³⁴

Outcome of This Case

In this case, we decided to continue with a second cycle of the ICI combination while the patient was tapering off steroids (at dose of prednisone 15 mg/day) after 35 days of treatment delay.

Is Re-Treatment With Immunotherapy in this Patient an Option?

Currently, the correct answer remains unclear because the benefit in survival with re-treatment is uncertain and some consider that patients with irAEs experience enhanced ICI efficacy and that re-treatment may be not be necessary. The current guideline recommendations state that for grade 2 and 3 irAEs, when symptoms and/or laboratory values return to grade 1 or less, cautious rechallenge with ICIs may be offered. However, ICIs should be permanently discontinued if patients have grade 4 irAEs, with the exception of endocrinopathies that are controlled with hormone replacement.² Another option following combination nivolumab and ipilimumab therapy would be a rechallenge with nivolumab only.

In the mRCC setting, there is 1 retrospective cohort analysis where 80 patients with clinically significant irAEs, defined as those requiring treatment interruption or discontinuation, were evaluated. The most common irAEs were transaminitis, colitis, and pneumonitis. In 36 (45%) patients, ICI treatment was restarted. Eleven (30.5%) patients were receiving nivolumab plus ipilimumab (like our patient); 7 (63.5%) patients were switched to nivolumab monotherapy and 4 (36.3%) patients restarted the combination. The initial grade of irAE did not predict whether the patient would be rechallenged with monotherapy or the combination.³⁵ After ICI retreatment, 12 (33.3%) patients developed a new type of irAE and 6 (16.6%) experienced the same one. This implied that 50% of patients with mRCC developed a new or recurrent

irAE after restarting treatment, similar to results in patients with NSCLC and melanoma.^{36,37}

Regarding posttreatment AEs, 39% of irAEs were grade 3 with there were no grade 4 or 5 events. Colitis was the most frequent irAE after rechallenge. The median time to an irAE was 2.8 months (range, 0.3-13.8 months), 6 (33.3%) patients required hospitalization, 11 (61.1%) required systemic steroids, and 13 (72%) patients required a therapy interruption for at least 1 week (10 (77%) of which permanently discontinued treatment). The median duration of immunotherapy after retreatment was 5.3 months (range: <1.0 to 21.3 months).³⁵

Two significant predisposing factors for developing irAEs after rechallenge have been identified in patients with metastatic melanoma given combined anti-CTLA-4 and anti-PD-1 therapy. The first is a shorter duration between final dose of combination therapy to resumption of an ICI, and the second is the use of steroids at the time of restart.³⁷

In conclusion, ICIs can cause irAEs involving multiple organ sites in the same patient, concurrently or sequentially. Careful monitoring and dose interruption of ICIs, and early initiation of corticosteroids when needed, are important. Rechallenge with ICIs may be appropriate for some patients but continued monitoring for new or recurrent irAEs is critical. ■

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.

ABOUT THE SERIES EDITORS:

MARIA T. Bourlon, MD is associate professor, head of the Urologic Oncology Clinic, national researcher. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. Mexico City, Mexico. She is also a member of ASCO's IDEA Working Group.

E. David Crawford, MD, is chairman, Prostate Conditions Education Council; editor in chief, *Grand Rounds in Urology*; and professor of Urology, University of California San Diego, La Jolla, California.

➤ For full reference list, visit cancernetwork.com/multiple-irAEs

FURTHER ANALYSES HIGHLIGHT BENEFITS OF PARP INHIBITORS AS FRONTLINE MAINTENANCE IN OVARIAN CANCER

Kevin Wright

Evidence for maintenance treatment with PARP inhibitors as the standard of care in the frontline setting for patients with ovarian cancer continues to mount, according to additional analyses from the phase 3 PRIMA trial and the phase 3 PAOLA-1 trial released as part of the virtual platform for the Society of Gynecologic Oncology (SGO) 2020 Annual Meeting on Women's Cancer.

BRCA and HRD status in the PRIMA Trial

As its primary end point, the phase 3 PRIMA trial demonstrated that frontline maintenance with niraparib (Zejula) improved median progression-free survival (PFS) by 5.6 months compared with placebo (13.8 vs 8.2 months; HR for disease progression or death, 0.62; 95% CI, 0.50-0.76; $P < .001$).¹

As part of that analysis, investigators looked at homologous recombination deficiency (HRD) and *BRCA* status as key biomarkers of PFS. Of the 733 randomized patients, 373 (51%) had tumors with HRD, while 249 (34%) of patients had homologous recombination-proficient tumors.²

The HR for PFS in the HRD cohort was 0.43 (95% CI, 0.310-0.588; $P < .0001$), while the HR in the homologous recombination-proficient group was 0.68 (95% CI, 0.492-0.944; $P = .0203$). In patients with *BRCA* mutations, the HR for PFS was 0.40 (95% CI, 0.265-0.618;

$P < .0001$), while the HR was 0.50 (95% CI, 0.305-0.831; $P = .0064$) in the *BRCA* wild-type patient population.

PFS2 and TFST as Secondary End Points

Also reported through the SGO virtual platform was an analysis of time to first subsequent therapy (TFST) and time to second objective disease progression (PFS2). In the overall population, an increase of 6.6 months in median TFST was shown for patients receiving niraparib versus placebo (HR, 0.65; 95% CI, 0.52-0.80; $P = .0001$).³

In the patients with HRD tumors, median TFST had not yet been reached for patients receiving niraparib, compared with 13.7 months in patients receiving placebo (HR, 0.64; 95% CI, 0.46-0.90; $P < .0105$). Data maturity for TFST in the overall population was at 47%.

With the available results for PFS2 at 20% data maturity, HR in the overall (0.81; 95% CI, 0.58-1.14), HRD (HR, 0.84; 95% CI, 0.49-1.45), and homologous recombination-proficient (HR, 0.56; 95% CI, 0.34-0.91) populations all favored the niraparib arm.

Olaparib Plus Bevacizumab Leads to Improved Outcomes

Results from the phase 3 PAOLA-1 trial showed that the combination of olaparib (Lynparza) plus bevacizumab (Avastin) led to improved PFS versus treatment with bevacizumab alone as frontline

maintenance in patients with newly diagnosed high-grade serous ovarian cancer, regardless of residual disease status or timing of surgery.

Previously published results of the trial found an overall improvement in median PFS of 5.5 months (22.1 vs 16.6 months; HR for disease progression or death, 0.59; 95% CI, 0.49-0.72; $P < .001$).⁴

New data, which were released through the 2020 SGO Annual Meeting on Women's Cancer digital platform, stratified the 537 patients by residual disease status and timing of surgery and showed the benefit of olaparib plus bevacizumab across all cohorts.

The regimen demonstrated the most significant improvement in patients who had upfront surgery with no residual disease, leading to an increase in median PFS of 17.2 months (39.3 vs 22.1 months; HR, 0.47; 95% CI, 0.29-0.75; $P < .001$) for those in the olaparib plus bevacizumab arm.⁵

Among all those who underwent upfront surgery, the investigative regimen led to a median PFS of 29.6 months (HR, 0.52; 95% CI, 0.40-0.69) versus 18.2 months in the control arm, while patients who underwent interval surgery had a median PFS increase of 10.3 months (29.6 vs 19.3 months; HR, 0.54; 95% CI, 0.42-0.71).■

For references visit cancernetwork.com/SGO2020RoundUp

Novel Neoadjuvant Treatment Strategies for Triple-Negative Breast Cancer

Andrew A. Davis, MD; William J. Gradishar, MD

Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University, Chicago, Illinois

Introduction

Triple-negative breast cancer (TNBC), which accounts for approximately 10% to 15% of breast cancers, remains the most aggressive subtype and is characterized by early disease relapse for a subset of patients. TNBC remains a clinical challenge, given the lack of effective targeted treatments such as endocrine therapy for hormone receptor–positive (HR+) tumors or therapies against HER2. In contrast to HR+ and HER2+ disease, TNBC remains a diagnosis of exclusion based on the 3 standard immunohistochemistry markers; it is characterized by the absence of tumor expression for estrogen receptor (ER), progesterone receptor (PR), and HER2. Despite the aggressive nature of TNBC, which is characterized by high-grade tumors with fast cell division and genomic instability, pathological complete response (pCR) rates of approximately 30% to 40% have been achieved for patients with TNBC with chemotherapy alone, while lower rates are achieved for patients with ER+, luminal A, or luminal B disease.¹⁻³ However, despite the higher pCR rates compared with other subtypes, risk of recurrence is considerably higher for patients with TNBC.⁴ Despite the significant molecular heterogeneity of the disease, chemotherapy-based regimens have served, until recently, as the primary treatment for these patients, given the lack of reliable molecular targets. Many molecular pathways are being explored in this space as

potentially druggable, including DNA repair mechanisms, PI3K/mTOR inhibition, and androgen deprivation. Recently, 2 classes of drugs have become available for a subset of TNBC patients: PARP inhibitors and immune checkpoint inhibitors (ICIs).

Prior molecular studies have defined TNBC as a distinct entity with defined subtypes. Specifically, TNBC is classified with basal-like breast cancers (BLBC), which are considered as a distinct molecular subtype from ER+ or HER2+ breast cancers. While not all-encompassing, BLBC represents the most common molecular subtype of TNBC. Other classification systems utilized gene expression profiling to divide TNBC into 6 classifications, including basal-like (BL1 and BL2), mesenchymal (M), mesenchymal stem-like, immunomodulatory, or luminal androgen receptor; this was subsequently revised into just 4 categories: BL1, BL2, M, and LR (for luminal receptor).⁵ Clinically, the most commonly observed mutations within TNBC are *TP53* and *PIK3CA*, with a diversity of other genomic alterations also encountered at lower frequency.⁶

The consideration of utilizing a neoadjuvant approach for TNBC relies on several factors. First, upfront therapy enables a better understanding of disease biology and responsiveness to chemotherapy and other systemic agents. Second, this approach is a useful tool in clinical trials to

evaluate pathological complete response (pCR) and other surrogate end points at the time of surgery. While achieving pCR is prognostic, there are conflicting data regarding whether pCR can serve as a surrogate end point for improved event-free survival (EFS) or overall survival (OS).^{1,7,8} Third, similar to other breast cancer subtypes, neoadjuvant treatment may enable pathologic downstaging, decreased need for axillary surgery, and/or improved cosmetic outcome.⁹ Therefore, this approach is most often utilized in stage II and III disease.

Standard-of-care chemotherapy is recommended for individuals with tumors of at least 1.0 cm (also considered for tumors >0.5 cm) or with lymph node positivity regardless of tumor size. The majority of patients receive anthracycline-, alkylator-, and taxane-based regimens, ideally in a dose-dense approach, despite the heterogeneity of molecular classification.¹⁰⁻¹² For patients with smaller, node-negative tumors or patients with medical comorbidity, docetaxel in combination with cyclophosphamide can be considered.^{13,14} Data for patients with tumors <1.0 cm who do not receive chemotherapy suggest high relapse-free survival rates—at least 90%—with a 5-year survival estimate of 94%.¹⁵ Further improvements in survival, while limiting toxicity, are needed for larger and/or node-positive tumors. Here, we

TABLE 1 Comparison From Key Reported Phase 2 and 3 Neoadjuvant Immune Checkpoint Inhibitor Trials

	GeparNuevo ⁵⁰ (NCT02685059)	-SPY2 ⁴⁹ (NCT01042379)	Keynote-522 ⁵¹ (NCT03036488)	NeoTRIPaPDL1 (NCT02620280)
Phase	II	II	III	III
Completed and published	Yes	Yes	Yes for pCR data	No
Number of patients	174 randomized; 88 experimental arm and 86 to control arm	250 randomized; 69 experimental arm (29 TNBC) and 181 to control arm	1174 randomized; 784 experimental arm and 390 to control arm	280 randomized; 138 experimental arm and 142 to control arm
Checkpoint inhibitor	Durvalumab	Pembrolizumab	Pembrolizumab	Atezolizumab
PD-1/PD-L1	PD-L1	PD-1	PD-1	PD-L1
PD-L1 Companion diagnostic	SP263	22C3	22C3	SP142
Key endpoints	Primary: pCR	Primary: pCR	Primary: EFS and pCR	Primary: EFS Secondary: pCR
Met primary end point	No	Yes	Yes for pCR EFS pending	No for pCR EFS pending
Chemotherapy	Nab-paclitaxel followed by epirubicin + cyclophosphamide	Paclitaxel followed by doxorubicin + cyclophosphamide	Carboplatin + paclitaxel followed by doxorubicin/epirubicin + cyclophosphamide	Carboplatin + nab-paclitaxel. Anthracycline + cyclophosphamide given as adjuvant therapy
Immune checkpoint schedule	1 cycle as monotherapy + 7 cycles with neoadjuvant therapy	4 cycles with paclitaxel	8 cycles neoadjuvant + 9 cycles adjuvant	8 cycles neoadjuvant

companion diagnostic: 22C3 pharmDX companion diagnostic assay; EFS: event-free survival; pCR: pathologic complete response

review the current landscape and potential use of neoadjuvant chemotherapy with additional novel agents for patients with localized TNBC.

Novel Therapeutic Approaches Chemotherapy

Given the suboptimal outcomes for patients with localized TNBC, the goal remains to identify novel drug targets to combine with chemotherapy. One strategy that has been studied involves a risk-adapted approach to escalate therapy for patients with residual disease post neoadjuvant therapy. These approaches are feasible with shorter-term follow-up as compared with other breast cancer subtypes, because TNBC recurrences occur earlier than non-TNBC recurrences. An example is the CREATE-X trial (UMIN000000843) that utilized capecitabine for patients with residual disease at the time of surgery. The study authors reported a 13.7% increase in disease-free survival (DFS) with capecitabine with a statistically significant increase in

OS rate of 78.8%, compared with 70.3% without capecitabine. In terms of adverse events (AEs), 73.4% of patients developed hand-foot syndrome and more than 40% developed cytopenias. However, these findings were not confirmed as statistically significant in a subsequent phase III trial (GEICAM/CIBOMA).^{16,17} The latter trial reported no improvement in DFS versus observation. In addition, prior trials utilizing platinum in combination with standard chemotherapy agents have reported modest benefits in pCR rate, with potential greater benefit for patients with *BRCA* mutations or *BRCA*ness.¹⁸⁻²⁰ However, given conflicting findings in 2 pivotal trials with respect to DFS, phase 3 confirmatory studies are warranted and pending.

PARP Inhibitors

With the emergence of next-generation sequencing, novel targets have been identified for patients with metastatic breast cancer, including the potential to utilize PARP inhibitors, PI3K inhibitors, MEK

inhibitors, and HDAC inhibitors, among others. While these pharmaceutical agents have been explored with varied success in metastatic breast cancer, none have been approved as neoadjuvant therapy to date.

PARP inhibitors have been investigated in neoadjuvant trials, particularly for patients with *BRCA* mutations or *BRCA*ness.^{21,22} PARP inhibition leads to double-strand breaks that cannot be repaired in patients with homologous recombination deficiency (HRD). PARP inhibitors may serve as chemosensitizers or radiosensitizers and can result in synthetic lethality for patients with germline mutations.

In metastatic disease, the first FDA approvals for PARP inhibitors included olaparib and talazoparib for germline *BRCA*-mutant, HER2-negative disease based on the OlympiAD and EMBRACA trials, respectively.^{23,24} The approach of incorporating PARP inhibitors into neoadjuvant trials has also been investigated. For example, the phase 2, single-arm PreCOG 0105 trial reported a high response rate (up

to 75%) for patients with *BRCA1/2* mutations who received gemcitabine, carboplatin, and iniparib.²⁵ High response rates were also observed for patients with HRD. These findings, however, were not confirmed in a subsequent phase 3 trial, and further data indicated that iniparib may not even inhibit the DNA repair enzyme PARP.²⁶ In the I-SPY 2 trial, adding veliparib and carboplatin to standard chemotherapy, including paclitaxel, doxorubicin, and cyclophosphamide, resulted in a doubling of pCR rate (26% to 51%).²⁷ The phase 3 BrightTness trial utilized carboplatin and paclitaxel, followed by doxorubicin and cyclophosphamide with or without veliparib.²¹ For patients with stage II or III TNBC, the study reported that the pCR rate was not significantly higher with the addition of veliparib. In addition, in a cohort of 20 patients with germline *BRCA* mutations (15 with TNBC), 6 months of neoadjuvant talazoparib for patients with operable TNBC resulted in a residual cancer burden-0 rate of 53%.²²

Two important limitations of combining a PARP inhibitor with chemotherapy exist. First, the combination of chemotherapy with an optimal dose of a PARP inhibitor may cause myelosuppression, suggesting the possibility of utilizing PARP inhibitors in a risk-adapted approach in the adjuvant setting. Second, it is unclear whether PARP inhibitors add additional benefit compared with adding a platinum agent alone. Further risk-adapted approaches are being explored to examine the potential benefit of single-agent PARP inhibitors for patients with high-risk features or residual disease at the time of surgery. In addition, preclinical work has suggested synergy for the combination of PIK3 inhibitors with PARP inhibitors.^{28,29} Such combinations are being studied in early-phase trials in the advanced setting.

There are several ongoing questions regarding the potential clinical utility of PARP inhibitors for TNBC. First, do somatic and germline *BRCA* mutations confer differential responses to PARP inhibitors? Prior studies for patients with metastatic TNBC receiving PARP inhibitor monotherapy

appear to indicate lower response rates for individuals with somatic mutations, indicating the need for combinatorial approaches.³⁰ Second, can DNA repair mutations beyond *BRCA1* and *BRCA2*, such as *ATM*, *RAD51*, *PALB2*, and *BARD1*, also confer response to PARP inhibitors? For example, ongoing work is examining the potential to utilize talazoparib for *BRCA* wild-type patients with either a germline or somatic mutation in the HRD pathway.³¹ Furthermore, a variety of biomarker tests define loss of heterozygosity and allelic imbalance, but more study of clinical utility is needed before applying these tools in routine clinical practice.^{32,33} Answering these questions will be critical to maximizing the benefit of PARP inhibitors in clinical practice.

Other Molecular Targets

Trials investigating the use of androgen deprivation, PIK3CA inhibitors, MEK inhibitors, and EGFR inhibitors are also being explored. To date, these drugs have been relatively disappointing in terms of clinically meaningful benefit for patients with metastatic TNBC. In terms of androgen blockade, single-arm phase 2 trials have reported a modest clinical benefit rate of 19% with bicalutamide and a small number of complete and partial responses ($n = 6$; 8% of evaluable subgroup) in a cohort of 78 patients from a total intention-to-treat cohort of 118 patients treated with enzalutamide.^{34,35} Subsequently, financial support for the phase 3 ENDEAR trial was discontinued. The combination of PIK3CA inhibitors, such as ipatasertib and buparlisib, with chemotherapy have resulted in modest (ipatasertib: 1.3-month increase in PFS; hazard ratio, 0.60; 95% CI, 0.37-0.98) to negligible (buparlisib: 1.2-month decrease in PFS; hazard ratio; 1.18, 95% CI, 0.82-1.68) benefits in PFS for patients with metastatic TNBC (LOTUS and BELLE4 trials, respectively).^{36,37}

In patients with metastatic TNBC, trials have largely been disappointing when exploring activity of other rare targets, including MEK inhibitors and EGFR inhibitors.³⁸⁻⁴⁰ Many other novel agents are being

studied, including HDAC inhibitors, drugs targeting integrins, and CCR5 antagonists. In addition, the antibody-drug conjugate sacituzumab govitecan-hziy, which targets Trop-2 and delivers a payload that inhibits topoisomerase-1, has recently shown significant activity in metastatic TNBC after multiple lines of therapy.⁴¹ Specifically, for TNBC patients who received multiple prior lines of therapy (range, 2-10), the response rate was 33.3%, with a median PFS of 5.5 months and OS of 13.0 months. In April 2020, due to compelling evidence of clinical efficacy, a data safety monitoring committee stopped the phase 3 ASCENT Trial of sacituzumab govitecan-hziy. Formal presentation of the final analyses of the study is pending. As a result of this agent's promise in the metastatic setting, it will also likely be studied as a neoadjuvant strategy for patients with early-stage TNBC.

Collectively, these data suggest that single-agent, targeted approaches will unlikely be successful treatment strategies. When considering the addition of targeted therapies to standard combination chemotherapy, overlapping toxicities must be considered carefully in order to ensure that adequate chemotherapy can be delivered and prohibitive toxicity is avoided. Similar to the advances in HER2-positive disease, trials designed to adapt therapy based on residual disease at the time of surgery may enable utilization of additional adjuvant therapy for patients with elevated risk of recurrence based on pathologic assessment.

Immune Checkpoint Inhibitors

To date, ICIs have been relatively disappointing in breast cancer as compared with other, more immunogenic tumor types, such as melanoma, renal cell carcinoma, and non-small cell lung cancer. However, of the subtypes of breast cancer, TNBC has demonstrated the most theoretical promise based on high genomic instability, level of tumor-infiltrating lymphocytes (TILs), and PD-L1 expression. As monotherapy for advanced disease, ICIs have resulted in response rates of approximately 5% to 19%, with some indication of higher response rate

TABLE 2 **Select Ongoing Neoadjuvant and Adjuvant Trials of Immune Checkpoint Inhibitors for Localized TNBC**

Trial	Phase	Drug(s)	Design	Primary endpoint(s)
NCT03356860 (B-IMMUNE)	1b and 2	Durvalumab with paclitaxel, cyclophosphamide, and epirubicin	Neoadjuvant	Adverse events pCR
NCT03366844	1 and 2	Pembrolizumab with radiation boost	Neoadjuvant	Treatment delay Changes in TILs
NCT02883062	2	Carboplatin and paclitaxel with or without durvalumab	Neoadjuvant	Increase in TIL percentage
NCT04188119 (IMpALA)	2	Avelumab and PPI with or without aspirin	Neoadjuvant window trial	Mean combined gene expression of COX-2 promoting genes
NCT02530489	2	Atezolizumab and nab-paclitaxel	Neoadjuvant	pCR
NCT02957968	2	Pembrolizumab and decitabine followed by doxorubicin, cyclophosphamide, paclitaxel, and carboplatin	Neoadjuvant window trial	Increase in percent of tumor and stroma with TILs
NCT03872505 (PANDoRA)	2	Durvalumab with carboplatin, paclitaxel, and radiation	Neoadjuvant	pCR
NCT03639948 (NeoPACT)	2	Pembrolizumab with carboplatin and docetaxel	Neoadjuvant	pCR
NCT03815890 (BELLINI)	2	Nivolumab or nivolumab and doxorubicin	Neoadjuvant	Tumor associated CD8 and expression of genes induced by IFN-gamma
NCT03740893 (PHOENIX)	2	3 arms, 1 includes durvalumab	Neoadjuvant window trial and adjuvant component	Multiple including change in CD8+ TILs and change in IFN-gamma positive signature
NCT03546686	2	Ipilimumab, nivolumab, and cryoablation with adjuvant nivolumab	Neoadjuvant and adjuvant	Event-free survival
NCT02954874	3	Pembrolizumab	Adjuvant	Invasive disease-free survival Quality of life (fatigue and physical function)
NCT02926196 (A-BRAVE)	3	Avelumab	Adjuvant	Disease-free survival
NCT03498716 (Impassion030)	3	Paclitaxel, dose-dense doxorubicin/epirubicin, cyclophosphamide with or without atezolizumab	Adjuvant	Invasive disease-free survival

IFN: interferon, pCR: pathologic complete response, PPI: proton pump inhibitor, TIL: tumor infiltrating lymphocyte

based on PD-L1 status.⁴²⁻⁴⁶ However, median progression-free survival (PFS) has been only about 1.4 to 2.1 months. To date, the first and only FDA approval in breast cancer is for first-line therapy in a subset of patients with advanced TNBC. Specifically, the FDA approved atezolizumab in combination with nab-paclitaxel for individuals with PD-L1 positivity defined by immune cell PD-L1 staining using the Ventana SP142 assay.⁴⁷

Importantly, there are several differences

between primary and metastatic breast cancers. Prior data have demonstrated that primary breast cancers may be more immunogenic. This is based on studies comparing TILs, PD-L1 expression, and immune gene signatures between primary and metastatic disease. This work reported significantly higher TIL counts, PD-L1 expression, and immune activation signatures in primary disease compared with metastatic disease.⁴⁸

Several studies have recently been pub-

lished investigating the use of neoadjuvant chemotherapy in combination with immune checkpoint inhibition. Phase 2 data from the I-SPY 2 trial examined pembrolizumab in combination with neoadjuvant chemotherapy (paclitaxel weekly for 12 weeks, followed by 4 cycles of standard doxorubicin and cyclophosphamide every 2-3 weeks) in early-stage breast cancer.⁴⁹ A total of 4 cycles of pembrolizumab was given during the paclitaxel portion of treatment. The sample

included both HR+, HER2-negative ($n = 40$) and TNBC patients ($n = 29$) with pCR as the primary end point. Compared with controls receiving standard neoadjuvant chemotherapy, the TNBC patients who received pembrolizumab had a 60% pCR rate compared with 22% for the control arm. Notably, given the design of I-SPY 2, no adaptive changes to the control arm, such as addition of carboplatin to achieve pCR, were counted, which possibly accounted for the lower-than-anticipated pCR rate of only 22% in that arm. In terms of immune-related AEs, diarrhea, thyroid dysfunction, adrenal insufficiency, and pruritus were notably higher in the experimental arm.

In contrast, a randomized, double-blind, placebo-controlled, phase 2 trial of neoadjuvant durvalumab with or without nab-paclitaxel, followed by epirubicin and cyclophosphamide, did not report favorable outcomes with the addition of an ICI.⁵⁰ This trial included a subgroup of patients treated without a window phase, while the majority of patients (117 of 174) received a single dose of durvalumab or placebo 2 weeks prior to the first dose of nab-paclitaxel as part of a window phase. In the overall population, no significant difference was seen between the experimental and control arms with respect to pCR (53.4% with durvalumab vs 44.2% control; odds ratio (OR), 1.45; 95% CI, 0.80-2.63; $P > .20$). For patients treated in the window phase, there was a statistically significant improvement in pCR rate (61.0% with durvalumab vs 41.4% control; OR, 2.22; 95% CI, 1.06-4.64; $P < .05$). However, this subgroup analysis was underpowered. TILs and PD-L1 expression were associated with increased overall response, but they were not predictive of response to durvalumab. The most common immune-related AE was thyroid dysfunction, present in 47% of patients.

In addition, interim results from 2 phase 3 studies were recently presented at the 2019 San Antonio Breast Cancer Symposium, specifically KEYNOTE-522 (NCT03036488) and NeoTRIPaPDL1 (NCT02620280) (see **Table 1** for comparison). KEYNOTE-522 evaluated neoadjuvant pembrolizumab

with or without chemotherapy with carboplatin and paclitaxel, followed by an anthracycline (doxorubicin or epirubicin) and cyclophosphamide, followed by 9 cycles of adjuvant pembrolizumab versus placebo. This study included 1174 patients with stage T1c N1-2 or T2-T4 N0-2 TNBC; they were from 21 countries and 124 sites.⁵¹ The study reported a significant improvement in pCR rate regardless of PD-L1 status, as revealed by the 22C3 pharmDX companion diagnostic assay for PD-L1 testing. In this study, a combined positive score of 1 or greater was utilized based on the number of PD-L1 positive cells—including tumor cells, lymphocytes, and macrophages—divided by the total tumor cells, then multiplied by 100. Interestingly, tumors with PD-L1 positivity had a higher rate of pCR compared with PD-L1-negative tumors. With short follow-up of 15.5 months, EFS trended in the favorable direction (91.3% with pembrolizumab vs 85.3% in the control arm), but longer-term follow-up is needed to adequately assess statistical differences between the groups for EFS.

In contrast, the NeoTRIPaPDL1 study (NCT02620280) did not report a favorable outcome with a neoadjuvant ICI with respect to pCR.⁵² This study enrolled high-risk patients with early-stage or locally advanced disease to receive carboplatin and nab-paclitaxel with or without atezolizumab for 8 cycles. In this trial, the anthracycline and cyclophosphamide were given as postoperative therapy. Based on initial evaluation of 280 patients, there was no statistically significant difference in pCR rate (43.5% vs 40.8%; OR, 1.11; 95% CI, 0.69-1.79). PD-L1-positive tumors (using the SP142 companion diagnostic) had a higher rate of pCR compared with PD-L1-negative tumors, but PD-L1 positivity did not predict which patients benefited. PD-L1 positivity was the only variable in multivariate analysis to significantly increase pCR rate. Serious AEs were significantly higher in the experimental arm (18.1%) versus without atezolizumab (5.7%).

Several hypotheses have been posited to account for differences in the results of these

2 phase 3 trials. First, the KEYNOTE-522 trial utilized pembrolizumab both as neoadjuvant and adjuvant therapy, and this may have enhanced the effect of the checkpoint inhibition. The trend toward improved EFS could at least partially be explained by the adjuvant use of pembrolizumab. Second, an anthracycline was given prior to surgery in KEYNOTE-522 and after surgery in NeoTRIPaPDL1. Prior data have indicated that doxorubicin was the most immunogenic chemotherapy backbone to prime the tumor microenvironment.⁵³ Third, the NeoTRIPaPDL1 study enrolled patients with more advanced tumors, and therefore the patients with defined PD-L1 positivity were lower by nearly 30%, taking into account differences in the companion diagnostics utilized in each study. Fourth, various studies define PD-L1 positivity differently based on thresholds, cell type examined, and companion diagnostics.⁵⁴ All of these factors may explain the discordant results that were observed.

In the future, more clearly defined biomarkers are required to help distinguish which patients may be more likely to respond to therapy. Unfortunately, PD-L1 status does not appear to be a predictive biomarker of pCR in this setting. In addition, further work is necessary to characterize the optimal chemotherapy backbone to combine with ICIs. The particular drugs and sequence of therapy may be very important for optimal patient outcomes. Toxicity and cost data will also be important considerations, given that some immune-related AEs are permanent and a small subset of these toxicities can be severe and even life-threatening. Finally, and most important, longer-term follow-up data regarding EFS, OS, and quality of life are truly necessary to verify that improvements in pCR will correlate with long-term outcomes that matter to patients.

Multiple additional studies utilizing ICIs are ongoing; some representative studies are shown in **Table 2**. The proposed strategies include a variety of approaches.

Continued on page 182

TEST YOUR IMAGE IQ

HEMATOLOGIC MALIGNANCIES

76-Year-Old Woman With a Bluish-Purple Lump in her Left Upper Medial Leg

Mehmet Sitki Copur, MD; and Whitney Wedel, MD
Mary Lanning Healthcare Morrison Cancer Center

PRESENTATION

A woman, aged 76 years, presented with a bluish-purple lump in her mid- to upper medial left thigh. It started initially as a flat rash, and over a 2-month period, it turned into a mass measuring 2.5 cm by 3.1 cm (**Figure 1**). Work-up, including a PET-CT scan, showed the soft tissue mass on the inner thigh to have a Standardized Uptake Value of 4 (**Figure 2**); there were no other sites of disease. A biopsy of the lesion was performed (**Figure 3**).

WHAT'S YOUR DIAGNOSIS?

- A. Kaposi sarcoma
- B. Malignant melanoma
- C. Adult soft tissue sarcoma
- D. Angiosarcoma
- E. Lymphoma

See page 182 for the answer.

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Kevin Wright, Senior Editor, at
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CORRECT ANSWER: E. Lymphoma

Continued from page 181

COMMENT: Primary cutaneous diffuse large B-cell lymphoma (LBCL), leg type, is a primary cutaneous LBCL of intermediate behavior. It represents 1% to 4% of all cutaneous lymphomas and approximately 10% to 20% of all primary cutaneous LBCLs.^{1,2} The disease predominantly affects elderly patients, with the male-to-female ratio ranging from 1:2 to 1:4. Typically, patients present with rapidly growing, solitary or clustered, red or bluish-red nodules or tumors located on 1 or both legs, which can ulcerate.³ These lymphomas are mostly limited to the skin at

presentation. Histologically, observed is either a dense, diffuse infiltrate of a monotonous population; or confluent sheets of medium to large B cells with round nuclei, prominent nucleoli, and coarse chromatin resembling centroblasts and/or immunoblasts within the dermis and subcutis. The neoplastic B cells usually express B-cell markers (CD19, CD20, CD22, CD79a). Additionally, Bcl-2, MUM1/IRF4, IgM, and FOXP1 proteins are strongly positive.⁴ The frequent relapses require appropriate treatment decisions and a strict follow-up of the patients. ■

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Copur

is a medical oncologist/hematologist at Morrison Cancer Center, Mary Lanning Healthcare in Hastings, Nebraska, and is a professor at the University of Nebraska Medical Center in Omaha, Nebraska. He is also editor-at-large and a Community Oncology Advisory Board member at ONCOLOGY.

Wedel

is a staff pathologist at Mary Lanning Healthcare.

Review Article: Novel Neoadjuvant Treatment

Continued from page 180

For example, some trials are studying the use of ICIs as sequential versus concurrent therapy, while others are exploring adjuvant ICIs for patients with residual disease at the time of surgery. Multiple trials are performing correlative studies examining TILs, interferon- immune signatures, and other biomarkers to better understand responders versus nonresponders.

Conclusions

Improving outcomes for patients with localized TNBC remains a significant unmet need in the breast cancer community. Given the fast rate of cell division, chemotherapy will likely remain a backbone of treatment. Therefore, the goal remains to add additional targeted and/or immune-based treatment, while balancing efficacy and minimizing compounding toxicities for patients with

the goal of cure. To date, early evidence from some studies has indicated that the combination of standard chemotherapy with immune checkpoint inhibition may improve pCR rates. Longer-term data with respect to EFS and OS are necessary to confirm that pCR will be validated as a surrogate end point in this setting. The optimal timeframe of neoadjuvant and/or adjuvant initiation of ICIs requires further study. At this time, the FDA has not approved the use of ICIs as neoadjuvant therapy, and these therapies should be viewed as experimental, pending final review and analysis of longer-term data. Evaluation of targeted therapies in combination with chemotherapy and/or immune checkpoint inhibition is also being explored in this setting. Collectively, recent data indicate that novel neoadjuvant approaches with ICIs hold promise for

patients with TNBC, while we await long-term follow-up data and take into careful consideration the cost and added short- and long-term toxicities of these approaches. ■

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.

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Davis

is fellow in hematology and oncology at Northwestern University.

Gradishar

is the director of the Maggie Daley Center for Women's Cancer Care and the chief of Hematology and Oncology and deputy director of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University.

CONTINUING MEDICAL EDUCATION (CME)

Current Knowledge and New Directions in Cholangiocarcinoma

FACULTY

Milind Javle, MD

Professor
Department of Gastrointestinal Medical
Oncology
Division of Cancer Medicine
The University of Texas MD Anderson
Cancer Center
Houston, TX

This activity was written by PER® editorial staff under faculty guidance and review. The Q&A portion of the activity was transcribed from a recorded interview with the faculty and edited by faculty and PER® editorial staff for clarity.

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- Explain the study design, rationale, and results of recent clinical trials evaluating novel strategies for the treatment of cholangiocarcinoma
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RELEASE DATE: May 1, 2020

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Cholangiocarcinoma (CCA) is a rare group of cancers that arise from the biliary tract epithelium.¹ Representing 3% of all gastrointestinal malignancies, CCA is categorized into 3 distinct cancers, depending on the site of origin: intrahepatic CCA (arising from hepatic bile ducts), perihilar CCA (arising from the extrahepatic biliary tree to the point of origin of the cystic duct), and distal CCA (arising from the distal bile duct).^{2,3} Although surgical resection is the only curative option currently available, the disease is most often diagnosed in advanced, unresectable stages.⁴ The unmet medical need of treatment options for this cohort is highlighted by the poor prognosis of patients with advanced CCA, who have a median survival of less than 2 years with current standard chemotherapy treatment (gemcitabine plus cisplatin).^{5,6} Recently, however, molecular studies have identified a number of potentially actionable targets in CCA, including alterations in *IDH1*, *IDH2*, *FGFR2*, *KRAS*, *PTEN*, and *CDKN2A*.⁷ Novel therapies that were developed based on these findings continue to undergo evaluation in clinical trials. Among these investigational therapies for CCA are ivosidenib, an isocitrate dehydrogenase 1 (*IDH1*) inhibitor being evaluated in the phase 3 ClarIDHy trial; futibatinib, a fibroblast growth factor receptor-2 (*FGFR2*) inhibitor being evaluated in the phase 3 FOENIX-CCA3 trial; infigratinib, an *FGFR2* inhibitor being evaluated in the phase

3 PROOF trial; and pemi-gatinib, an *FGFR2* inhibitor being evaluated in the phase 2 FIGHT-202 trial.⁸⁻¹¹

Milind Javle, MD, reviews recent data from clinical trials investigating the aforementioned novel therapies for the treatment of CCA and how they will impact the treatment landscape and clinical management of patients with CCA in the near future.

Q: What are the key initial steps for medical oncologists to take when a patient presents with suspected CCA?

JAVLE: When a patient presents to the clinic, one of the first things we do is evaluate the clinical status, including the performance status of the patient. We order tests that include laboratories for liver function, blood counts, and imaging such as CAT scan to assess the extent of the disease. These studies will determine the need for specialty referral, for instance gastroenterology for stent placement or surgical referral if the patient is surgically resectable. We will also obtain a tumor biopsy and request next generation sequencing to detect any actionable mutations.

Q: What is the current treatment approach for patients with advanced CCA?

JAVLE: Biopsy is essential to confirm that the tumor is adenocarcinoma and is coming from biliary origin and not from any other site. Increasingly, next generation sequencing

is becoming standard of care to help inform both first-line and second-line treatment options. The standard of care at this time in the advanced CCA setting is first-line chemotherapy with gemcitabine and cisplatin or enrollment in a clinical trial.⁶ In the case of tumor progression despite chemotherapy, the current second-line treatment option is FOLFOX, based on data from the phase 3 ABC-06 trial, or enrollment in a clinical trial.^{6,12} We hope that in the near future, with approval of targeted therapies, both first-line and second-line options will include targeted therapy based on the underlying mutation profile. In all of these instances, we also consider a multidisciplinary approach that includes radiation therapy, chemoembolization or radioembolization in the appropriate clinical setting.

Q: What are some of the promising genomic or molecular targets for which you would test to aid in the diagnosis and treatment choice for your patients with CCA, and when should molecular testing be performed for patients with CCA?

JAVLE: Molecular testing should be performed, in my view, universally in patients with CCA, if there is an adequate core biopsy. There are several targets in CCA, particularly in intrahepatic CCA, which include *IDH1*, *FGFR*, *BRAF*, and of course microsatellite instability (*MSI*) for immunotherapy. Other targets that are somewhat less common but

still important include *HER2/neu*, *c-MET*, and *EGFR*.

Q: What is the rationale for immunotherapy in advanced CCA?

JAVLE: Immunotherapy has demonstrated significant efficacy results in several cancers, including the closely related hepatocellular cancer. It is intuitive, then, to consider its implementation in CCA and biliary tract cancer as well. Biliary tract cancer and CCA are diseases of chronic inflammation. In certain countries, these cancers are related to infection; for instance, fluke infection and hepatitis B in Asia, and hepatitis C and nonalcoholic steatohepatitis (*NASH*) in the Western world have been linked with both malignancies. There are a small number of cases that are related to *MSI*. For all of these reasons, immunotherapy is worthy of consideration in CCA.

Q: What are some of the key clinical findings from recent immunotherapy trials in advanced CCA?

JAVLE: The largest experience so far has been with pembrolizumab in the KEYNOTE-158 study which enrolled 104 patients.¹³ Although 5.8% response rate was modest, those responses were sustained and long lasting, some for up to 15 months or more. Interestingly, there were no patients with *MSI*-high disease enrolled in the study. Overall, immunotherapy was very well tolerated. Besides KEYNOTE-158, there are single-institution experiences,

TABLE. Select Investigational Agents for the Treatment of CCA

Investigational agent	Clinical trial identifier	Patient enrollment	Key eligibility criteria	Preliminary efficacy	Preliminary safety
Immune checkpoint inhibitors					
Pembrolizumab ¹³	NCT02628067 Phase 2 KEYNOTE-158	N = 104	2L advanced BTC	ORR: 5.8%	TEAEs: fatigue (14%), rash (12%), pruritus (9%) Grade ≥3 AEs: 13%
Nivolumab ¹⁵	NCT02829918 Phase 2	N = 54	2L advanced BTC	PR: 22% (10/45)	Grade ≥3 AEs: hyponatremia (3/45), elevated ALP (2/45)
IDH inhibitors					
Ivosidenib ⁸	NCT02989857 Phase 3 ClarIDHy	Ivosidenib (N = 124) Placebo (N = 61)	2L advanced mIDH CCA	Median PFS; Ivosidenib: 2.7 mo Placebo: 1.4 mo	Grade ≥3 AEs: Ivosidenib: 46% Placebo: 36%
FGFR inhibitors					
Debio 1347 ²⁰	NCT01948297 Phase 1	n, CCA = 9	2L advanced FGFR- altered CCA	PR: 22% (2/9)	Grade ≥3 TEAEs: Hyperphosphatemia (33%)
Derazantinib ²¹	NCT01752920 Phase 1/2	N = 29 n, treatment naïve = 2 n, prior treatment = 27	1L advanced FGFR-fusion CCA	ORR: 20.7%	TEAEs: hyperphosphatemia (75.9%), asthenia/fatigue (69.0%), eye toxicity (41.4%) Grade ≥3 AE: 27.6%
Erdafitinib ²²	NCT02699606 Phase 2	N = 14	2L advanced FGFR- altered CCA	ORR: 50% (PR, 6/12)	Grade ≥3 AEs in 75% (9/12) of patients
Futibatinib ⁹	NCT04093362 Phase 3 FOENIX-CCA3	N = 216	1L advanced FGFR- rearranged CCA	NR	NR
Infigratinib ¹⁰	NCT02150967 Phase 2	N = 61	2L advanced FGFR- altered CCA	ORR: 14.8%	Grade ≥3 AEs: Hyperphosphatemia (16.4%), stomatitis (6.6%), PPE (4.9%)
Pemigatinib ¹¹	NCT02924376 Phase 2 FIGHT-202	N = 146	2L advanced FGFR- altered CCA	ORR: 35.5%	Grade ≥3 AEs: hypophosphatemia (12%), arthralgia (6%), stomatitis (5%), hyponatremia (5%), abdominal pain (5%), fatigue (5%)

1L, first-line; 2L, second-line; AE, adverse event; ALP, alkaline phosphatase; BTC, biliary tract cancer; mIDH, mutant IDH; NR, not reported; ORR, overall response rate; PPE, palmar-plantar erythrodysesthesia; PR, partial response; TEAE, treatment-emergent adverse event.

for instance pembrolizumab with GM-CSF, nivolumab monotherapy, and several other combination studies, that demonstrate that there is a subset of patients with CCA that appear to benefit from

immunotherapy.¹⁴⁻¹⁶ It remains to be identified, however, who these patients are and what biomarkers can be used in the setting.

Q: What is the mechanism of action of IDH1 inhibitors and the rationale for these agents in the treatment of advanced CCA?

JAVLE: IDH1 inhibitors are

among the first targeted agents to be investigated in this cancer. IDH1 is involved in the Krebs cycle in the conversion of isocitrate to α-ketoglutarate. In the presence of an IDH1 mutation, α-ketoglutarate is

further reduced to 2-hydroxyglutarate, which is responsible for oncogenic activity in CCA and glioma.¹⁷ Clearly, this is an important area to target in CCA, as approximately 20% of patients have *IDH1* R132 mutation.¹⁸

Q: What are the key efficacy and safety findings from the phase 3 ClarIDHy trial?

JAVLE: The ClarIDHy trial was a phase 3 trial in the second-line setting for patients with advanced CCA and an *IDH1* mutation (R132) after failure of first-line gemcitabine and cisplatin. Approximately 185 patients were randomized 2:1 to ivosidenib versus placebo in a crossover design with progression-free survival (PFS) as the primary endpoint of the study. The results were presented at the ESMO meeting in 2019.⁸ The overall response rate was modest at 2%; however, 50% of patients had stable disease. The primary endpoint of this trial was met with a hazard ratio for PFS of 0.5. Although numerically the PFS was quite low at 2.7 months, it was significantly higher as compared with the placebo. The regimen was well tolerated. There were very few side effects, which included nausea, fatigue, and anemia. Drug discontinuation due to treatment-related adverse events was more likely to occur in the placebo arm than in the treatment arm. Clearly, this is an advancement in this setting, and we hope that this option will soon be available for our patients.

Q: What is the mechanism of action of FGFR inhibitors and the rationale for these inhibitors in the treatment of advanced CCA?

JAVLE: *FGFR* genetic aberrations, particularly *FGFR* fusions, occur in about 15% of patients with intrahepatic CCA.¹⁹ There are also less-described *FGFR* mutations in the kinase domain which are rarer, but the *FGFR* fusions have been found to be susceptible to targeted tyrosine kinase inhibitors and are currently being investigated in phase 1 and 2 clinical trials.

Q: What FGFR inhibitors are under investigation for the treatment of CCA, and what are the key efficacy and safety findings from recent clinical trials?

JAVLE: There are 6 *FGFR* inhibitors being investigated for CCA, mostly in the phase 2 and some now in the phase 3 setting. These include Debio 1347, derazantinib, erdafitinib, futibatinib, infigratinib, and pemigatinib.^{9-11,20-22} The phase 2 studies of futibatinib, infigratinib, and pemigatinib have been completed.⁹⁻¹¹ The results of most of these studies are, so far, relatively similar. The median PFS appears to be about 6 months. The response rate in the second-line setting ranges from 20% to 30%. The median overall survival ranges from about 12 months to 20 months depending on treatment line. Most of these drugs lead to hyperphosphatemia as a class effect. They also lead to onycholysis, or nail

changes, and palmar-plantar erythrodysesthesia, and can result in some fatigue and nausea. Some drugs that have *FGFR-4* activity are also associated with diarrhea, and the nonselective *FGFR* inhibitors have off-target effects such as AST/ALT enzyme elevations.

Q: How do you foresee the results from these studies impacting the treatment paradigm for patients with advanced CCA?

JAVLE: Clearly, as far as *IDH1* and *FGFR* targets are concerned, these account for almost 40% of patients with intrahepatic CCA. I foresee that, in the second-line setting, chemotherapy will be substituted with *FGFR* or *IDH1* inhibitors. In the very near future, we will see combination regimens with chemotherapy with one or both of these targeted inhibitors. These will constitute a significant change in the management of this disease certainly in the second-line setting, but also in the first-line setting in the near future.

Q: What key clinical trials or novel agents in CCA should we be on the lookout for next?

JAVLE: We should be on the lookout for other actionable targets in CCA. These include DNA repair aberrations, which occur in about one-third of patients with CCA, and *HER2/neu* amplifications and mutations, which occur in 5% to 10% of patients.²³ We expect to see chemotherapy plus targeted therapy combi-

nations. Last but not least, we will expect immunotherapy trials with chemotherapy or immunotherapy trials with targeted therapy in the near future. ■

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