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How Pharmaceutical Innovation Helped Save Our World

In March 2020 the United States was in the early stages of the coronavirus disease 2019 (COVID-19) pandemic. We shut down the entire country and ground the economy to a halt to slow the spread of the virus. It was a time of incredible uncertainty.

Now, a mere 11 months later, the FDA has approved 2 COVID-19 vaccines for use under emergency authorization. By New Year's Day 2021, millions of Americans had received the vaccine, including frontline physicians and health care providers and nursing home patients, our most vulnerable citizens.

At times, the mainstream media has crafted a narrative about the COVID-19 pandemic that's almost entirely negative. They have often described the United States response to the pandemic as blundering from 1 mistake to the next.

There is of course, another way—perhaps a more accurate and underappreciated way—to tell the story of the past 10 months. It is a story of heroism, innovation, and precise science, performed under unbelievable pressure.

Let's not mince words: The world must appreciate the role of the pharmaceutical industry—the investigators, physicians, and business leaders—who are working tirelessly to rescue the world from COVID-19. It's the medical breakthrough of our lifetime.

Instead of dwelling on why many in the media are ignoring this, let's review some facts.

- Since the discovery of COVID-19, scientists have identified a novel virus, unlocked and sequenced its genetic code, created new therapies to save lives, and developed multiple safe and effective vaccines using messenger RNA technology, a technology applicable to future vaccine development.
- The United States has 2 vaccines approved for emergency use, 1 from Pfizer/BioNTech and another from Moderna, and the AstraZeneca/Oxford vaccine has been approved for emergency use in the UK. In addition, there are more than 60 vaccines undergoing clinical trial at the moment, including 20 in phase 3 trials.
- This was the fastest vaccine development program in history, and it's not even close. Vaccines

typically take 10 to 15 years to develop. Until the COVID-19 pandemic, the fastest development timeline was 4 years, for the mumps vaccine.

- Many government systems moved quickly to lessen the burden of onerous regulations and provide funding so that vaccines could be developed quickly but with rigorous standards. Perhaps it should be a lesson to all of us that regulation and innovation can be calibrated more effectively during “normal” times as industry races to develop new therapies for other epidemics—cancer, diabetes, heart disease, and more.

The next step of the process—distribution of the vaccine—has been as challenging as the development phase, if not more so. But the pharmaceutical industry is once again rising to the occasion. Factories worldwide are working overdrive to produce hundreds of millions of vaccine doses.

Less than a month after the Pfizer vaccine was approved, more than 15.4 million doses of vaccine have been distributed throughout the country, and more than 4.6 million individuals have received their first dose, according to CDC data. Many patients are already receiving their second dose.

Although 15.4 million doses are impressive, some expected 20 million doses by this time. But that is moving the goal line, as 6 months ago many observers didn't think a vaccine would be available until later in 2021.

Members of our COVID Coalition told us that the holidays slowed the rollout considerably. But every day, more people will be vaccinated. After health care workers and our most vulnerable citizens, other frontline workers will be next. Teachers will be vaccinated so our children can return to school. And soon, all Americans will be able to receive the vaccine at their doctor's office or at a CVS or Walgreens.

Remember, we accomplished this in 10 months, with the help, dedication, and expertise of our pharmaceutical industry heroes. Next time you turn on the TV and see negativity, turn it off and imagine instead where we will be 11 months from now.

Mike Hennessy Sr

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

LETTER TO THE READERS

WANTED: An “All-Out” National Vaccination Program

Howard S. Hochster, MD, Julie M. Vose, MD, MBA

Anyone who has run a marathon knows that while the first 25 miles are no fun, it is the last 1.2 miles when you have to double down and drag yourself over the finish line.

This lesson has been widely ignored in the marathon development and logistic planning for vaccines against coronavirus disease 2019 (COVID-19). Somehow, we can't make it the last few feet to the arms of the awaiting public. Yes, we have pumped billions of dollars into Moderna for mRNA technology (actually, funded largely by NIH for the last decade) and purchased millions of doses from Pfizer, but with those millions of doses of Pfizer and Moderna vaccines now in the hands of our government, where is the requisite massive vaccination effort? We need to vaccinate 200 million Americans, requiring 400 million injections. Even if we get up to 1 million inoculations per day, this would take more than 1 year.

We have millions of doses sitting in state and county repositories, yet who is administering these vaccines? Are there extra staff to draw up syringes, set up vaccination stations, and register those receiving vaccine? Are there nurses to administer the vaccine in the hospitals that are already stretched beyond capacity with COVID-19 cases? Is there extra capacity among the pharmacists and nursing injectors at the CVS and Walgreens stores across the country? (Ask yourselves this question in light of your last wait in line for medication.)

At many health care institutions, pharmacists are arriving 2 hours early on a volunteer basis to draw up syringes every day; our nurses are volunteering days or shifts off to inject, hoping to reach the maximum number of injections per day that the supply will allow. But this will get us only so far. Our colleagues all have jobs and do not have the time to make this happen in a concerted, efficient, and massive way. And, that was before the intense increased burdens of the sick patients with COVID-19. The medical system is overworked, exhausted, and burning out. This says nothing about the number of health care professionals who will be needed when the general public starts to receive the COVID-19 vaccine.

We need a coordinated national effort involving the Red Cross, National Guard, and retired medical professionals. We need every auditorium and sports arena across the country to be set up with hundreds of stations, injecting thousands of patients per day. The sooner we get the 400 million injections in people's arms, the sooner the pressure will be relieved from our overburdened medical system and the sooner we can go back to some semblance of our pre-COVID-19 lives.

President Biden, we call on you to engage the troops and personnel necessary to get the job done. Letting the states figure out how to stagger across the finish line without additional personnel and resources is not the pathway to success that America needs. ■

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Pediatric Locally Advanced Synovial Sarcoma: What Would Be the Best Treatment Option?

Meri Petrosyan, MD^{1,2}; Anna Avagyan, MD^{1,2}; Arianna Mesrobian, BA²; Shushan Hovsepyan, MD^{1,2}; Zaven Koloyan, MD³; Gevorg Tamamyanyan, MD, PhD, MSc^{1,2}; Ruzanna Papyan, MD^{1,2}

¹Yerevan State Medical University, Yerevan, Armenia.; ²Pediatric Cancer and Blood Disorders Center of Armenia, Hematology Center after Prof. R.H. Yeolyan, Yerevan, Armenia.; ³Wigmore Clinic, Yerevan, Armenia.

THE CASE

A female patient, age 11 years, presented with a firm, palpable mass in the left lower quadrant of the

abdomen. Upon ultrasound imaging, the 3.5 cm × 5 cm lesion was assessed as a benign cyst and a laparoscopic resection of the mass was performed. The initial pathological evaluation reported a diagnosis of fibromyxoid sarcoma. However, after an additional immunohistochemical examination, the diagnosis was changed to grade III synovial sarcoma (CD45–, Bcl+, Desmin–, WT1–, SMA–, Ki65-15%) (**Figure 1**). Detection of t(X;18) (p11.2; q11.2) translocation was not yet available in Armenia at that time. The pathology report did not include the state of margins. CT and bone scans revealed no metastatic disease at the time.

■ **Figure 1.** Histopathology of the Lesion

Discussion

Despite the fact that synovial sarcoma (SS) is a rare disease, it is the second most common type of soft tissue sarcoma (STS) in children and adolescents after rhabdomyosarcoma. This subtype of neoplasms affects both children and adults, with its peak incidence occurring in the third decade of life.¹ Despite its name, SS can develop anywhere in the body, not just the joints. The most common location is the soft tissue of the extremities, especially in the large joints, followed by the upper extremities, trunk, abdomen, head, and neck.

What would be the best choice for further management of this patient?

- A. Observation
- B. Radiotherapy
- C. Resurgery, with further treatment including radiotherapy and chemotherapy
- D. Chemotherapy

➔ **TURN TO PAGE 58** for the answer and a discussion of this case by experts.

CORRECT ANSWER: C. The best choice for further management of this patient would be resurgery, followed by radiotherapy and chemotherapy

Continued from page 57

Specific detection of a t(X;18) (p11.2; q11.2) translocation is an important diagnostic tool for SS, but it was not available in Armenia at that time. However, given that, radiologically, the tumor is usually well defined, it is often misdiagnosed as a benign lesion. Tumors of this type tend to be overlooked by general physicians or surgeons because they can be surgically removed as a benign tumor or inflammatory lesion without the need for wide surgical margins.²⁻⁴ According to results of a study performed by

St Jude Children's Research Hospital, 81% of patients with a diagnosis of non-rhabdomyosarcoma STSs underwent unplanned resections before being referred to their institution. According to results of another study, residual disease was present in nearly half of the cases (48%) in patients who underwent such unplanned surgery.^{5,6}

In 2017, Gingrich et al performed a prospective study including 76 patients diagnosed with primary STS located in the trunk or extremities who had

undergone unplanned excision of the tumor. They concluded that 70% of the patients who underwent repeat excision after the initial unplanned tumor resection indeed had residual tumor.⁷

Commonly, a patient with STS is referred to an oncologist if a postoperative pathological evaluation reveals a malignancy, or if a local recurrence or distant metastases are detected, to plan reexcision with wider margins, adjuvant chemotherapy, or radiotherapy. Microscopic residual disease is often the result of the surgical removal of soft tissue sarcoma without proper preoperative imaging, biopsy, or correct execution of wide (R0) resection margins; it leads to high risk of local recurrence for patients with STS.⁵

In 2013, Umer et al performed a retrospective cohort study consisting of 135 patients in 2 groups: those who had planned tumor excisions (group 1; n = 84) and those who had unplanned tumor excisions (group 2; n = 51). Mean followup in group 1 (starting from the date of surgery) was 52.6 plus 39.8 months (median, 36 months). Minimum follow-up duration in group 2 (starting from the date of revision surgery) was 36 months. The incidences of local recurrence in group 1 and group 2 were 14.3% (n = 12) and 21.4% (n = 11), respectively. Distant metastasis occurred in 7.3% and 13.7% of the patients, respectively.⁸

Grimer et al concluded that unplanned surgery leads to higher rates of recurrence, metastasis, and overall fatality; they recommended that soft tissue masses be assessed and managed by specialized oncology teams.⁹ Similarly, Bhangu et al (2004) concluded that patients who were treated outside a specialized tumor center had a higher rate of local recurrence (39%) compared with those who were treated at specialized centers (19%).¹⁰

Therefore, **answer A** (observation) is not the preferred path for management for this patient, because there is support-

■ **Figure 2.** Painless Mass on the Abdominal Scar.

■ **Figure 3.** MRI: Grape-Shaped Mass in Abdominal Wall.

ing evidence that unplanned surgical removal of STS often leads to probable recurrence (both local and distant) and the inevitable need for more extensive measures.

The most important prognostic factors in STS are the presence of any metastases and the tumor's resectability, size, and location. The optimal approach to treat a localized synovial sarcoma includes wide excision of the tumor with clear margins, resulting in no loss of function. Wide reexcision, which is ideally done within 3 weeks of unplanned surgery, is the standard treatment in most hospitals.¹¹ In cases when reexcision is not possible, radiotherapy alone is the preferred treatment option, but some research results indicate that it has inferior local control compared with surgical treatment. Even in the case of positive margins, the necessary dosage of radiation is high and increases the risk of complications. Therefore, radiation alone (**answer B**) would have been a viable option only if reexcision would not have been possible to perform.^{6,7}

The choice of an adjuvant treatment regimen is based on factors including tumor size, grade, and margins. For high-risk tumors, the treatment includes radiotherapy in combination with chemotherapy. SS seems to have relatively more sensitivity to chemotherapy than

other STSs. The most commonly used chemotherapeutic agents in such a regimen are ifosfamide and doxorubicin, which showed higher response in SS than in other nonrhabdomyosarcoma soft-tissue sarcomas (NRSTSs).¹² Chemotherapy alone, without proper local control, cannot be curative. In the majority of studies, it is reserved as adjuvant treatment or in the palliative setting. Hence, performing chemotherapy without adequate surgical and/or radiotherapy will lead to the failure to control local disease, making **answer D** a poor choice.¹³

Pediatric NRSTSs have a poor prognosis without multimodal treatment. Ingley et al have recently outlined that for patients with localized disease who received multimodal therapy, including chemotherapy and radiotherapy, 5-year overall survival is 90.7% and event-free survival is 80.7%, based on risk classification.¹⁴ Given this information, the best course of action for this case is **answer C**, resurgery, along with further treatment including radiotherapy and chemotherapy.

Outcome

The patient's parents initially refused further treatment. One year later, the patient noticed a painless mass beneath the postoperative scar on the anterior

abdominal wall (**Figure 2**). The MRI revealed a grape-shaped, well-defined soft tissue mass in the left lower quadrant of the abdominal wall, measuring 15 cm (**Figure 3**). The CT showed left inguinal lymphadenopathy without signs of distant metastases. A bone scan revealed no abnormalities. A tumor biopsy confirmed disease relapse.

Overall, the child received 7 courses of chemotherapy with ifosfamide and doxorubicin (according to COG-ARST0332; outside of a clinical trial) and underwent 3D radiotherapy (70 Gy).¹²

Subsequently, a PET-CT was performed, showing lesions (ranging in size from 50 mm x 62 mm to 16 mm x 24 mm) on the anterior abdominal wall, extending into the left inguinal region with moderate metabolic activity (SUV_{max} , 2.84-3.03). Because of logistical issues, wide re-resection of the previous surgical scar, tumor bed, and the new palpable mass was performed in Armenia 4 months after the neoadjuvant treatment. Soft tissue reconstruction consisted of a rectus femoris pedicled musculocutaneous flap. Final pathology showed no viable tumor.

As of October 2020, the child was disease free. She had painless lymphedema of the involved extremity but was able to participate in daily life activities. ■

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ABOUT THE SERIES EDITORS:

Maria T. Bournon, MD, is associate professor, Head 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.

Key Points

- Synovial sarcomas are often mistreated with unplanned tumor resection.
- Attention from specialists early in the course of SS can minimize the risk of recurrence, metastases, and the necessity for resurgery, all of which are increased with unplanned tumor resection.
- Chemotherapy alone does not provide sufficient local control of the tumor.
- Resurgery, in conjunction with radiotherapy and chemotherapy, is the best choice of management for this patient.

Koloyan

is an orthopedic surgeon and the director of the Wigmore Clinic.

Hovsepian

is a pediatric oncology and hematology fellow at the Yerevan State Medical University and Pediatric Cancer and Blood Disorders Center of Armenia.

Mesrobian

is a visiting scientist at the Pediatric Cancer and Blood Disorders Center of Armenia.

Petrosyan

is a pediatric oncology and hematology fellow at the Yerevan State Medical University and Pediatric Cancer and Blood Disorders Center of Armenia.

Avagyan

is a pediatric oncology and hematology fellow at the Yerevan State Medical University and Pediatric Cancer and Blood Disorders Center of Armenia.

Papyan

is an assistant professor at the Department of Pediatric Oncology and Hematology, Yerevan State Medical University and chair of the Musculoskeletal Tumors Working Group, Pediatric Cancer and Blood Disorders Center of Armenia.

Tamanyan

is the chairman of the Department of Pediatric Oncology and Hematology, Yerevan State Medical University and the head of the Pediatric Cancer and Blood Disorders Center of Armenia, Hematology Center after Prof. R.H. Yeolyan. He is also the chairman of the ASCO's IDEA Working Group.

Phase 2 LEAP-005 Study Yields Promising Results Among Multiple GI Cancer Types

The combination therapy of lenvatinib (Lenvima) plus pembrolizumab (Keytruda) produced positive antitumor outcomes in previously treated patients with advanced gastric cancer, advanced or metastatic microsatellite instability-high (MSI-H) or mismatch repair (MMR)-deficient colorectal cancer, and advanced biliary tract cancer, according to results presented at the 2021 American Society of Clinical Oncology Gastrointestinal Cancers Symposium.

The phase 2 LEAP-005 trial (NCT03797326), which aimed to evaluate the safety and efficacy of the lenvatinib/pembrolizumab combination across a number of different solid tumor types, enrolled patients in 7 different cohorts. Only data specific to 3 gastrointestinal cancer types were presented at the meeting.

Gastric Cancer Cohort Results

The gastric cancer cohort¹ enrolled 31 patients (87% male) with metastatic or unresectable gastric cancer who had received at least 2 prior lines of therapy. More than half (58%) of the patients were 65 years or younger, and 71% had a PD-L1 combined positive score of 1.

Patients received lenvatinib 20 mg once daily plus pembrolizumab 200 mg every 3 weeks for up to 35 cycles (approximately 2 years) of pembrolizumab or until disease progression, unacceptable toxicity, or consent withdrawal. In patients who experienced a clinical benefit, treatment with lenvatinib could continue beyond 2 years.

Overall response rate (ORR) and safety were the primary end points of the study, with secondary end points including disease control rate (DCR; which included complete response [CR], partial response [PR], and stable disease [SD]), duration of response (DOR), progression-free survival (PFS), and overall survival (OS).

Although 19 patients (61%) discontinued treatment, the ORR was 10% (95% CI, 2%-26%) at the time of data reporting. One patient had a CR (3%), 2 had a PR (6%), and 12 patients (39%) had SD, leading to a DCR of 48% (95% CI, 30-67). Median PFS was 2.5 months (95% CI, 1.8-4.2) and median OS was 5.9 months (95% CI, 2.6-8.7). However, median DOR was not reached (range, 2.1+ to 2.3+ months).

Follow-up imaging was done every 9 weeks for 54 weeks, then every 12 weeks until week 102, and every 24 weeks beyond that.

In terms of safety, 90% of patients experienced treatment-related adverse events (TRAEs), 13 (42%) of whom experienced grade 3 to 5 AEs. One patient died as a result of a treatment-related hemorrhage. Immune-mediated AEs were less frequent, found in 8 patients (26%), and included hypothyroidism (n = 5), hyperthyroidism (n = 2), and pneumonitis (n = 1). No infusion-related reactions occurred.

Colorectal Cancer Cohort Results

In the colorectal cancer cohort, 32 patients with advanced or metastatic MSI-H or MMR-deficient colorectal cancer received lenvatinib 20 mg once daily plus pembrolizumab 200 mg every 3 weeks for up to 35 cycles (as in the gastric cancer cohort). Investigators determined that treatment with lenvatinib could continue beyond the 35 cycles in patients who saw clinical benefit.²

The participants' median age was 56 years, and 91% of patients (n = 29) had received 2 prior lines of therapy.

The study's primary end points were ORR and safety, with secondary end points including DCR, DOR, PFS, and OS. The median time from first dose to data cutoff was 10.6 months (range, 5.9-13.1).

At data cutoff, the ORR was 22% (95% CI, 9%-40%) and the DCR was 47% (95% CI, 29%-65%). Median PFS

was 2.3 months (95% CI, 2.0-5.2) and median OS was 7.5 months (95% CI, 3.9 to not reached [NR]). Median DOR was not reached (2.1+ to 10.4+ months).

Safety data indicated that grade 3 to 5 TRAEs occurred in 16 patients (50%). Three patients discontinued treatment as a result of TRAEs, including a grade 2 ischemic stroke (n = 1), grade 3 increased liver transaminases (n = 1), and grade 5 intestinal perforation (n = 1).

Biliary Tract Cancer Cohort Results

The biliary tract cancer cohort³ included 31 patients with metastatic and/or unresectable disease with progression after 1 prior line of therapy. The treatment schedule was the same as in the gastric and colorectal cancer cohorts, with primary end points of ORR and safety. Secondary end points included the combined DCR, DOR, PFS and OS.

The median time from first dose to data cutoff was 9.5 months (range, 3.1-11.9), with 16 patients remaining on treatment at data cutoff. There were 3 (10%) PRs and 18 (58%) SDs. ORR was 10% (95% CI, 2%-26%), and DCR was 68% (95% CI, 49%-83%). Median DOR was 5.3 months (range, 2.1+ to 6.2). Median PFS was 6.1 months (95% CI, 2.1-6.4) and median OS was 8.6 months (95% CI, 5.6 to NR).

In terms of safety, 30 patients (97%) experienced TRAEs, 15 (48%) of whom had grade 3 or 4 TRAEs. In a presentation on the findings, lead author Luis Villanueva, MD, MSc, noted that the most frequent TRAEs included hypertension (42%), dysphonia (39%), diarrhea (32%), fatigue (32%), and nausea (32%).

Fourteen patients (45%) experienced immune-mediated AEs, including hypothyroidism (n = 11; 36%), hyperthyroidism (n = 2; 6%), and hepatitis (n = 2; 6%). One patient (3%) had an infusion-related reaction, and 2 patients (6%) discontinued treatment due to treatment-related AEs of myocardial

tis and pyrexia (n = 1 each). No treatment-related deaths occurred. ■

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Pembrolizumab-Lanreotide Combination Shows High Response Rates for Patients With GEP-NETs

Roughly 40% of patients with advanced, progressive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) treated with pembrolizumab (Keytruda) in combination with lanreotide (Somatuline Depot) achieved stable disease, according to results from the phase 1b/2 PLANET clinical trial (NCT03043664).¹

In this study, 22 patients with GEP-NETs who had been treated with a median of 2 prior systemic therapies (range, 1-9) were treated with 90 mg of lanreotide and 200 mg of pembrolizumab every 3 weeks until disease progression or intolerable toxicity. A median of 6 doses of pembrolizumab (range, 2-15) and 7 doses of lanreotide (range, 2-15) were administered.

Median age at the time of enrollment was 60.9 years (range, 51.1-82.0). Twelve of the patients were male, and 10 were female. To be eligible for the study, participants were required to have a diagnosis of a nonresectable, recurrent,

or metastatic well- or moderately differentiated GEP-NET; disease progression in the last 12 months; receipt of prior somatostatin analogue therapy; a minimum of 1 measurable lesion based on RECIST 1.1 criteria; ECOG performance status of 0 or 1; adequate organ function; and a tumor mitotic rate of 20/10 hpf or less and/or Ki67 index of 20% or less.

The median time since diagnosis for all patients was 5.3 years; 6 patients had received prior locoregional therapy and 3 patients had received prior external beam therapy. Of the 12 tumors that were analyzed, 4 had detectable PD-L1 expression and 11 had tumor-infiltrating lymphocytes.

Thirty-nine percent of patients showed stable disease (SD) and 52% of patients had progressive disease (PD). ORR, as measured by irRECIST to better assess the effect of immunotherapeutic agents, included 43% of patients with SD and 48% with PD, while 9% of patients were not evaluable.

Secondary end points were progression-free survival (PFS) and overall survival (OS). The median PFS was 5.4 months (95% CI, 1.7-8.3) and median OS at a median follow-up of 15 months was not reached.

Six of the 22 patients (27.3%) experienced serious treatment-related adverse events (TRAEs) including abdominal pain, pneumonitis, colitis, and hyperglycemia, which were all related to treatment with pembrolizumab. The most common TRAE was hypothyroidism (23%), with other notable TRAEs including colitis (9%), hyperglycemia (14%), and pneumonitis (5%). Three patients (13.6%) discontinued treatment due to AEs.

No new safety signals were identified in the study. ■

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Bemarituzumab is Effective for Patients With FGFR2b-Positive GEJ

Results of the phase 2 FIGHT study (NCT03694522), which compared treatment with bemarituzumab plus mFOLFOX6 with treatment of placebo plus mFOLFOX6, demonstrated a 56% reduction with bemariuzumab in the risk of disease progression or death for patients with FGFR2b-positive advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma.¹

For patients with FGFR2b overexpression via immunohistochemistry (IHC) 2+/3+ at 10% or more (n=96), the median progression-free survival (PFS) was 14.1 months in the bemarituzumab arm versus 7.3 months in the placebo arm (HR, 0.44; 95% CI, 0.25-0.77). The 1-year PFS rates were 57.0% and 26.4% in the combination and placebo arms, respectively.

In those with FGFR2b overexpression via IHC 2+/3+ at 5% or more (n = 118), the median PFS was 10.2 months in the bemarituzumab arm vs 7.3 months with the placebo arm (HR, 0.54; 95% CI, 0.33-0.87). The 1-year PFS rates were 56.3% and 28.6%, respectively.

In the intent-to-treat (ITT) population, the median PFS was 9.5 months and 7.4 months for the combination and placebo arms, respectively (HR, 0.68; 95% CI, 0.44-1.04; P = .0727). The 1-year PFS rates were 52.5% and 33.8%, respectively.

Prior single-agent activity with bemarituzumab in later-line FGFR2b-positive gastric cancer elicited an 18% objective response rate (ORR) with no dose-limiting toxicities.²

This study randomized patients 1:1 to receive bemarituzumab with mFOLFOX6 (n = 77) or placebo/mFOLFOX6 (n = 76), every 2 weeks.

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Guidelines for Palliative Treatment of Spinal Metastases: Choosing Between Stereotactic Body Radiation Therapy and Conventional Fractionation

Jacob Eckstein, MD; Daniel Koffler, MD; Bhupesh Parashar, MD, DrPH; Louis Potters, MD; and Ashwatha Narayana, MD

ABSTRACT: Symptomatic spinal metastasis is a frequent complication of cancer that had been treated, until relatively recently, with primitive techniques to modest radiation dose levels, with a baseline assumption of limited survival and poor patient performance in that setting. In the era of targeted and personalized therapies, many patients are living longer and more functionally and are able to manage their disease on the model of chronic illness. Given these developments, an attractive option is the use of stereotactic body radiation therapy (SBRT) to deliver high biologically effective doses of radiation conformally to maximize the palliative gains of treatment. However, randomized data to guide practice are scarce. We review the extant literature and present an algorithmic approach to selecting patients with metastatic disease for palliative spinal SBRT favoring the results of available randomized studies and remaining within the safety constraints supported by evidence from randomized trials.

Background

Spinal metastasis is noted in many common primary cancer sites such as breast, prostate, and lung, making palliation of symptomatic spinal metastases both a frequent and heterogeneous indication for radiation therapy.¹

Historically, palliative radiation therapy for spinal disease was delivered using

2-dimensional (2D) planning techniques that delivered moderate doses of radiation to the involved portion of the spine over 5 to 15 treatments; beams coming from the anterior and posterior directions were placed and shaped using the location of involved spinal levels on a radiograph.^{2,3} Treatment with 2D technique is limited both by the detail provided by radiographs

and the inability to spare the spinal cord and viscera located near the treatment target. Over time, the advent of CT and MRI, along with paradigm-shifting improvements in radiation planning and delivery technologies, facilitated the development of intensity modulated radiation therapy (IMRT). IMRT uses accurate 3D anatomical data, dynamic beam shaping, and inverse planning software to create radiation plans that treat the target to a desired dose and selectively spare organs at risk with millimeter-level accuracy.⁴ IMRT has made it possible to treat patients with ablative intent using larger doses in fewer treatments than ever before, a practice termed stereotactic body radiotherapy (SBRT).

In palliation of spinal metastases, SBRT offers the prospect for improvements in pain palliation and local control with the delivery of ablative doses, making the use of this technique compelling to many radiation oncologists.⁵⁻⁸ Nevertheless, randomized data to guide the selection of spinal metastasis patients for SBRT versus conventionally fractionated external beam radiotherapy (EBRT) are sparse. While we await the reporting of further randomized data, the need for objective

decision-making guidelines in this setting is pressing. We therefore present the following effort to synthesize the present literature into guidelines for radiation oncologists to prescribe treatment for spinal metastasis grounded in the best available evidence.

This guideline is meant to guide the use of radiotherapy to treat spinal metastases *only with palliative intent*. If the patient is considered to be oligometastatic and meets criteria for recently published phase 2 trials^{9,10} in which ablative therapies have been suggested to prolong survival, their treatment should not be influenced by this guideline but rather by a decision focused around potential overall survival benefit.

Additionally, spinal radiation should be delivered only after the necessity of prior surgical intervention has been ruled out. Neurosurgical consultation should be obtained if active neurological symptoms are present (due to myelopathy caused by malignant cord/cauda equina compression) or if significant mechanical instability exists, as assessed by the Spinal Instability Neoplastic Score (SINS)(**Table 1**); such instability could be exacerbated by radiotherapy-induced cytoreduction¹¹.

Assuming that neurosurgical intervention has been diligently considered, the delivery of palliative radiation therapy for spinal metastases should be guided as follows:

Will conventional palliative regimens (20 Gy in 5 fractions, 30 Gy in 10 fractions) provide durable control?

The likelihood of response to conventionally fractionated palliation for bone metastases is stratified by tumor histology.^{6,12} Primary tumor histologies for which conventional palliation is more likely to be successful in eliciting a significant tumor response include breast, ovarian, small cell, seminoma, and hematologic malignancies.^{13,14} For example, a Radiation Therapy Oncology Group (RTOG) study published in 1982 found superior pain relief in patients with breast and

TABLE 1. Spinal Instability Neoplastic Score (SINS)³⁴

	Score
Location	
Junctional (occiput-C2, C7-T2, T11-L1, L5-S1)	3
Mobile spine (C3-C6, L2-L4)	2
Semirigid (T3-T10)	1
Rigid (S2-S5)	0
Pain*	
Yes	3
Occasional pain but not mechanical	1
Pain-free lesion	0
Bone lesion	
Lytic	2
Mixed (lytic/blastic)	1
Blastic	0
Radiographic spinal alignment	
Subluxation/translation present	4
De novo deformity (kyphosis/scoliosis)	2
Normal alignment	0
Vertebral body collapse	
>50% collapse	3
<50% collapse	2
No collapse with >50% body involved	1
None of the above	0
Posterolateral involvement of spinal elements**	
Bilateral	3
Unilateral	1
None of the above	0

*Pain improves with recumbency and/or pain with movement/loading of spine

**Facet, pedicle, or costovertebral joint fracture or replacement with tumor

prostate histology compared with those with lung cancer.¹⁵ Moderately radioresistant histologies such as thyroid and colorectal cancers and non-small cell lung cancer (NSCLC) and, even more so, significantly radioresistant histologies such as sarcoma, melanoma, and renal cell carcinoma are unlikely to elicit favorable responses with EBRT.^{11,12} Radioresistant histologies include sarcoma, melanoma, renal cell carcinoma, thyroid and colorec-

tal cancers, and NSCLC.^{6,12-14} Patients with favorable histology are more likely to remain ambulatory for longer periods of time and have good pain response after conventional radiation therapy.^{12,16}

Because conventional palliation will likely provide poor results in radioresistant histologies, is SBRT a better option?

The poor outcomes with conventional

TABLE 2. **Bilsky Cord Compression Score**³⁵

Score	Definition
0	Bone-only disease
1a	Epidural impingement, without deformation of the thecal sac
1b	Deformation of the thecal sac, without spinal cord abutment
1c	Deformation of the thecal sac with spinal cord abutment, but without cord compression
2	Spinal cord compression, but with CSF visible around the cord
3	Spinal cord compression; no CSF visible around the cord

Key: CSF, cerebrospinal fluid.

palliation in radioresistant spinal metastases have led to a shift in practice toward SBRT (16-24 Gy in 1 fraction, 24-30 Gy in 3 fractions) for these lesions. These fractionation schemes result in an enhanced biologically effective dose (BED), double-stranded DNA breaks, immunogenicity, and vascular supply disruption relative to conventional fractionation.^{17,18} Multiple patient series⁶⁻⁸ and a randomized phase 2 trial⁵ have shown that these biological differences translate into improved clinical local control and pain relief when SBRT is used for spinal metastases, with local control at 24 months post treatment ranging from 84% to 98%.⁶⁻⁸ A phase 2/3 randomized trial investigated 16 Gy in 1 fraction compared with 8 Gy in 1 fraction with a primary end point of pain control at 3 months, and although the phase 2 portion of the study found 16 Gy/1 fraction to be safe,¹⁹ the phase 3 portion's preliminary results reported at the 2019 national meeting of the American Society for Radiation Oncology did not find any improvement in pain control at 3 or 6 months after treatment. Although 3-month pain control is felt to be an important end point, previously mentioned data sets suggest that SBRT is more likely to provide durable pain and local control over time.

Importantly, the available randomized

data select a primary end point of pain relief at 3 months post treatment.¹⁹ As metastatic cancer is fundamentally a systemic disease, this end point provides for a good balance between optimization of quality of life and expected survival. Pain relief at 6 months, prevention of neurological events, etc, are legitimate secondary end points, but they should not supervene upon the 3-month end point in terms of guiding treatment decisions. Likewise, outside of the context of treatment for control of oligometastatic disease, the theoretical biological prospect of improved local control at the treated site is not helpful in guiding management of patients who are overwhelmingly likely to develop further spinal disease progression.

Could weaknesses of RTOG 0631 underrepresent the therapeutic potential of SBRT with regard to its primary end point of short-term pain control?

In addition to the limited follow-up in RTOG 0631, which raises questions about the durability of the pain response demonstrated by the 8-Gy arm, some have suggested that 16 Gy may be an inadequate single-fraction dose to maximize the benefit of disease control.²⁰ Sprave et al reported in a randomized phase 2 trial that utilizing 24 Gy in 1

fraction compared with 30 Gy in 10 fractions did show that complete pain response in the SBRT group was significantly more likely at 6 months (53% vs 10%; $P = .0034$) and trended toward significance at 3 months (43% vs 17%; $P = .0568$).⁵ Because 30 Gy in 10 fractions was deemed to be equivalent to 8 Gy in 1 fraction with respect to pain control in a randomized phase 3 trial,²¹ the phase 2 data from Sprave et al showing superiority of 24 Gy/1 fraction over 30 Gy/10 fractions in conjunction with RTOG 0613 reporting equivalency of 16 Gy/1 to 8 Gy/1 suggest 16 Gy may be an inadequate single fraction dose for maximal pain response.

This concern is bolstered by a retrospective series by Yamada et al consisting of 657 patients and 811 lesions; the results indicated inferior local control when the dose received by 95% of the gross tumor volume (GTV D95) was less than 18.3 Gy.⁸ Although the entire cohort experienced an impressive local failure rate of only 3.1% at 48 months, those who received GTV D95 < 18.3 Gy had a failure rate of 14% and those with a GTV D95 > 18.3 Gy had a failure rate of 2.5%.⁸ A larger SBRT dose is being employed in a phase 3 trial (CCTG-SC24) run by the Canadian Cancer Trial Group, which is comparing 24 Gy/2 fractions with 20 Gy/5 fractions in the treatment of spinal metastases, with a primary outcome of 3-month pain control. Assuming an alpha/beta ratio of 10, BED10 of the SBRT regimen used in CCTG-SC24 (52.80 Gy) is similar to the dose cut point for superior local control described by Yamada et al (51.79 Gy) and significantly larger than the BED of the dose used in SBRT arm of RTOG 0613 (41.6 Gy). In summary, we cannot generalize the results of RTOG 0631 to SBRT with higher doses, and recently closed phase 3 trials such as CCTG-SC24 will help the community decide if SBRT dose escalation can improve pain control beyond what is possible with conventional fractionation.

Despite the previously mentioned

concerns grounded in retrospective and phase 2 evidence, RTOG 0613 has supplied the only randomized phase 3 evidence that compares SBRT with conventional palliation of spine metastases. Its 3-month pain response end point minimizes risk of confounding in pain reporting due to new symptomatic metastases and allows adequate time for cytoreduction and pain response. Additionally, 16 Gy, in contrast with 24 Gy, is a dose that can be delivered in a single fraction without invasive cord localization procedures such as CT myelogram, which many institutions will not have available. Thus, until we have results of other phase 3 trials, such as CCTG-SC24, RTOG 0631 should guide clinical practice for all patients in whom 3-month or 6-month pain control is the outcome of interest.

What are the limits of eligibility for SBRT with respect to spinal disease burden and proximity of disease to the cord?

In contrast with conventional fractionation, which can be safely delivered over multiple dose levels simultaneously using a 2D setup with acceptance of planning target volume (PTV) dose spill into the spinal cord, SBRT must be delivered with meticulous motion control and IMRT planning in order to enable ablative dose delivery to the vertebrae while avoiding the cord. Despite advancements in treatment planning and high conformality achieved by these techniques, concern remains about treating disease with high-risk characteristics such as epidural extension, cord compression, paraspinal extension, and multiple consecutive vertebrae involved. For example, the results of RTOG 0613 deemed any lesion within 3 mm of the spinal cord ineligible for randomization, although lesions with Bilsky 1a and 1b cord compression (Table 2) were still permitted as long as they were at least 3 mm away from the cord. Additionally, no more than 2 consecutive vertebrae could be included. In CCTG-SC24, patients with up to 3 consecutive

TABLE 3. Rerevised Tokuhashi Score³³

Factors	Score
General condition (KPS)*	
Poor and moderate (KPS 10-70)	0
Good (PS 80%-100%)	2
Extraspinal bone metastases	
≥3	0
1-2	1
0	2
Number of metastases in the vertebral body**	
≥2	1
1	2
Metastases to major internal organs	
Unremovable	0
Removable	1
No metastases	2
Primary site of the cancer	
Lung, osteosarcoma, stomach, bladder, esophagus, pancreas	0
Liver, gallbladder, unidentified	1
Others	2
Kidney, uterus	3
Rectum	4
Thyroid, breast, prostate, carcinoid tumor	5
Neurological status	
Complete (Frankel A, B)	0
Incomplete (Frankel C, D)	1
None (Frankel E)	2

Key: KPS, Karnofsky Performance Score; RTS, Rerevised Tokuhashi Score.

This remodified version of RTS was raised according to the results in the meta-analyses and remodifications on the cutoff of KPS(*) and number of involved vertebrae(**) were conducted for the scoring system. The patients with KPS 10-40/50-70 and patients with single/double involved vertebrae were merged.

vertebrae requiring treatment were eligible for randomization, and no distance requirement was set forth with respect to cord compression. Rather than distance, neurologic deficit (eg, motor, bowel, bladder dysfunction) due to cauda equina syndrome or cord compression was used as an exclusion criterion.²² With respect to paraspinal extension, RTOG restricted the size of paraspinal lesions to

no larger than 5 cm, while CCTG does not have a restriction for paraspinal extension.

The previously mentioned high-risk features increase the risk of excessive doses of radiation to the spinal cord and other regional organs at risk (OARs), due to close proximity of disease to the cord or increased volume of disease (eg, epidural extension, cord compression, multiple

consecutive vertebrae treated), increased dose spill into other important regional OARs (eg, large-volume paraspinal extension and multiple consecutive vertebrae), and inadequate setup accuracy (eg, multiple consecutive vertebrae in a field). Additionally, cord compression has been associated with increased risk for local relapse. In a series of 98 spinal lesions including 60 with epidural extension treated with multifraction SBRT, Mehta et al reported that Bilsky grade trended toward increased risk of local failure ($P = .09$).²³ Despite epidural extension being present in 61% of lesions, the patients in that series experienced a local control rate of 93% at 6 months and 84% at 1 year. Toxicity was also well controlled, with 4.2% of treated patients experiencing vertebral body fracture and no reported radiation myelopathy.²³ Kowalchuk et al evaluated high-risk treatments—defined as those including at least 2 consecutive vertebrae, epidural involvement of the tumor, or paraspinal soft tissue involvement of the tumor—in 54 patients with 62 lesions. All lesions were treated with 24 Gy in 3 fractions, and at a median follow-up of 14.36 months, local failure was only 8% and pain had improved in 76% of patients. Toxicity outcomes were excellent, with no cases of myelopathy and no new vertebral fractures of the treated vertebrae.²⁴ The outcomes in these series, along with the recommendations of other recently published reviews,^{20,25} indicate that treating with a hypofractionated approach is an effective and safe accommodation for patients with paraspinal extension, moderate cord compression (Bilsky 1a, 1b, and occasionally 1c), and involvement of multiple consecutive vertebral levels. These retrospective series indicate that there may be room for expanding the eligibility for SBRT in the future, but at this time there are not phase 3 data indicating safety for SBRT to spinal metastases that don't meet the RTOG 0631 eligibility criteria.¹⁹

How many contiguous spinal levels can be treated with SBRT?

RTOG 0631 restricted SBRT to at most 2 contiguous spinal levels.¹⁴ Chief concerns in the application of SBRT to disease that occupies 3 or more spinal levels include exacerbated setup error and toxicity to adjacent long OARs such as the spinal cord and esophagus. Experience has shown that numerous centers do prescribe SBRT to multilevel spinal disease. Wang et al, as noted above, have shown that concerns of setup error can be alleviated by appropriate immobilization and utilization of a 6D couch, such that as many as 9 contiguous levels can be treated without exceeding 1-mm residual error. However, these findings do not apply above the level of T2, where natural spinal curvature amplifies setup risks, and we consequently counsel caution in the treatment of bulky disease superior to T2. Well-established protocols have been accepted to treat, for example, central lung tumors to significantly greater BED¹⁰ than is given in spine SBRT, as per RTOG 0813. We defer to the constraints used in such protocols and suggest that treatment of multilevel disease should not be restricted by concern for normal tissue dose, provided these constraints can be met. Conversely, SBRT should not be utilized when coverage goals cannot be met without violating those constraints.

When treating consecutive levels, bulky lesions, or lesions with epidural extension, how can we ensure the safety of treatment with respect to OARs if treating with SBRT compared with conventional palliation?

As with all radiation treatments, OAR dose must be kept below the established organ-specific constraints to ensure safety. Accurate contouring of OARs is important for accurate dose calculation. Additionally, if the patient requires more radiation in the future, an understanding of the cumulative dose received across

multiple treatments will be necessary to build a safe treatment plan. The proper constraint for a given OAR depends on the number of fractions used, due to changes in the BED-dependent fraction size. One of the first sets of guidelines about safe OAR constraints in SBRT was published by Timmerman et al in 2008.²⁶ These were followed shortly after by new but similar guidelines in 2010 from the American Academy of Physicists in Medicine (AAPM), which published the TG 101 report,²⁷ and the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) group effort in 2010.²⁸ As an update to the AAPM TG 101 dose constraint guidelines, Saghal et al published an updated set of recommendations for spinal cord constraints in 2019.²⁹ At our institution, we follow TG 101 guidelines for OAR constraints during treatment of spinal metastases with SBRT.

Although the TG 101 and QUANTEC guidelines report constraints for the cord itself, many physicians choose to account for movement of the cord within the spinal canal by adding a 1- to 3-mm margin around the cord to create a planning OAR volume (PRV). Alternatively, the avoidance structure can be defined as the thecal sac, which applies an anatomically defined margin of approximately 1.5 mm beyond the spinal cord. In this case, the size of the margin varies among spinal segments, with the largest typically in the upper cervical spine.²⁹ It should be noted that when reviewing OAR constraints in literature, the presence and size of PRV margin varies by report, which makes aggregating data and drawing conclusions from the literature as a whole difficult. These inconsistencies among reports were acknowledged in the 2019 guidelines published by Saghal et al, and they proposed reporting standards for subsequent case series evaluating radiation myelitis.

Furthermore, we propose that PTV volume and OAR definitions in spinal SBRT should adhere strictly to the

FIGURE. Spinal SBRT vs EBRT Decision Tree

Key: EBRT, external beam radiation therapy; RRTS, rerevised Tokuhashi Score; RTOG, Radiation Therapy Oncology Group; SBRT stereotactic body radiation therapy; SINS, Spinal Instability Neoplastic Score

RTOG guidelines governing the available randomized data. Practically speaking, this means that an inability to meet requirements for both clinical target volume/PTV coverage and OAR constraints should rule out the use of SBRT, at least until such time as more liberal guidelines are validated in a randomized trial. In particular, RTOG makes use of the MRI-defined spinal cord as an OAR, and this should not be substituted with a spinal canal OAR or replaced with a non-MRI-defined structure. Likewise, given the available safety data, SBRT reirradiation of volumes previously treated with conventional EBRT, but not

volumes previously treated with SBRT, is an option.¹⁴

Recommendations

The following recommendations are presented algorithmically in the **Figure**. Because 3-month pain control has been shown to be noninferior to conventional palliation and we have reasonable suspicion to believe that long-term local control and pain control might be better with SBRT, the proper selection of palliative therapy for patients with radioresistant histology depends on their expected survival. Multiple survival scoring systems have been proposed for patients with

spinal metastases including the revised Tokuhashi score,³⁰ the Bauer modified score,³¹ and the Tomita score.³² These survival scores are all greater than 10 years old and lag behind the previous decade's innovations in systemic therapy, surgery, and radiotherapy; thus, they may underestimate survival. Of the above scoring systems, the Tokuhashi scale was subject to a robust systematic review and meta-analysis published in 2018,³³ and for that reason we defer to the rerevision of the Tokuhashi score in adducing patients' estimated survival (**Table 3**).³³

■ Patients with oligometastatic disease being treated with the aim of dura-

ble long-term control and possible improved survival based upon promising findings with the use of SBRT are outside and beyond the scope of these guidelines.

- Initial consideration should be made for surgical evaluation. Patients with definite or indeterminate spinal instability, defined as a SINS score >6, should be referred to neurosurgery prior to radiotherapeutic decision-making and considered for RT only upon clearance from neurosurgery.
- Patients with a stable spine and a treatment aim of palliation can be considered for SBRT. Nevertheless, those who do not meet RTOG 0631 eligibility criteria should be treated with conventional EBRT. For those with disease in more than 2 consecutive vertebrae per site, >3 nonconsecutive sites, or any disease within 3 mm of the spinal cord, conventional radiotherapy is recommended at this time, because RTOG 0631 excluded patients outside these parameters and safety and efficacy data do not currently support exceeding these constraints.¹⁹
- In patients who meet RTOG 0631 criteria, we stratify by survival. For patients with estimated survival less than 6 months, equivalent to a rerevised Tokuhashi score (RRTS) of 0-8, it is likely that 3-month pain control may be the most relevant outcome, so we recommend conventional palliation for initial treatment regardless of histology.

- For patients with estimated survival greater than or equal to 1 year, equivalent to RRTS 12 to 15, we favor an SBRT approach unless contraindicated by other considerations (such as highly radiosensitive histology such as seminoma, myeloma, lymphoma, or neuroendocrine tumor).
- For patients with estimated survival between 6 months and 1 year, equivalent to RRTS 9 to 11, careful individualized selection of candidates for SBRT is favored. Radioresistant histology in such cases weighs in favor of offering SBRT and radiosensitive histology weighs against it.
- Patients who progress after an initial course of conventional radiotherapy can be reirradiated by either conventional or SBRT technique, and the foregoing algorithm applies mutatis mutandis. However, SBRT is not an option for reirradiation of volumes previously treated by SBRT, regardless of other considerations, until safety data from randomized trials are available to validate this application of SBRT. ■

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For full reference list, visit cancernetwork.com/SBRTguidelines

Eckstein

is a resident physician in the Department of Radiation Medicine, Northwell Health Cancer Institute and Zucker School of Medicine.

Koffler

is a resident physician in the Department of Radiation Medicine, Northwell Health Cancer Institute and Zucker School of Medicine.

Parashar

is a radiation oncologist in the Department of Radiation Medicine, Northwell Health Cancer Institute and Zucker School of Medicine.

Potters

is chairman of the Department of Radiation Medicine, Northwell Health Cancer Institute and Zucker School of Medicine.

Narayana

is a radiation oncologist in the Department of Radiation Medicine, Northwell Health Cancer Institute and Zucker School of Medicine.

IN A WORLD FILLED WITH COVID-19...

CIN CAN STRIKE AT ANY MOMENT

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With the ongoing threat of chemotherapy-induced neutropenia (CIN), the COVID-19 pandemic is making oncologists and their care teams revisit their approach as they use aggressive regimens to treat their patients with cancer. Along with this, current treatment guidelines are now recommending the expanded prophylactic use of granulocyte-colony stimulating factors (G-CSFs) to intermediate-risk cancer patients as well.¹

When your patients are left unprotected, particularly in Cycle 1,² CIN may lead to life-threatening events, such as fever, infection, and hospitalization³—severely disrupting the predictability of your treatment plan. These chemotherapy delays and decreases can ultimately impact outcomes and decrease overall survival.⁴⁻⁶

It's time to take a crucial new look at CIN, the dire consequences of leaving patients unprotected, and how the COVID-19 pandemic is changing guidelines as well as your approach to providing the best standard of care.

**TO LEARN MORE, VISIT
[CCINRisk.com](https://www.ccinrisk.com)**

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MEET OUR EXPERT

Gomella is professor and chair, Department of Urology, Thomas Jefferson University, and clinical director of the Sidney Kimmel Cancer Center Network.

Redefining Prostate Cancer Care

“It’s been an amazing 10 years”

The past decade has seen a sea change in the treatment of prostate cancer. The implementation of genetic sequencing and the rise of targeted therapies have led to tailored treatment regimens and positive outcomes for often even the most advanced disease.

Ahead of the *14th Annual Interdisciplinary Prostate Cancer Congress*, ONCOLOGY® sat down with Leonard G. Gomella, MD, professor and chair of Thomas Jefferson University Hospital’s Department of Urology and clinical director of the Sidney Kimmel Cancer Center Network, to discuss 10 years of breakthroughs for patients with prostate cancer and the hope that continued research will fully transform prostate cancer from a deadly disease into a chronic, manageable condition.

Q: Can you discuss some of the recent advances in prostate cancer, and in genitourinary (GU) cancers as a whole?

GOMELLA: It’s been an amazing 10 years, particularly in prostate cancer, where we’ve had so many new FDA approvals. But we’ve also had approvals in other areas—in bladder cancer, [certainly], and of course we now have so many different drugs in kidney cancer.

At the upcoming [New York GU®] meeting, we’ll talk a little bit about what’s happened over

the past year in prostate cancer. The developments in biomarkers and genetics have been explosive. We now have circulating tumor DNA that can be evaluated in patients with prostate cancer to determine genetic susceptibility not only to the disease but to new medications. This is a big breakthrough. We have PARP inhibitors now that were just approved for advanced metastatic castration-resistant prostate cancer (mCRPC), opening up a whole new spectrum of oral agents for the management of prostate cancer. We’ve also had FDA approval for an oral agent, a luteinizing hormone-releasing hormone (LHRH) antagonist, for the treatment of advanced prostate cancer. So, many men who didn’t like their shots will now be able to take a pill when they’re undergoing androgen deprivation therapy.

Another big area in prostate cancer, which we’ll discuss at our meeting, is the new PET imaging: the prostate-specific membrane antigen (PSMA)-PET scan. PSMA-PET scan is designed to pick up metastases from prostate cancer at a very low prostate-specific antigen (PSA) level, so it’ll be really taking off, [especially because] it is now FDA approved. Right now, outside a clinical trial, the only place in the United States you [can] get those PSMA scans is at the University of Southern California or the University of

California, Los Angeles, but it’s very important for our colleagues who work in prostate cancer to understand these PET imaging technologies, [to understand] what we have available today and what we’ll have more widely available in the next year or 2.

Also very interesting in this area is theranostics—meaning therapeutics plus diagnostics—in which you combine a PET imaging study with a lethal radionuclide like lutetium [177]. Essentially, what happens is when you have a prostate cancer, an avid tracer finds the [cancer] cell and [delivers] the radioactive payload that’s associated with it. Once that antibody goes to the cell, it’s connected to something like lutetium, which is a destructive nuclide, and it kills the cancer cells. Theranostics is a growing area in prostate cancer. The PSMA lutetium studies are not yet FDA approved, but [this therapy] has worked its way through the system quite far. And at some point, it will be evaluated by the FDA in the United States.

There have also been some very interesting developments in bladder cancer. In particular, we had one of the first agents—pembrolizumab (Keytruda)—approved for non-muscle-invasive bladder cancer (NMIBC). It’s administered systemically, and it’s for NMIBC refractory to BCG. What was particularly fascinating about this approval, and perhaps

even exciting, is the fact that it's a systemic therapy for NMIBC, not an intravesical agent. In that regard, it's a first-in-class [therapy]. Several other new medications had very prominent clinical trials reported for NMIBC as well, including nadofaragene firadenovec; clinical trial results showed that this was a very effective intravesical gene therapy for NMIBC. It's currently being evaluated by the FDA, but trial data reported in 2020 were very promising.

Q: How big of an innovation is having PARP inhibitors available to treat patients with advanced mCRPC?

GOMELLA: Since 2010, we've had an amazing run of approvals of new agents for advanced mCRPC. The latest entries into that category are the PARP inhibitors olaparib (Lynparza) and rucaparib (Rubraca), approved in May 2020 within 5 days of each other. Essentially, you consider them to be second-, third-, or fourth-line therapies; [a patient has] to have failed other therapeutic interventions for mCRPC to be eligible for olaparib or rucaparib. But further, the way the FDA labels are written, you actually have to identify a problem with the DNA repair pathway genes. So, it's not only failing therapies, but also identifying that you have what are known as homologous recombinant repair gene abnormalities in the DNA repair pathways. Those [abnormalities] tend to be in genes such as *BRCA1*, *BRCA2*, *ATM*. When 1 gene is mutated, and certainly when 2 are mutated, the body can't do a normal repair of the

DNA, and then the [cancer] cells become very aggressive, very metastatic. Not all patients with advanced prostate cancer have these DNA repair pathway abnormalities, but those who do can actually add several years to their life using these oral PARP inhibitors. Medical oncology has been using these for several years—different ones for breast cancer, different ones for pancreatic cancer. But now we have them available to use as an oral agent in advanced mCRPC.

Q: Looking back, the early 1990's had chemotherapy, radiation and maybe a little bit of hormonal therapy to treat prostate cancer. Could you have ever foreseen the changes and advances in treatment that we have now?

GOMELLA: The reality is that for a while, we were pretty quiet in prostate cancer. In the late 1980s, we had the development of the LHRH agonists, where instead of cutting a man's testicles off, you could give him a shot and turn his testicles off relatively safely. Then we had the amazing discovery of PSA and its association with prostate cancer. That really kicked off in a big way in the early 1990s—but then things got kind of quiet. A lot of work was done with surgery, [though]. Because of the pioneering work of Patrick C. Walsh, MD, in the 1980s, more and more doctors were doing surgery for prostate cancer. At the same time, there were improvements in radiation, with brachytherapy and different ways to deliver radiation. That

continued into the 21st century in the treatment of local prostate cancer, with the development of robotic prostatectomy and proton therapy.

In advanced prostate cancer, we didn't really have a lot until the early 2000s, when we had docetaxel (Taxotere) come out, but again, after that it was quiet. Then 7 or 8 years later, boom! We were hit with sipuleucel-T (Provenge), one of the first immunotherapies for any advanced cancer. Then we [saw the approvals of] enzalutamide (Xtandi), darolutamide (Nubeqa), apalutamide (Erleada), abiraterone (Zytiga), cabazitaxel (Jevtana), rucaparib, olaparib. In just a 10-year period, we had at least 9 or 10 different new drugs available to treat various stages of prostate cancer. And now, of course, we have the oral LHRH antagonists as well. So, yes, it's been an amazing run, the last 11 years, to see all of these new drugs approved for advanced prostate cancer.

Q: Where is the research headed now?

GOMELLA: One concept we talk about in prostate cancer is a shift to the left. What do we mean by that? We get drugs that are approved for advanced mCRPC, for the worst-case scenarios; [here,] men are not doing well and have failed [every prior treatment]. Then, once you get that approval, you start to move into earlier and earlier stages to try to delay the spread of cancer. That's what we're doing now with drugs such as enzalutamide, apalutamide, and darolutamide. We're using them to slow the spread of advanced

prostate cancer. I think [the research is] moving us back to the left and identifying things that we may be able to do earlier and earlier, to convert prostate cancer from an acute life-threatening disease to, [potentially,] a chronically managed disease like diabetes or hypertension. A lot of the research now is looking at drugs that may alter that trajectory of prostate cancer by understanding the genetic triggers that we may be able to interact with earlier in the course of the disease: to slow it down, or even prevent it from metastasizing, or, if it is metastasizing, to [get it to stay] there in a holding pattern.

Q: Your institution has had great success with the use of a multidisciplinary approach to cancer care. Can you describe the philosophy behind that?

GOMELLA: We've been utilizing a multidisciplinary approach here at the Kimmel Cancer Center since way back in 1996; we [believe no] other center has been doing it as long as we have. We've found it to be an amazing experience. Many other centers have started to do it now, because it's a very patient-friendly and family-friendly approach to prostate cancer.

Most of the men who come to our multidisciplinary clinic have early prostate cancer, and they're trying to decide between active surveillance and active treatment with something like radiation or surgery. But for those patients who come in with prostate cancer that's a little bit more advanced, we have a whole team of radi-

ation oncologists, as well as medical oncologists, clinical trials specialists, radiologists, pathologists—and all [of us are] at the same place at the same time to talk to the patient and their family, and to give them our best recommendation for what path they should start on.

With regard to genetic testing, we're very proud of the fact that in 2014, we incorporated what we believe is the first genetic testing clinic where all patients who come in receive a quick consultation with a genetic testing team. [The team discusses testing, and asks,] "Could this be something you'd be interested in pursuing further?" The focus on that first visit is on treatment, [of course], but if there's an indication the patient could have a familial form of prostate cancer, the option is there to talk to our genetic counselors after

[the visit is] over.

For patients who may have a genetic predisposition, [the consultation] may be important to them, especially when it comes to screening for other cancers, such as pancreatic cancer, melanoma, or male breast cancer. It also might be very important to them, from a perspective of cascade testing, to know if this is something they may need to worry about in their children. Should their children be aware that they might have this inherited gene? Again, this requires a very up-close-and-personal discussion with the patient or family, but we believe this is the future of precision medicine in all of cancer.

Q: Is there a particular achievement in your career of which you are most proud?

GOMELLA: When it comes to a basic science discovery, something that doesn't get a lot of attention, that I'm particularly proud of, is the fact that way back in 1993, we described the first molecular test to identify circulating prostate cancer cells. I think that that really laid a lot of groundwork for others who started to look and say, "Hm, can we use these molecular tests to look at circulating tumor cells?" Over the last 25 years, the work that we did has now been eclipsed and expanded dramatically. At the time, it was too early; we didn't really know what we were doing. We just said, "Hey, we're doing this RT PCR [reverse transcription polymerase chain reaction] for PSA, and we're seeing stuff out in the blood that shouldn't be there." That was a very early indication that something was

going on. The problem was, we didn't know enough about the circulating cell-free DNA and all the other circulating tumor cells that we actually got involved with about 8 or 10 years later. So, identifying micrometastasis in the early 1990s is something that I was pretty proud of.

But [something else I'm very proud of is] the team building—working with my amazing colleagues in medical oncology, radiation oncology and cancer biology. A lot of the basic science translational things come out of the lab, and we're able to bring [the results of that work] to our patients. ■

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ASCO Conference Round Up

Continued from page 62

In the ITT population, data showed that the median OS was not reached in the bemarituzumab arm vs 12.9 months in the placebo arm (HR, 0.58; 95% CI, 0.35-0.95; $P = .0268$). The 1-year OS rates were 65.3% and 56.9%, respectively. The OS benefit with bemarituzumab increased with higher levels of FGFR2b overexpression, similar to findings for PFS.

The ORR in the ITT population was 47% with the combination and 33% with placebo/mFOLFOX6. For patients who had measurable disease at baseline, the ORRs

were 53% and 40%, respectively, with a best change in tumor size at -41.7% and -29.9%, respectively. The median time to response was 1.84 months with the combination and 1.67 months with placebo/mFOLFOX6, and the median duration of response was 12.2 months and 7.1 months, respectively.

Grade 3 or higher adverse events (AEs) were seen in 82.9% of patients on bemarituzumab/mFOLFOX6 vs 74.0% of those on placebo/mFOLFOX6, with stomatitis (9.2% vs 1.3%, respectively) and dry eye (2.6% vs 0%, re-

spectively) showing the largest increase in grade 3 or higher AEs with bemarituzumab vs placebo.

Serious AEs occurred in 31.6% of bemarituzumab-treated patients and in 36.4% of patients on the placebo arm. Corneal-related toxicities, which tend to be associated with FGFR inhibitors, occurred in 67.1% and 23.7% of bemarituzumab-treated patients vs 10.4% and 0% of those on placebo/mFOLFOX6, respectively. The mean time to onset of an AE of any grade was 16.1 weeks on bemarituzumab/mFOLFOX6 and 11.6 weeks on placebo. Twenty patients discontinued bemarituzumab treatment due to corneal AEs. Twelve corneal

AEs ultimately resolved with a median time to resolution of 27.0 weeks. ■

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ONCOLOGY

FDA Grants Breakthrough Therapy Designation to Tiragolumab Atezolizumab Therapy for Metastatic NSCLC

Hannah Slater

The FDA has granted breakthrough therapy designation (BTD) to the novel cancer immunotherapy tiragolumab in combination with atezolizumab (Tecentriq) for the first-line treatment of individuals with metastatic non-small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression and no *EGFR* or *ALK* genomic tumor aberrations.¹

Tiragolumab becomes the first anti-T cell immunoglobulin and ITIM domain (TIGIT) molecule to be granted this designation. The FDA granted BTD based on data from the global, double-blind, randomized phase 2 CITYSCAPE trial (NCT03563716). The study is evaluating tiragolumab plus atezolizumab compared with atezolizumab plus placebo in the first-line setting for patients with PD-L1-positive, locally advanced, unresectable or metastatic NSCLC. Patients enrolled onto the study are randomized 1:1 to receive either 600 mg tiragolumab intravenously plus 1200 mg atezolizumab IV or placebo plus atezolizumab every 3 weeks until disease progression or loss of clinical benefit. The study's dual primary end points are overall response rate (ORR) and progression-free survival (PFS). Key secondary end points include safety and overall survival.

Thus far, the tiragolumab combination has demonstrated promising efficacy

and safety based on trial results that were presented at the 2020 American Society of Clinical Oncology Virtual Scientific Program.²

On the primary analysis date of June 30, 2019, the ORR was 31.3% in the tiragolumab arm (95% CI, 19.5%-43.2%) vs 16.2% in the placebo arm (95% CI, 6.7%-25.7%), with an odds ratio of 2.57 (95% CI, 1.07-6.14). Moreover, the median PFS was 5.4 months for patients who received tiragolumab plus atezolizumab (95% CI, 4.2 to not evaluable) versus 3.6 months for those who received placebo plus atezolizumab (95% CI, 2.7-4.4), with a hazard ratio of 0.57 (95% CI, 0.37-0.90).

Regarding safety, treatment-related adverse events (TRAEs) were reported in 80.6% of those in the tiragolumab arm and in 72.0% of the placebo arm; grade 3 or higher TRAEs occurred in 14.9% and 19.1%, respectively. Further, AEs leading to treatment discontinuation occurred in 7.5% and 10.3%, respectively.

At the new cut-off date of December 2, 2019, investigators found that with an additional 6 months of follow-up (median follow-up, 10.9 months), the improvements observed in ORR and median PFS were maintained for those receiving tiragolumab plus atezolizumab as compared with patients receiving placebo plus atezolizumab. For the tiragolumab arm,

the ORR was 37.3% (95% CI, 25.0%-49.6%) and the median PFS was 5.6 months (95% CI, 4.2-10.4) vs 20.6% (95% CI, 10.2%-30.9%) and 3.9 months (95% CI, 2.7-4.5), respectively, in the atezolizumab monotherapy arm. The safety profile also remained tolerable.

Biomarker analyses from the CITYSCAPE study will be presented at the International Association for the Study of Lung Cancer 2021 World Conference.

TIGIT has emerged as a key inhibitor of antitumor responses, with the ability to interfere with multiple steps of the cancer immunity cycle.

Vibostolimab, another anti-TIGIT antibody, is currently being tested in combination with pembrolizumab (Keytruda) in patients with anti-PD-1/PD-L1-refractory NSCLC. Results from that phase 1b trial (NCT02964013), presented at the 2020 European Society of Medical Oncology Virtual Congress, showed promising antitumor activity.³

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➔ For full reference list, visit cancernetwork.com/TIGIT_FDA

Utility of the 21-Gene Recurrence Score in Node-Positive Breast Cancer

Alison Laws, MD^{1,2,3}; Ana C. Garrido-Castro, MD^{2,3,4}; Philip D. Poorvu, MD^{2,3,4}; Eric P. Winer, MD^{2,3,4}; Elizabeth A. Mittendorf, MD, PhD^{1,2,3}; and Tari A. King, MD^{1,2,3}

¹Division of Breast Surgery, Department of Surgery, Brigham and Women's Hospital, Boston, MA; ²Breast Oncology Program, Dana-Farber/Brigham and Women's Cancer Center, Boston, MA; ³Harvard Medical School, Boston, MA; ⁴Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

ABSTRACT: The 21-gene Recurrence Score (RS) assay has been validated as both a prognostic and predictive tool in node-negative (pN0), estrogen receptor–positive (ER+), HER2-negative (HER2–) breast cancer. A large body of evidence supports the clinical utility of the RS in the node positive (pN+) population as well. Retrospective analyses of archived tissue from multiple clinical trials have found the RS to be prognostic in both endocrine therapy (ET)-treated and chemotherapy-treated patients with pN+ disease. Distribution of RS results in pN+ patients have also been consistent with those of pN0 populations. Data from the SWOG 8814 trial and large population-based registries further support the prognostic and potential predictive value of the RS. Specifically, patients with 1 to 3 positive nodes and RS less than 18 derived negligible benefit from adjuvant chemotherapy in these studies. In the prospective West German Study Group PlanB and ADAPT trials, pN+ patients with RS less than 11 and RS 25 or less, respectively, who were treated with ET alone experienced excellent outcomes. Finally, 5-year results of the RxPONDER clinical trial randomizing patients with 1 to 3 positive nodes and RS 25 or less to ET alone vs ET plus chemotherapy confirmed an absence of chemotherapy benefit in postmenopausal patients. Clinical practice guidelines support use of the RS in the pN+, ER+/HER2– population, and many institutions have adopted the RS to guide clinical decision-making, resulting in a net reduction of adjuvant chemotherapy use. This review highlights the existing data supporting the prognostic and predictive ability of the RS in pN+ disease, current practice patterns related to RS use in this population, and emerging applications.

Introduction

Insights from gene expression profiling have vastly expanded our understanding of distinct molecular subtypes of breast cancer, and of tumor biology's influence on response to therapy and outcomes. Efforts to develop genomic assays for clinical use have resulted in a new era of molecularly tailored breast cancer management. The Oncotype DX Breast Recurrence Score® (RS) analyzes gene expression using a reverse transcriptase-polymerase chain reaction method. After evaluating 250 candidate genes in archived tissue from node-negative (pN0) estrogen receptor–positive (ER+) patients, a panel of 21 genes (16 cancer-related genes and 5 reference genes) was selected.¹⁻³ A proprietary algorithm produces a recurrence score of 0 to 100, with a higher score correlating to an increased risk of distant recurrence (DR). Substantial efforts have focused on demonstrating the clinical utility of this tool, through both its prognostic and predictive value. For review, a prognostic tool provides information about the likelihood of a clinical outcome. A predictive tool provides information about the effect of an exposure (for example, a medical treatment) on a particular individual. To definitively demonstrate predictive value of the RS, a comparison is needed between

patients randomized to either receive or not receive a treatment of interest, within RS categories.

The prognostic value of the RS and its ability to predict adjuvant chemotherapy benefit is well established in pN0 ER+ disease.⁴⁻⁶ The TAILORx study assigned patients with RS less than 11 to endocrine therapy (ET) alone and those with RS greater than 25 to ET plus chemotherapy; it randomized those with RS 11 to 25 to ET with or without chemotherapy. Excellent outcomes with ET alone were demonstrated in patients with RS less than 11, with 96.8% free from DR at 9 years. Further, among patients with RS 11-25, ET alone was noninferior to ET plus chemotherapy overall, with a difference of less than 1% in 9-year DR rates between the 2 groups. In an exploratory analysis, a small reduction in DR was seen with ET plus chemotherapy in women 50 years or younger with RS 16-20 (1.6% absolute difference) and RS 21-25 (6.5% absolute difference). However, this may be explained by chemotherapy-induced ovarian function suppression, and the clinical relevance of this finding remains controversial.⁶

The RS has now been incorporated into the American Joint Committee on Cancer (AJCC) 8th edition staging system, such that all T1-2 N0 disease with RS less than 11 is classified as Prognostic Stage IA.⁷ The role of the RS for adjuvant systemic therapy decision-making in pN0 ER+ disease is supported in multiple clinical practice guidelines.⁸⁻¹⁰ In the TAILORx trial, 16% and 67% of patients had RS less than 11 and RS 11-25, respectively⁶; omitting chemotherapy in the majority of these patients has had substantive clinical impact. There are now retrospective and prospective data using the RS in node-positive (pN+) disease as well, including 5-year results from the RxPONDER clinical trial. In this study, patients with 1 to 3 positive nodes and RS ≤25 were randomized to receive ET with or without chemotherapy,¹¹ providing level I evidence to support the clinical

utility of the RS in pN+ disease. Here, we will review this literature in detail, along with published institutional experiences regarding the use of RS in pN+ disease and emerging applications for the RS beyond adjuvant chemotherapy decision-making.

Prognostic and Predictive Value of the RS: Retrospective Analyses of Clinical Trials

Studies supporting the prognostic and predictive ability of the RS are presented in **Table 1** and **Table 2**, respectively. The first retrospective analysis of a prospective phase 3 clinical trial evaluating the RS in pN+ patients was performed in patients from the SWOG 8814 trial. This study evaluated tamoxifen alone vs chemotherapy (cyclophosphamide, doxorubicin, and fluorouracil) with concurrent or subsequent tamoxifen in postmenopausal pN+ patients. For a preplanned translational study, the RS was performed on banked tumor specimens. The prognostic ability of the RS was demonstrated in 148 patients from the tamoxifen-only arm, 64% and 36% of whom had 1 to 3 and 4 or more positive nodes, respectively. Ten-year disease-free survival (DFS) adjusted for the number of positive nodes was 60% in those with RS less than 18, 49% with RS 18-30, and 43% with RS of 31 or more ($P = .017$).¹²

To evaluate the predictive value of the RS in SWOG 8814, outcomes were compared between patients in the tamoxifen-only arm ($n = 148$) and those who received chemotherapy followed by tamoxifen ($n = 219$). Among patients with RS less than 18 or RS 18-30, there was no DFS benefit with chemotherapy (RS <18: HR, 1.02; 95% CI, 0.54-1.93; $P = .97$; RS 18-30: HR, 0.72; 95% CI, 0.39-1.31; $P = .48$), whereas a significant benefit was observed in those with RS of 31 or more (HR, 0.59; 95% CI, 0.35-1.01; $P = .033$). Results were similar for breast cancer-specific survival (BCSS) and overall survival (OS). Adjusting for number of positive nodes, there was a signifi-

cant interaction between the continuous RS and chemotherapy effect on DFS ($P = .053$), particularly in the first 5 years ($P = .029$).¹² While these data are compelling, the sample size was small and the study may have been underpowered. In addition, the parent trial was conducted more than 25 years ago and is thus not reflective of modern therapy.

Multiple additional “retrospective-prospective” studies lend further support to the prognostic ability of the RS in both ET-treated and chemotherapy-treated pN+ patients. The TransATAC trial randomized postmenopausal patients to adjuvant anastrozole, tamoxifen, or a combination of the 2. Among 306 pN+ patients from the single-agent arms treated without chemotherapy, both the continuous and categorical RS were independent predictors of DR and OS on adjusted analysis.¹³ The NSABP B-28 trial randomized pN+ patients to doxorubicin and cyclophosphamide chemotherapy with or without paclitaxel. RS was performed retrospectively in 1065 patients; 10-year DFS was 75.8% for RS less than 18, 57.0% for RS 18-30, and 48.0% for RS of 31 or more ($P < .001$). RS was also correlated with distant recurrence-free survival (DRFS), OS, and BCSS, and the association of the continuous RS with each outcome remained significant on adjusted analyses (HRs for 50-point increase, 2.42-3.38; all $P < .001$).¹⁴

Among 530 pN+ patients from the PACS-01 trial randomized to fluorouracil, epirubicin, and cyclophosphamide chemotherapy with or without docetaxel, the continuous RS was again strongly associated with DR, DFS, and OS on multivariable analysis (all $P < .001$).¹⁵ Finally, the ECOG E2197 trial included pN+ and high-risk pN0 patients, randomized to doxorubicin with either cyclophosphamide or docetaxel. Among 465 patients, 44% had 1 to 3 positive lymph nodes. The RS outperformed a modified version of the Adjuvant! Online tool, which uses traditional clinicopathologic risk factors, in predicting 5-year risk of recurrence.

TABLE 1. Summary of studies demonstrating the prognostic value of the RS in pN+ patients

Study	Design	Relevant population	Outcomes	Key finding
WSG PlanB²¹⁻²²	Prospective clinical trial	n=2,642 HR+ HER2- pN0-1 Post-amendment/ per protocol tx ^a (41% pN+) RS<11: ET RS≥11: CT + ET	5-y DFS pN0, RS≤11, ET alone (n=238): 94.2% pN1, RS≤11, ET alone (n=110): 94.4% pN0-1, RS 12-26, CT + ET (n=1,200): 94.3% pN0-1, RS ≥25, CT + ET (n=478): 84.2% Adjusted^b hazard ratio for DFS (pN0-1): 75 th vs. 25 th percentile of RS ^c (whole population): 1.68 [1.04-2.74], P=0.035 75 th vs. 25 th percentile of RS ^c (CT-treated): 2.43 [1.21-4.88], P=0.013	In this modern trial, RS was prognostic of DFS in both ET-treated and CT-treated patients. Further, among patients prospectively assigned to ET alone when RS was ≤11, 5-year DFS was excellent at 94%, regardless of pN0/pN1 nodal status.
WSG ADAPT²³	Prospective clinical trial	n=595 HR+ HER2- pN1 RS<12 or RS 12-25 & ET-response: ET	5-y DDFS: RS<12 (n=208): 94.6% RS 12-25 & ET-response (n=387): 92.7%	Another modern trial supporting excellent outcomes in pN1 patients with RS<25 treated without chemotherapy.
SWOG 8814¹²	Retrospective analysis of clinical trial	n=148 Postmenopausal HR+ pN+ ET-only arm	10-y DFS: RS<18 60% vs. RS 18-30 49% vs. RS≥31 43% Log-rank P=0.017 [†] Adjusted^d hazard ratios for DFS: 50-pt increase ^e : 2.64 [1.33-5.27], P=0.006	These analyses support the prognostic ability of both the continuous and categorical RS in ET-treated patients.
Trans-ATAC¹³	Retrospective analysis of clinical trial	n=306 Postmenopausal HR+ pN+ No adjuvant CT Single-agent ET	9-y DRFS: RS<18 83% vs. RS 18-30 72% vs. RS≥31 51% Log-rank p-value<0.001 Adjusted^d hazard ratios for DRFS: 50-pt increase ^e : 3.47 [1.64-7.38], P=0.002 RS≥31 vs. <18: 2.7 [1.5-5.1] RS 18-30 vs. <18: 1.8 [1.0-3.2]	
NSABP B-28¹⁴	Retrospective analysis of clinical trial	n=1,065 Operable BC ER+ pN+ CT + ET	10-y DFS: RS<18 76% vs. RS 18-30 57% vs. RS≥31 48% Log-rank p-value<0.001 Adjusted^d hazard ratios for DFS: 50-pt increase ^e : 2.53 [1.90-3.38], P<0.001	
PACS-01¹⁵	Retrospective analysis of clinical trial	n=530 Operable BC HR+ pN+ CT + ET	5-y DRFS: RS<18 94% vs. RS 18-30 87% vs. RS≥31 69% Log-rank p-value<0.001 Adjusted^d hazard ratio for DRFS: 50-pt increase ^e : 3.36 [1.88-6.00], P<0.001	These analyses support the prognostic ability of both the continuous and categorical RS in CT-treated patients.
ECOG E2197¹⁶	Retrospective analysis of clinical trial	n=465 HR+ pN+ or high-risk pN0 (44% pN+) CT + ET	Adjusted^{d,e} hazard ratio for RFI: 50-pt increase ^g : 2.12 [0.97-4.65], P=0.06 50-pt increase ^g : 2.64 [1.80-3.87], P<0.001	
SEER¹⁷	Population-based registry (USA) 2004-2012	n=4,059 pT1-2 pN1mi HR+/HER2- ET +/- CT	Adjusted^d hazard ratio for BCSS: RS 11-25 vs. <11: 3.51 [1.08-11.42], P=0.036 RS >25 vs. <11: 13.04 [3.85-44.20], P<0.001	This study demonstrates prognostic ability of the RS in a mixed treatment population, even after adjustment for the AJCC 8 th edition pathologic prognostic stage.
SEER¹⁸	Population-based registry (USA) 2004-2014	n=6,182 HR+/HER2- pN1 ET +/- CT	9-y BCSS (unadjusted) RS<11, no CT (n=1,005) 97.8% vs. CT (n=283): 97.8% vs. 98.6% RS 11-15, no CT (n=1,193) vs. CT (n=453): 98.5% vs. 96.4% RS 16-20, no CT (n=992) vs. CT (n=587): 96.2% vs. 95.8% RS 21-25, no CT (n=397) vs. CT (n=431): 92.9% vs. 94.3% RS≥26, no CT (n=223) vs. CT (n=618): 84.8% vs. 89.2%	In this large real-world cohort, all pN1 patients with RS≤20 had >95% 9-yr BCSS, regardless of CT use. Outcomes were numerically worse for patients with RS≥26.

^aPatients enrolled after a trial amendment recommending omission of chemotherapy for patients with RS<11^bAdjusted for stage, grade, Ki-67, ER %, PR %, nodal status, CT vs. ET treatment^cRS modeled as a continuous variable^dAdjusted for number of positive nodes^eAdjusted for age, tumor size, grade and number of positive nodes^fAdjusted for age, tumor size, grade, number of positive nodes, surgery type and chemotherapy regimen^gAdjusted for tumor size, grade, Ki-67, number of positive nodes and chemotherapy regimen^hAdjusted for age, tumor size, HER2 status, grade and number of positive nodesⁱAdjusted for low/intermediate/high risk groups as determined using the Adjuvant! Online tool^jAdjusted for age, AJCC 8th edition pathologic prognostic stage, chemotherapy use

Key: ET, endocrine therapy; CT, chemotherapy; ER, estrogen receptor; HR, hormone receptor; RS, recurrence score; tx, treatment; pt, point; DFS, disease-free survival; DDFS, distant disease-free survival; DRFS, distant recurrence-free survival; RFI, recurrence-free interval; BCSS, breast cancer specific-survival

The prognostic effect of the RS remained for all levels of Adjuvant! Online risk assessment.¹⁶

The distribution of RS results was very consistent in the SWOG 8814, NSABP B-28, and PACS-01 pN+ populations; less than 18 in 36%-40%, 18-30 in 28%-34%, and 31 or greater in 30%-32%.^{12,14-15} TransATAC patients had a higher proportion of RS less than 18 (52%) and a lower proportion of RS of 31 or greater (17%),¹³ although this analysis excluded patients treated with chemotherapy, which likely explains this finding. In historical studies validating the prognostic ability of the RS in pN0 patients, the distribution of RS results was less than 18 in 51%-54%, 18-30 in 21%-22%, and 31 or greater in 25%-27%.^{4,5} Thus, while the mean RS may be slightly higher in pN+ patients, the distribution is not substantially different than in the pN0 population.

The percentage of patients evaluated in the above trials with 1 to 3 positive nodes vs 4 or more positive nodes ranged from 60% to 79%.¹²⁻¹⁵ In NSABP B-28, the distribution of RS results was similar between patients with 1 to 3 vs 4 or more positive nodes.¹⁴ Further, the RS remained prognostic in both those with 1 to 3 and 4 or more positive nodes in the TransATAC, NSABP B-28, and PACS-01 studies.¹³⁻¹⁵ In the PACS-01 study, patients with 4 or more nodes and an RS less than 18 had a 5-year DR rate of less than 10%, which was similar to those with 1 to 3 nodes and RS less than 18 or 18-30, and lower than those with 1 to 3 positive nodes and RS of 31 or greater.¹⁵ Similarly, in NSABP B-28, 10-year DFS and BCSS in those with 4 or more nodes and RS less than 18 were similar or greater than in patients with 1 to 3 positive nodes and RS 18-30 or 31 or greater.¹⁴ Overall, these findings suggest that the RS may have a role even in patients with 4 or more nodes, a population that is not included in the RxPONDER trial.

Prognostic and Predictive Value of the RS: Population-Based Studies

Population-based series have further confirmed the prognostic ability of the RS in larger, "real-world" samples of pN+ patients. These studies provide support for the predictive value of RS as well, although they are limited by the fact that chemotherapy use is not randomized but selected. Wang et al evaluated outcomes by TAILORx RS cut points in 4059 pT1-2 pN1 patients from the Surveillance, Epidemiology and End Results (SEER) database. Patients with RS 11-25 and RS greater than 25 vs RS less than 11 experienced inferior BCSS and OS, independent of the AJCC 8th edition pathologic prognostic stage.¹⁷ In a larger, more recent SEER study of greater than 6000 pN1 patients, unadjusted rates of 9-year breast cancer-specific mortality were less than 5% for RS up to 20, regardless of chemotherapy use. Notably, in those treated without chemotherapy, the differences in breast cancer-specific mortality between pN0 and pN1 patients were less than 1% for RS 0-15 and less than 2% for RS 16-20.¹⁸

An analysis of the National Cancer Database (NCDB) included 13,163 pN+ patients with an intermediate RS, defined as 11-30, and stratified into groupings of 11-17, 18-25, and 26-30. On multivariable analysis, 5-year risk of mortality by chemotherapy use statistically differed for all RS groupings; however, in those with RS 11-17, the absolute benefit was only 1.3% (HR, 0.63; 95% CI, 0.40-0.99; $P = .044$). With RS 18-25 and 26-30, the use of chemotherapy was associated with larger gains in OS (3.3% and 6.7% absolute benefit, respectively). When the continuous RS score was modeled, no benefit from chemotherapy was seen for an RS less than 14.¹⁹ Neither the SEER database nor NCDB capture DFS, a limitation of these series as patients with ER+/HER2- disease may survive for years with recurrent or metastatic disease.

Finally, in an analysis of 709 patients

with micrometastases (pN1mi) or pN1 disease from the Israeli Clalit Health Services registry, adjuvant chemotherapy was used in 9% with RS less than 18, 41% with RS 18-30, and 78% with RS of 31 or greater in the pN1 subset. Five-year DR rates were 5% or less for those with RS less than 18 or RS 18-30, regardless of having 1 vs 2 to 3 positive nodes. Among all patients (pN1mi-pN1) treated without chemotherapy, 5-year DR rates were 2.9% for RS less than 18. The RxPONDER cut point of 25 was also evaluated; chemotherapy was used in only 15% of those with RS of 25 or less, in whom the 5-year DR rate was 4.4%, vs 2.3% in those treated without chemotherapy ($P = .521$).²⁰

Prognostic and Predictive Value of the RS: Prospective Validation and Summary

The West German Study Group (WSG) PlanB trial was the first to prospectively validate the prognostic ability of the RS in pN+ disease, as well as the ability of the RS to identify a subset of pN+ patients with excellent outcomes in the absence of chemotherapy. Initially designed to compare chemotherapy regimens with or without anthracyclines, this study included 2449 pN+ and high-risk pN0 patients. An early amendment recommended omission of chemotherapy for all patients with RS of 11 or less, regardless of nodal status. In both the overall population and the chemotherapy-treated subgroup (with RS >11), the continuous RS was an independent predictor of DFS.²¹ Further, as a result of the early amendment, chemotherapy was omitted in 86% of patients with RS of 11 or less. Among those who received ET alone, 5-year DFS was excellent at 94.2%, and it did not differ significantly between pN1 and pN0 patients (94.2% and 94.4%, respectively).²²

Findings from 2 important clinical trials using the RS in pN+ disease were reported at the San Antonio Breast Cancer Symposium in December 2020. In the WSG ADAPT trial, patients who

TABLE 2. Summary of studies evaluating oncologic outcomes in pN+ patients stratified by use of chemotherapy and RS

Study	Design	Relevant population	Outcomes	Key finding
RxPONDER¹¹	Prospective clinical trial (interim analysis) ET vs CT + ET	n=5,015 HR+ HER2- pN1 RS≤25	5-yr iDFS All: ET (n=2,506) vs. CT (n=2,509): 91.0% vs. 92.4% Postmenopausal: ET (n=1,675) vs. CT (n=1,675): 91.9% vs. 91.6% Premenopausal: ET (n=831) vs. CT (n=834): 89.0% vs. 94.2% Hazard Ratio for effect of CT on iDFS All: 0.81, [0.67-0.98], p=0.026 Postmenopausal: 0.97, [0.78-1.22], P= 0.82 Premenopausal: 0.54, [0.38-0.76], P<0.001	In this large, modern randomized trial, pN1 postmenopausal patients with RS≤25 did not benefit from chemotherapy, whereas pN1 premenopausal patients had a small improvement in iDFS with chemotherapy.
SWOG 8814¹²	Retrospective analysis of clinical trial ET vs CT + ET	n=367 Postmenopausal HR+ pN+	10-yr DFS RS<18, ET (n=55) vs. CT (n=91): 60% vs. 64% RS≥31, ET (n=47) vs. CT (n=71): 43% vs. 55% Hazard ratio for effect of CT on DFS RS<18: 1.02, [0.54-1.93], P=0.97 RS 18-30: 0.72, [0.39-1.31], P=0.48 RS≥31: 0.59, [0.35-1.01], P=0.033	In patients randomized to receive ET alone versus CT, 10-yr DFS did not differ by treatment for those with RS<18 or RS 18-30
NCDB¹⁹	Population-based registry (USA) 2010-2014	n=13,163 HR+/HER2- pN1-2 RS 11-30	Adjusted 5-year death from any cause[†] RS 11-17, no CT vs. CT [‡] : 3.5% vs. 2.3% RS 18-25, no CT vs. CT [‡] : 7.3% vs. 4.0% RS 26-30, no CT vs. CT [‡] : 14.5% vs. 7.8% Adjusted hazard ratio for effect of CT on any death RS 11-17: 0.63, [0.40-0.99], P=0.044 RS 18-25: 0.53, [0.37-0.76], P=0.001 RS 26-30: 0.50, [0.28-0.89], P=0.018	Adjusting for multiple patient, tumor and treatment characteristics, pN1-2 patients with RS<18 derived negligible overall survival benefit from CT
Clalit²⁰	Population-based registry (Israel) 2006-2011	n=709 ER+/HER2- pN1mi-1	5-year DR, amongst pN1: RS<18, 1 positive node (n=140, 9% CT): 4.4% RS<18, 2-3 positive nodes (n=76, 8% CT): 5.4% RS 18-30, 1 positive node (n=98, 44% CT): 5.2% RS 18-30, 2-3 positive nodes (n=60, 37% CT): 5.1% RS≥31, 1 positive node (n=26, 85% CT): 11.5% RS≥31, 2-3 positive nodes (n=11, 64% CT): 0.0% 5-year DR, amongst all pN1mi-1, by CT use: RS<18, no CT (n=352) vs. CT (n=27): 2.9% vs. 7.7% RS 18-25, no CT (n=136) vs. CT (n=62): 8.2% vs. 0.0% RS ≤25, no CT (n=488) vs. CT (n=89): 4.4% vs. 2.3% RS 26-30, no CT (n=20) vs. CT (n=40): 20.3% vs. 2.5% RS ≥31, no CT (n=10) vs. CT (n=62): 10.0% vs. 18.0%	5-year rates of distant recurrence were ≤5% in patients with pN1mi/pN1 disease and RS≤25 treated without CT, as well as those with pN1 and RS<18 in whom <10% received CT in clinical practice.

[†]Adjusted for age, year of diagnosis, Charlson Comorbidity Index, race, tumor size, histology, grade, progesterone receptor status, lymphovascular invasion, number of positive nodes

[‡]Number of pN+ who received CT for each RS category not reported, however in overall cohort of all stage I-IIIa, CT was used in 9%, 35% and 67% of patients with RS 11-17, RS 18-25 and RS 26-30, respectively

Key: ET, endocrine therapy; CT, chemotherapy; ER, estrogen receptor; HR, hormone receptor; RS, recurrence score; DFS, disease-free survival; DR, distant recurrence

were considered candidates for adjuvant chemotherapy by conventional criteria received a short (3-week) course of pre-operative ET, followed by surgery. Those with pN0-1 disease and RS less than 12, or RS 12-25 plus evidence of response to ET (defined by Ki67 expression ≤10% on surgical pathology) were treated with ET alone. In the subgroup of 595 patients with pN1 disease, 5-year distant DFS was excellent, and it did not significantly differ between those with RS 0-11 vs RS 12-25 (94.6% vs 92.7%, respectively).²³

Finally, highly anticipated 5-year results were presented from RxPONDER, the first trial to randomize chemotherapy

use in 5015 patients with 1 to 3 positive nodes and RS of 25 or less. Chemotherapy benefit did not differ by the continuous RS ($P = .30$) but did differ by menopausal status ($P = .008$). In postmenopausal patients, there was no difference in 5-year invasive DFS (iDFS) or OS between treatment arms. In premenopausal patients, 5-year iDFS was significantly improved in the ET plus chemotherapy group, with an absolute difference in iDFS of 5.2%. A small (1.3%) but statistically significant OS benefit was also seen in premenopausal patients with ET plus chemotherapy.¹¹ Similar to the age-based differences in chemotherapy benefit observed in the

TAILORx trial, some or all of the benefit from chemotherapy in premenopausal women could be a result of the indirect effect of chemotherapy on ovarian function. Two findings in subgroup analyses of premenopausal women suggest that chemotherapy-induced ovarian suppression is playing a role. First, the benefits of chemotherapy were as great or greater in those with a lower RS category (RS 0-13, HR, 0.45; vs RS 14-25, HR, 0.56), which would be consistent with an endocrine effect. Second, there was an absence of significant chemotherapy benefit in premenopausal women 50 years or greater (≥50 years, HR, 0.84; vs <50 years, HR,

0.43-0.44), who would be close to natural menopause and less likely to gain the benefit of chemotherapy-induced menopause.

In summary, the RS has consistently shown a strong association with oncologic outcomes in both ET-treated and chemotherapy-treated patients, independent of traditional risk factors such as age, tumor size, grade, and number of positive nodes. Further, data from SWOG 8814 and multiple population-based registries strongly support that pN1 patients with RS less than 18 have excellent oncologic outcomes in the absence of chemotherapy. The WSG PlanB and ADAPT trials provide prospective validation of excellent outcomes with ET alone in patients with RS 11 or less and RS of 25 or less, respectively. Finally, findings from RxPONDER demonstrate that ET alone provides equivalent outcomes to ET plus chemotherapy in postmenopausal pN1 patients with RS of 25 or less. Though small benefits from chemotherapy were observed in premenopausal patients in RxPONDER, chemotherapy-induced ovarian function suppression may be driving this finding. As a result of this substantial body of evidence, the National Comprehensive Cancer Network guidelines support the 21-gene RS to assist in adjuvant chemotherapy decision-making for patients with hormone receptor-positive/HER2- pN1 disease.⁸

Multi- and Single-Institution Experience Using RS in pN+ Patients

Numerous institutions across North America, Europe, Asia, and Australia have reported on their experience incorporating the use of the RS into adjuvant chemotherapy decision-making in ER+/HER2- disease (Table 3). Changes in treatment recommendations based on RS results have ranged from 11% to 42%.²⁴⁻³³ While many series include both pN0 and pN1 patients, recommendation changes are often greatest in the pN1 group.^{24,26-28,32} A multicenter Australian

TABLE 3. Summary of multi- and single-institution studies using RS in the clinical care of pN+ patients

Study/institution	Population	Pre- vs post-RS chemotherapy recommendation	Proportion of patients recommended chemotherapy by RS
<i>pN+ patients reported separately:</i>			
Dana-Farber Cancer Institute (USA) ³⁵	272 HR+/HER2- pT1-2 pN1	—	RS<18: 21% RS 18-30: 35% RS≥31: 63%
University of Pittsburgh (USA) ³⁴	152 ER+/HER2- pN1	—	RS<18: 4% RS 18-25: 13% RS 26-30: 100% RS≥31: 88%
Multi-institution, Australia ³³	118 HR+/HER2- early stage pN+	65% vs 23% (↓42%)	Amongst n=382 pN0/pN+: RS<18: 2% RS 18-25: 25%; RS 26-30: 89% RS≥31: 97%
ROXANE (Multi-institution, Italy) ³²	99 ER+/HER2- pT1-3 pN1	55% vs 27% (↓28%)	RS<11: 10% RS 11-17: 20% RS 18-25: 45% RS≥26: 100%
Sunnybrook Health Sciences Centre (Canada) ²⁹	72 ER+/HER2- pT1-3 pN1	79% vs 52% (↓27%)	RS<18: 29% RS 18-30: 78% RS≥31: 100%
Greater Manchester (United Kingdom) ³⁰	65 ER+/HER2- postmenopausal/pN1	100% (assumed) vs. 30% (↓70%)	RS<18: 8% RS 18-30: 63% RS≥31: 83%
Multi-institution, Australia ²⁷	50 HR+/HER2- early stage pN1	74% vs 52% (↓22%)	—
Instituto Nacional de Cancerologia (Mexico) ²⁶	34 ER+/HER2- pN1	59% vs 32% (↓27%)	—
<i>pN0/pN+ patients reported together:</i>			
PONDx (Multi-institution, France) ³¹	882 ER+/HER2- pN0-1 (29% pN1)	66% vs 30% (↓36%)	RS<18: 5% RS≥31: 98%
National Cancer Center (Korea) ³²	448 HR+/HER2- pN0-1 (34% pN1)	—	RS<18: 20% RS 18-30: 38% RS≥31: 97%
Multi-institution, Germany ²⁸	366 ER+/HER2- pN0-1 (33% pN1)	57% vs 46% (↓11%)	—
SAKK 26/10 (Multi-institution, Switzerland) ²⁴	221 ER+/HER2- pN0-1 (38% pN1)	40% vs. 27% (↓13%)	RS<18: 7% RS 18-30: 45% RS≥31: 100%
Multi-institution, United Kingdom ²⁵	137 ER+/HER2- Age ≤50 pN0-1mi Age>50 pN1 (19% pN1)	50% vs. 28% (↓22%)	RS<18: 4% RS 18-30: 47% RS≥31: 100%

Key: ER, estrogen receptor; HR, hormone receptor; RS, recurrence score

study of 382 patients included 118 (32%) who were pN+; of these, chemotherapy was recommended in 65% pre-RS versus 23% post RS. In the overall cohort, 98% with RS less than 18 and 78% with RS 18-30 were ultimately treated with ET alone, while 97% with RS 31 or greater received chemotherapy.³³ The prospective ROXANE study included 251 pN0-1 patients from 9 centers in Italy, of whom

99 (39%) were pN1. Of these, 55% were recommended chemotherapy pre-RS versus 27% post RS; this reduction in chemotherapy use was observed exclusively in patients with RS of 17 or less.³² Similarly, in a prospective Canadian cohort of 72 pN1 patients, changes in treatment recommendation were most common for RS less than 18. In this group, 76% were recommended chemotherapy pre-RS, nearly

two-thirds of whom were subsequently recommended ET alone post RS.²⁹

The University of Pittsburgh Cancer Center has developed and implemented a clinical pathway for patients with ER+/HER2- pN0-1 disease, in which those with RS less than 18 are recommended ET alone, those with RS greater than 30 are recommended chemotherapy, and those with RS 18-30 are left to the discretion of the treating oncologist. In their experience, use of RS was high in eligible patients (93%). Among patients with 1 to 3 positive nodes, there was strong adherence to the pathway; chemotherapy was used in 4% of those with RS less than 18, 25% with RS 18-30, and 88% with an RS of 31 or greater.³⁴

At the Dana-Farber Cancer Institute, since 2016, we have performed “reflex” RS testing for patients aged 65 years or less with hormone receptor-positive/HER2- pT1-2 pN1 disease; RS can also be ordered outside of these criteria at the oncologists’ discretion. In 347 women with pN1 disease treated with upfront surgery between 2016 and 2019, 272 (78%) had RS testing. Chemotherapy was used in 21.0% with RS less than 18, 34.8% with RS 18-30, and 62.5% for RS 31 or greater ($P = .01$). Furthermore, RS less than 18 was a significant predictor of chemotherapy use on adjusted analysis (odds ratio, 0.47; 95% CI, 0.24-0.92; $P = .028$). While follow-up was limited in duration (median, 27.0 months), our study is among the few institutional experiences to report outcome data. In the overall cohort, we observed no difference in 3-year recurrence-free survival in those treated with or without chemotherapy (97.7% vs 97.5%; $P = .97$), nor were there differences in 3-year OS (98.5% vs 100%; $P = .19$).³⁵

Special Populations

Consideration for the available evidence in underrepresented populations, including young patients, elderly patients, and patients of ethnic minorities, is warranted. While the SWOG 8814 and TransATAC

studies evaluated only postmenopausal patients, 48% and 53% of subjects in the NSABP B-28 and PACS 01 analyses were aged less than 50 years,¹⁴⁻¹⁵ and 24% in the ECOG E2197 study were aged 45 years or less.¹⁶ In the NCDB and Clalit registry studies, women less than 50 years accounted for 15% to 24% of the study populations.¹⁹⁻²⁰ In the prospective trials, median age in the overall hormone receptor-positive cohort of WSG PlanB was 56 years.²² Approximately one-third of the patients in the RxPONDER trial were premenopausal, although a specific age breakdown has not been reported.¹¹

The prognostic impact of the RS has been evaluated in the Young Women’s Breast Cancer Study, a multicenter prospective cohort of women aged 40 years or less at diagnosis. Among 163 pN1 patients, RS distribution was similar to nonyoung cohorts: 33% had RS less than 18, 42% had RS 18-30, and 25% had RS 31 or greater. Chemotherapy use was high overall: 83%, 97%, and 97%, respectively. The categorical RS was prognostic; 6-year DRFS was similar for RS less than 18 and RS 18-30 (85.9% and 87.3%, respectively), but markedly worse (62.8%) for RS 31 or greater ($P = .004$). Using TAILORx categories, 6-year DRFS for RS 11-25 was similar to the RS less than 18 and RS 18-30 categories (85.2%), but substantially lower for RS greater than 25 (71.3%).³⁶

The utility of RS in older women was evaluated in a SEER study of pN0 and pN+ patients that compared patients aged more than 70 years with those 18 to 69 years. In the older cohort, 18% were pN+; the distribution of RS results was similar between age groups. On adjusted analysis, RS greater than 25 was associated with inferior OS compared with RS less than 11 in both age groups, although the magnitude of effect was lower in the older group (>70 years: HR, 1.47, $P = .003$; 18-69 years: HR, 2.35, $P < .001$). Among patients with RS greater than 25, chemotherapy was used in 73% and 52% of those aged 18 to 69 years and greater than 70 years, respectively. Use of chemotherapy was significantly associ-

ated with improved adjusted OS and BCSS in the younger cohort, but not in patients aged more than 70 years.³⁷

Few studies have compared the clinical value of the RS across ethnic groups. A recent NCDB analysis of pN0 and pN+ patients identified small but statistically significant differences in the prognostic performance of the RS across racial/ethnic groups ($P < .001$). The c-index was used to compare the predictive ability per 10-unit RS increase, where a value of 1 indicates perfect prediction and a value of 0.5 indicates no better predictive ability than random chance. The c-index was highest for patients who were non-Hispanic White (0.581) and Asian/Pacific Islander (0.586), and lowest for those who were African American (0.535) and Hispanic (0.542).³⁸ Further study is warranted in minority populations, who are also underrepresented in clinical trials.

Other Emerging Applications

There is increasing interest in incorporating the 21-gene RS into other elements of clinical decision-making beyond those choices related to adjuvant chemotherapy. In pN0 patients, gene expression profiles can prognosticate likelihood of locoregional recurrence (LRR)^{39,40}; this has now been shown in pN+ disease as well. Among 1065 pN+ patients from NSABP B-28, 43% were treated with breast-conserving surgery (BCS) and 57% with mastectomy. The 10-year LRR rate was 3.3% for those with RS less than 18, 7.2% with RS 18-30, and 12.2% with RS of 31 or greater ($P < .001$). On adjusted analysis, the continuous RS remained a significant predictor of LRR; for any 50-point increase in the RS result, the risk of LRR more than doubled (HR for 50-point increase, 2.59; 95% CI, 1.28-5.26; $P = .008$).⁴¹

Among 316 pN+ patients treated with BCS and radiation or mastectomy without radiation in SWOG 8814, 10-year LRR rates were 9.7% for RS less than 18 versus 16.5% for RS ≥ 18 ($P = .02$), and an RS 18 or greater remained significantly associated with LRR after adjustment for

surgery type, number of positive nodes, and use of chemotherapy. In the mastectomy subgroup, 10-year LRR was particularly low (1.5%) in those with 1 to 3 positive nodes and RS less than 18. In patients with 4 or more positive nodes, 10-year LRR was similar regardless of RS category (RS <18, 25.9% vs RS ≥18, 27.0%; $P = .27$).⁴² Together, these findings suggest a potential role for tailoring use of radiation therapy based on RS results. The ongoing TAILOR RT trial will be the first randomized control trial evaluating this concept, with a recurrence-free interval primary end point. Patients with ER+/HER2– disease, 1 to 3 positive nodes, and RS less than 18 are eligible; those treated with BCS are randomized to whole breast radiation with or without regional nodal radiation, and those treated with mastectomy are randomized to no radiation or chest wall/regional nodal radiation.⁴³

Another potential application for the 21-gene RS in pN+ patients is to guide neoadjuvant systemic therapy decisions. The feasibility and reliability of performing the RS assay on core biopsy specimens has been demonstrated in greater than 100,000 samples.⁴⁴ Unlike other biologic subtypes, hormone receptor–positive patients are eligible for either neoadjuvant chemotherapy (NAC) or neoadjuvant endocrine therapy (NET). Rates of pathologic complete response (pCR) to NAC are low in this population,⁴⁵ and even lower in patients with low or intermediate RS.⁴⁶⁻⁴⁸ Further, a meta-analysis of nearly 3500 patients demonstrated that NET is associated with equivalent response rates and rates of BCS, but with lower toxicity compared with NAC.⁴⁹ Therefore, using the RS to identify patients who may not require chemotherapy as part of their treatment could help select those most suited to an NET approach. A small but prospective, multicenter study evaluated the feasibility of selecting NAC vs NET based on the RS in 64 pN0-1 patients. NET was recommended for RS less than 11 and NAC for RS greater than 25, and those with RS 11-25 were randomized to

either regimen; compliance with assigned treatment was high in the randomized arm (85%), supporting feasibility of this strategy.⁵⁰ We anticipate that oncologists will increasingly incorporate the RS into neoadjuvant treatment recommendations in patients with hormone receptor–positive disease.

Conclusions

Substantial existing data support the clinical utility of the RS in patients with hormone receptor–positive/HER2– pN+ breast cancer. In particular, those with 1 to 3 positive nodes and RS less than 18 have excellent outcomes and appear to derive negligible benefit from adjuvant chemotherapy in retrospective analyses of clinical trials and large population-based series. Prospective validation of these findings is provided by the excellent outcomes observed with ET alone in those with RS less than 11 and RS of 25 or less in the WSG's PlanB and ADAPT trials, as well as an absence of chemotherapy benefit in postmenopausal women with RS of 25 or less in RxPONDER. Premenopausal patients have been underrepresented in many studies; while RxPONDER demonstrated a small benefit to chemotherapy in premenopausal patients with RS of 25 or less, future analyses are needed to determine the attributable effect of chemotherapy-induced ovarian function suppression in this population. Based on existing retrospective data, we may be able to cautiously extrapolate the findings in postmenopausal women in RxPONDER to patients with 4 or more positive nodes as well. It is unlikely that there will ever be a prospective randomized trial of ET vs ET plus chemotherapy in this group of women with multinode-positive breast cancer.

While the focus of this review was the 21-gene recurrence score, the MINDACT trial now provides prospective evidence for the use of another genomic assay in adjuvant chemotherapy decision-making in pN+ patients. In this phase 3 study, pN0-1 patients with high clinical-risk but low genomic-risk disease (determined by

the MammaPrint® 70-gene signature test) were randomized to ET alone vs ET plus chemotherapy. In a preplanned subset analysis of 738 patients with pN1 disease, DRFS was 96.3% with chemotherapy vs 95.6% with ET alone.⁵¹ This lends further support for the ability of genomic assays to select patients who do not benefit from adjuvant chemotherapy. We have highlighted that many institutions have already adopted the RS assay in clinical decision-making for adjuvant chemotherapy in the pN1 population, with a resultant net reduction in chemotherapy use. Emerging applications for the RS in clinical care include decision-making related to radiation therapy as well as selection of neoadjuvant systemic therapy. ■

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➤ For full reference list, visit cancernetwork.com/RS_breastcancer

CONTINUING MEDICAL EDUCATION (CME)

Contextualizing COVID-19 Consequences for Cancer Care

FACULTY

Karen M. Winkfield, MD, PhD
Executive Director
Meharry Vanderbilt Alliance
Nashville, TN

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LEARNING OBJECTIVES

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

- Describe the major challenges in the clinical management of patients with cancer brought upon by the COVID-19 pandemic
- Outline clinical practice recommendations proposed by oncology societies regarding cancer care during the COVID-19 pandemic
- Assess individualized cancer screening and treatment modifications in the context of changing epidemiological characteristics of COVID-19

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The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) rapidly escalated to a pandemic with significant morbidity and mortality resulting from the associated coronavirus disease 2019 (COVID-19).¹ Approximately one-third of patients developing COVID-19 experienced severe complications, including acute respiratory distress syndrome, acute renal failure, acute respiratory injury, septic shock, and severe pneumonia.² Populations particularly vulnerable to COVID-19 include older adults and immunosuppressed patients. Patients with cancer are often immunosuppressed, whether caused by the malignancy or the treatment regimen they receive. As such, patients with cancer have an increased risk of infection with SARS-CoV-2 and greater COVID-19–related morbidity and mortality compared with the general population.³ In 2021, with COVID-19 remaining at the center of focus for healthcare professionals across disciplines, dynamic treatment strategies adapting to the demands of the pandemic have continued to be refined and implemented.

Karen M. Winkfield, MD, PhD, discusses the challenges that the COVID-19 pandemic has presented in the clinical care of patients with cancer and epidemiological trends emerging for patients with cancer.

Q: Which subpopulations of patients with cancer appear to be most

susceptible to severe COVID-19 morbidity and/or mortality?

WINKFIELD: We are learning a lot about COVID-19 and cancer. We are gathering information from all over the world. Some of the first information that we received about the populations at greatest risk related to COVID-19 and cancer came from China. We had some data from Europe and now more data from practices in the United States. One of the patient populations that has some of the greatest impact related to COVID-19, including both incidence and mortality, was patients who had lung cancer.³ It makes sense that because SARS-CoV-2 is associated with respiratory illness, individuals who already have diminished lung capacity are going to be at greatest risk. These patients are already struggling with lung function and may need chemotherapy or radiation directed at their lung, which can further cause more inflammation.

Those patients are at incredibly high risk of not only developing COVID-19, but also having significant morbidity associated with the virus. And that morbidity oftentimes translates into mortality. We also know that individuals with hematologic malignancies tend to do worse with COVID-19.⁴ Many of the hematologic malignancies, such as lymphoma, are disorders of the immune system in which white blood cells are not functioning properly. This dysregulation of the immune system may put them at higher risk of developing COVID-19

and COVID-19–related illnesses. Additionally, in anyone getting different types of chemotherapy, their immune system is impacted.

In patients receiving cytotoxic therapy that may have an impact on bone marrow production and splenic function, those individuals may indeed be more susceptible to the development of COVID-19 and COVID-19–related morbidity and mortality. It varies by age, which I think is fascinating. If you look at the literature, individuals who are older are generally at greater risk of developing morbidity and mortality related to COVID-19. We are seeing the same thing in the oncology space as well.

Generally, when we look at COVID-19, we know that Black and Hispanic patients are at higher risk of contracting COVID-19.⁵ And often Black individuals will have worse morbidity and mortality. It's interesting, not so much for Hispanic populations, but they call that the Hispanic paradox where although Hispanic individuals and Latinos may have a higher risk of contracting the virus, they may not necessarily have the same morbidity. Some of that may be associated with reduced age, but also reduction in the number of comorbid conditions that may exist in that sub-population. African Americans tend to have higher risk of hypertension and diabetes. And when we looked at some of the early data about which patients are going to have increased mortality from COVID-19, it was those individuals who had cardiovascular

disease or diabetes.

Q: How has cancer screening and diagnosis changed in the management of patients for whom suspicion, or increased risk of cancer exists?

WINKFIELD: Screening is a major issue. In March 2020, following the lockdown, cancer screening facilities were shut down, including radiologic subspecialties that closed because we were not sure how to proceed with those things safely. But when those sites started to open up, we did not see the same bounce back with patients getting screened. There has actually been some work done that shows that there are approximately 80,000 cancers that are going to have delayed diagnoses this year.⁶ And that only includes data from March through June. When you have that number of people who have delayed diagnoses, the estimation is that probably about 35,000 individuals are at increased risk for mortality due to cancer because of that delay.

So one of the things that I have been really stressing both to community members and to patients is to please get your cancer screening done. We have safety in place to allow for patients and providers to be safe during the screening process. And so that's the big message that I think needs to get out there because if we don't get on top of the screening, we're going to be in trouble. There was a reduction during that time period of May through June, which was

about an 80% reduction in the number of mammograms that were done.⁷ We almost went down to zero, and we know that that can translate, unfortunately, into increased morbidity and mortality. For instance, say a woman did have a mammogram and then a lump was found. There were then delays in terms of getting patients into surgery, which again, translates into worse outcomes and morbidity/mortality. Those delays have decreased because we again have learned a lot. The American Society of Clinical Oncology actually put out a report or essentially guidelines around how to practice oncology safely during the COVID-19 pandemic.⁸ These guidelines make certain recommendations in terms of calling the patient in advance and making sure they don't have symptoms before scheduling surgeries, or 24 hours or 48 hours before a surgery is done.

So we have pulled together as an oncology community to determine the safety measures that we can put in place to ensure that someone who may potentially have a cancer diagnosis, or maybe they need a diagnostic image because they felt a lump in their breast or had symptoms related to colorectal cancer, we know cancer doesn't stop because of COVID-19. So we've got to keep doing the care that we need to. But it has been a huge learning curve. And I've been very impressed by not only the oncology community, not just the radiation oncology, not just the surgeons, the medical oncologists, everyone

pulling together and figuring out the things that we need to do to ensure that there are not further delays in terms of diagnostic testing or anything that needs to be done to help patients.

From a screening perspective, the biggest thing is to encourage folks to get screened; do not allow for the delays in screening to happen. If there are diagnostic tests that need to be run, those are all being done safely now with fewer delays, and even fewer delays going into surgeries.

Q: Which therapeutic regimens in patients with cancer appear to impact susceptibility to severe infection and increased morbidity/mortality?

WINKFIELD: Regarding chemotherapies and those that reduce the immune system, people will say that any cancer treatment can impact the immune system, and they're right. Even radiation therapy, even though it's external beam, the body's immune system reacts to the inflammation caused.

But I can tell you that radiation to someone's arm is very different than radiation to someone's lung. And particularly for this virus, individuals who have underlying lung pathology, cancer, or asthma are more susceptible and more at risk for developing bad things that happen due to COVID-19. But say a patient has lymphoma that is in the mediastinum in the central part of the chest, and they need radiation therapy; radiation to the lung is going to put that

patient at higher risk than if their lymphoma were in their groin or another area. So radiation therapy in and of itself is not necessarily a risk factor for developing more conditions related to COVID-19, unless it's directed at the organ that is most effected by COVID-19, which are the lungs.

When it comes to systemic therapies, in addition to those that actually reduce your blood counts and have impact on marrow or impact marrow suppression, there are also data to suggest that immune checkpoint inhibitors like the PD-L1 and the PD-1 Inhibitors may be associated with worse outcomes and may actually be associated with increased morbidity and mortality, although it's fascinating because there was another study seemed to contradict these results.^{9,10} But all the data that we have suggest that patients getting new checkpoint inhibitors as part of their care may be at increased risk. This is consistent with the fact that checkpoint inhibitors tend to have some impact on the

lung parenchyma itself. So I think that's one where, when it comes to systemic therapy, the immune checkpoint inhibitors do contribute to a slight increased risk, both in terms of the getting the disease, but then if they do get COVID-19, they end up having more COVID-19-related diseases and morbidity/mortality.

Q: What have been the most substantial changes in cancer care that were implemented during the COVID-19 pandemic?

WINKFIELD: The number 1 thing that has changed is how individuals who have a cancer diagnosis are moved through the system. We are trying to do it virtually. We try to do more virtual visits. We try to protect the patients from exposures in the cancer center. But that also means that, in some ways, it becomes less personal. And that, to me, hurts my heart because cancer is such a challenging thing for patients to go through, whether it be through the diagnosis, when

"From a screening perspective, the biggest thing is to encourage folks to get screened; do not allow for the delays in screening to happen. If there are diagnostic tests that need to be run, those are all being done safely now with fewer delays."

-Karen M. Winkfield, MD, PhD

patients want to have their family members there. And sometimes they can't. At our cancer center, we initially did not allow family members to even come into the room. It was only the patient who came back to talk to the provider. And can you imagine learning that you have cancer, how do you even hear anything after that? How do you even hear about what the treatments are going to be? So we have really had to adapt as providers to consider that this person might be sitting in the room by herself, but let's call the family member on the phone or let's make sure we get somebody on a Zoom call.

Telemedicine has really taken off and we've been able to utilize that in a way where we can have family members present to have discussions and review lab tests. We have really been able to shift gears quickly. But it was hard during the first months, in March and April, because we put all these stops in place and barriers that changed the way that we practice oncology. But now we are utilizing technology and the government is recognizing the importance of us being able to use technology. For example, prior to this, telehealth was not covered. So although for my rural patients, for whom I would have loved to have been able to do telehealth visits, they were forced to drive 2 hours in for a 15-minute visit because we were not able to bill for that virtually.

Now, there is this protection that allows for oncologists to utilize the technology of telehealth in a very different way.

And we are doing that. That is a big difference, thinking about safety and how can we do our job where people are giving information or getting information but not having to bring them into the centers, or if they are there by themselves, how do we make sure we're inclusive of family members.

The other change has been around the timing of treatments, including surgeries. We know how to take good care of patients during COVID-19. There still is some discussion around whether we can shorten the course of therapy safely. For example, in the United States, breast cancer radiation therapy used to take anywhere from 5 to 7 weeks, depending on how much radiation and what needed to be treated. In Europe, they had been using much shorter courses of therapy of 4 weeks. In Canada, they actually had been doing it for a long time as well. And the papers had been out there and published for a long time. And we called it hypofractionated radiation therapy for breast cancer. In the United States, we were a little bit slow adapting, although we had started adopting it several years ago. But in the COVID-19 era, now most women are getting the hypofractionated course of therapy. We know that the outcomes are exactly the same, so people are still able to get safe care. Now it's almost universal.

I'm seeing that from a chemotherapy standpoint, being thoughtful about whether we can take out a taxane to make this regimen have less of an impact on the immune system,

but still give them the same benefit and have the same outcome. All those discussions are currently being held regarding the timing of therapies. The oncology community has done a really good job putting our heads together and determining the best course of action for a patient: should treatment be delayed, shortened, etc.

Q: What strategies are being utilized to maintain clinical trial enrollment for patients with cancer during the COVID-19 pandemic?

WINKFIELD: The clinical trials enrollment question is a big one. We know that access to clinical trials for patients is essential for some who may have already gone through standard-of-care therapy and have progressed and need a new therapeutic option. Clinical trials provide that. Again, we had some growing pains during the COVID-19 season to learn how best to do things. But we really wanted to maintain the clinical trial treatment options. It is important to remember that cancer research is varied in that there are cancer therapy trials, there are interventional trials, and there are patient-reported outcome trials or observational studies.

But the cancer therapy trials are really important. One of the strategies that I've seen at a couple of different cancer centers is determining whether visits can be conducted virtually. So instead of having the patient come in and sign consent in person, can we do that through a virtual visit and then have a virtual signature?

There was some technological integration that needed to be completed, as well as getting approval from the Institutional Review Board. It is important that this keeps in consideration that people are able to get their questions answered so that they could provide informed consent before entering into a treatment trial. The other thing that's been fascinating to watch is researchers and providers really thinking hard about whether particular blood tests are necessary and asking if we really need it to give us the outcome or to show us whether or not this particular treatment is safe or effective. So there is more thought going into the way that trials are conducted, including those that had been in process. There has been some tailoring of the way that clinical trials are actually done, the logistics of clinical trials, and making sure that patients have access. But I think the bottom line is that we are still learning and growing. But the biggest thing is making sure that patients who have cancer have access to those postclinical treatments that may indeed prolong their life and may actually result in a cure.

Q: How can we best distinguish toxicities associated with cancer therapy from symptoms of COVID-19 and other infections?

WINKFIELD: We know that cancer therapies can result in some of the same exact symptoms that people with COVID-19 experience. We tell patients who are getting systemic

therapy and chemotherapies if you have a fever over 101 °F, you need to call or go to the emergency room. We have those conversations routinely. But guess what, it's one of the side effects lung cancer patients have, so they call. So how do you differentiate? And it's hard. So I have a colleague of mine who actually runs the COVID-19 response in the emergency room, in a hospital in San Francisco, and he has to deal with undifferentiated patients, those who may have symptoms that seem similar to COVID-19 but they're also cancer patients. And he talks a lot about the work that they do in the emergency room.

Part of it is asking people what their risks for exposures are. But there are going to be times where there are patients where you are not sure if they have COVID-19 or not. And so those oftentimes are considered patients under investigation who may have had an exposure or may have fever and chills. And you just have to run the test. Testing is now more readily available, although it is not universally available. It's really a problem for cancer patients where they are symptomatic because we can't get rapid tests for everybody. It's better at some institutions than others, but I can tell you that sometimes you have a patient that you want to test and you want to start a treatment for, they have some symptoms, we test them, but then it's several days before they get the response back for the COVID-19 test. And then they may have had additional exposures, so it's hard. If we

had better testing and more onsite rapid tests, that would be the ideal thing to be able to do in order to differentiate. But frankly, right now we just do the best we can. Occasionally, if patients have fever and even though they're getting chemotherapy, they have to come in and get triaged. That's just the best way to do it.

Q: In your experience, what have been the concerns of your patients with cancer regarding COVID-19's impact on their cancer care?

WINKFIELD: Patient response to COVID-19 and cancer has been varied, as you can imagine. I must say one of the things that I hear the most is that they feel alone, that they're on the journey by themselves because they may not be able to have their loved one with them. That is a challenge, it's really hard during COVID-19 when people are having to take this journey on their own. They can't have their loved one with them in the infusion center. And it's hard on providers, too, because again, many of our oncology providers are also getting pulled in now that the COVID-19 numbers are going up.

We are all scrambling. So not only are we trying to do our job as oncologists, but some of us are being asked to also kind of work on the COVID-19 wards because the numbers keep going up. And so I do feel that the journeying alone aspect has been one of the biggest concerns that I hear from my patients with cancer. I don't think that they

fear that their treatments are worse or not as optimal. It's really about having to take this journey by themselves and also the uncertainties of when they can see their family again. I hear them ask these questions, "Is it safe?", "My daughter just had my first grandchild, when can I see her?", "I know I haven't been on chemotherapy for 4 months now, is it safe now? Can I go and see my grandchild?" Those are the sorts of things, the journeying alone, the when is it safe to reconnect? And some of these questions, we're not 100% sure of what the right answer is. But that's where you try to give information so that people can make an informed decision. And so I would say that that inability to have people around you during a very challenging time has been one of the biggest issues related to cancer care that I've heard from my patients. ■

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Final Analysis Shows GP2 Immunotherapy Vaccine Induces 100% DFS Rate for Patients With HER2 3+ Breast Cancer

Gina Mauro

Treatment with GP2 immunotherapy and granulocyte-macrophage colony-stimulating factor (GM-CSF) led to a 100% disease-free survival (DFS) rate for patients with HER2 3+ disease who received adjuvant trastuzumab (Herceptin), according to study results presented at the 2020 San Antonio Breast Cancer Symposium.¹

GP2, a HER2-derived cancer vaccine, is a 9 amino acid transmembrane peptide of the HER2 protein. The vaccine is designed to provoke the body's immune system, allowing it to recognize and fight tumor cells that express HER2. Administering GP2 in combination with GM-CSF stimulates the proliferation of antigen-presenting cells, with the goal of preventing breast cancer recurrence.²

The final, 5-year efficacy analysis of this prospective, placebo-controlled, multicenter phase 2b basket trial (NCT00524277) showed that the estimated 5-year DFS rate in patients with HER2 3+ disease who were treated with GP2 plus GM-CSF and completed the Primary Immunization Series (PIS) was 100% compared with 89.4% (95% CI, 76.2%-95.5%) in patients who received placebo and GM-CSF ($n = 50$; $P = .0338$). GP2 was also found to be well tolerated, with no serious adverse events reported.

Patients with node-positive and high-

risk node-negative breast cancer with tumors expressing any degree of HER2 expression (immunohistochemistry 1+ to 3+) were randomized to receive GP2/GM-CSF vs GM-CSF alone. The intent-to-treat (ITT) population consisted of 180 patients; across 16 clinical sites, 168 patients were treated, 96 of whom had HER2 3+ disease.

All patients enrolled in the study received 6 intradermal injections of GP2 plus GM-CSF (500 μ g GP2; 125 μ g GM-CSF) or placebo plus GM-CSF at 125 μ g every 3 to 4 weeks as part of the PIS for the first 6 months. Four intradermal injections of either GP2 plus GM-CSF or placebo GM-CSF were administered every 6 months thereafter.

Ninety-six patients with HER2 3+ disease received standard adjuvant trastuzumab and subsequently completed the complete PIS or placebo; the PIS was started a median of 17.1 months following surgery. Seventy-two patients with HER2 1+ to 2+ disease, who did not receive trastuzumab following surgery and then completed the full PIS or placebo, started the PIS at a median of 10.8 months following surgery.

The primary end point of the trial was recurrence rate; unexpected toxicities, as well as the correlation between immune response and clinical outcomes, were secondary end points.

The investigators noted that since GP2 is synergistic with trastuzumab, and the patients with HER2 1+ to 2+ disease were not treated with trastuzumab, the study design was prespecified to compare recurrence rates with ITT vs per protocol in these 2 distinct, independently reported populations, excluding those who did not complete the PIS.

Results also showed that the estimated 5-year DFS rate in those with HER2 1+ to 2+ disease who received the combination and completed the PIS ($n = 35$) was 77.1% (95% CI, 59.5%-87.9%) vs 77.6% (95% CI, 60.1%-88.2%) in those who received placebo/GM-CSF ($n = 37$; $P = .9142$). ■

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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Telehealth 2021: Where Do We Go From Here?

The rise of telehealth in 2020, mainly attributed to the coronavirus disease 2019 (COVID-19) pandemic, has been well documented. The pandemic accelerated what was at the time mostly niche telehealth technology and introduced it, out of necessity, to a much larger patient population. With the approval and subsequent distribution of multiple COVID-19 vaccines, a long-awaited return to normalcy may finally be on the horizon. Will regular implementation of telehealth visits continue and become a part of the new normal?

Medical Economics®, a sister publication of *ONCOLOGY®*, spoke with Thomas Conroy, cofounder and CEO of MedSign, about what the future of telehealth might look like.

Q: How well has the massive expansion of telehealth during the pandemic worked out for both doctors and patients?

CONROY: When we talk about telehealth, [we have to be grateful] that the government sort of got it right by expanding the use of telehealth across the board. In the beginning, telehealth was positioned for rural areas, and now it's across the nation. I think it's a learning process. Because of COVID-19 and the inability to get to physicians' offices, the door opened up to telehealth, but we've got to do a lot more. We need to make some technology changes to address people who are, let's say, technology averse. I'm talking [mainly] about seniors. They should be able to access telehealth in the comfort of their

home. For doctors, I think, overall, you find that the younger doctors are totally open-minded and want to embrace telehealth, and maybe the older doctors are the type who would like to see the patient in the home. And they'll learn over time that this is an incredible tool to have in their war chest to help to keep people healthy and well in the home.

Q: In the past, Medicare primarily focused telehealth benefits on rural areas, where care could often be hard to access. Is that the right approach?

CONROY: Centers for Medicare & Medicaid Services (CMS) took what they were doing in the rural areas and applied it to a nationwide program. Absolutely, it was a great way to start, and they understood some of the shortfalls there. Being a technologist, I [believe that] what we need to do, though, is make sure that the information that's provided and the connectivity that's provided are for all Americans, and not just young people. Young people all understand just having happiness in your hand in the form of a cell phone is the way to go, because that's what they live by. We're going to see more and more of that as we progress in the telehealth arena. But we have to embrace [everyone beyond young] people and get others to adopt the system, and I think CMS has done that in the beginning here very well.

Q: Many patients who used telehealth have since returned to in-office visits, and doctors who

reported a lot of telehealth usage in early 2020 now say it's declined. What does that say about the long-term future for telehealth in medicine?

CONROY: I think this is a generation issue. The older generation wants to be able to go into the doctor's office, look them in the whites of their eyes, and get the [clinicians] to care for them personally. But young people are [accustomed] to the use of technology that exists today, and it's just only going to grow. We're not really seeing a real reduction; [rather, it's] an increase in in-home and in-office care. The seniors would like to actually talk to and see the doctors themselves, but that will change over time as telehealth becomes commonplace.

You also have to consider [a segment of the senior population] who is really important: those who have chronic diseases. They don't want to go to the hospitals, they don't want to see their doctors, they want to sit and stay in the comfort of their home—but you have to provide technology that enables them to do that. And the technology is out there. The one I'm working on, for example, enables seniors to talk to the physician or their nurse, or even their loved ones, in the comfort of their home by using a home television set. I think that if we can apply that common technology, televisions that are in 120 million homes, we get to sell a winner here. You have to provide seniors with what they know best, and that's access to a product that they use every day in their home: a television set. So that will be the embracement part.

The adoption part that telehealth needs is bringing in those people who are using pretty much most of the Medicare and Medicaid dollars: the seniors aged more than 75 years, especially. And here's the other thing: That population is growing. Think about it: Because of all the health care that they're receiving, they are living longer. We have to make sure that we can embrace those folks, and the way you do it is by providing technology that they can adopt with ease.

Q: How have private insurers approached telehealth? Have they gotten it right?

CONROY: Yes, and no. There's still a weeding-out factor, and the government and the private insurers really have to get together on this. Let's face it: COVID-19 forced us into this new arena called telehealth across the country. Before, telehealth was rural. I think on the private insurers' side, there's currently a real lack of understanding of the potential of telehealth. They understand it [somewhat], but I think over time they will start seeing the analytics or statistics showing that it's better to have telehealth to reduce the cost of a hospital stay than it is not to have it. Now, I will say that a problem right now is that companies have to build controls into the telehealth sessions. You may recall that in early 2020, a telehealth fraud occurred in Florida on the order of \$1.2 billion. The [perpetrators] made cases up and they were caught. Roughly 300 people are involved in this, because no control mechanisms were built in. It's the Wild West of telehealth right now; it's "get a session—get paid." But if you can build controls that enable even Medicare to look in and make sure that it's a true telehealth session—even with using HIPAA [the Health Insurance Portability and Accountability Act] [privacy rules] as a baseline—you'll see that the economics will be a lot better with telehealth built into the system. It's still a learning process for these folks, but it will change over time. It will [eventually] be as common

as going into your doctor's office and getting your blood pressure, weight, and temperature [measured].

Q: Does telehealth still have technological challenges? If so, how can they be fixed?

CONROY: Yes, the [main] technological challenge is the fact that you're not reaching 35 million people who are senior citizens. And every day, for the next 15 years, that number grows by 10,000. Some of those people are ready. They understand the iPhone, smartphones, and tablets, but 35 million people out there do not. And so they're technologically a challenge. About 260 telehealth companies are out there, all vying for the same space, [but their technologies are based on] smartphones and tablets. Seniors don't use those things. So, the challenge is to develop a technology that seniors will adopt. How do you get into that senior home? How do you get them to adopt it? Then, the second challenge is how can you perform an examination in a home? And that, to me, is very critical to providing a better health and wellness system for people, especially the elderly, many of whom are disabled. You have to take that technology aversion away, and you have to gain adoption.

Q: What will ultimately drive greater telehealth adoption: reimbursement that's on par with in-office visits or just patient demand for it?

CONROY: Both. Appropriate reimbursement is critical and the doctors have to get reimbursed for [telehealth], but you have to have [patients] wanting to do this. Seniors want to stay at home. They don't want to go out on the road. I don't want my dad, a 92-year-old World War II veteran, to have to go down to the VA to see a physician. I don't want him getting in a car traveling. He's sitting there [in the waiting room and office] for an hour potentially getting COVID-19, and then [I have to worry about him] driving

back and forth and [possibly] getting in an accident. So, I think the [motivation] here is creating systems that are easy for seniors to use.

On the medical side, full reimbursement for a telehealth session is important. Another point that's really important is that medical equipment is reimbursed, but telehealth-specific equipment is not being reimbursed at this time. I understand why the government is hesitant to reimburse telehealth equipment: Anybody can say a computer or a laptop [was purchased for telehealth purposes and] is [thus] reimbursable, [so reimbursement for those items] isn't going to happen. But if you design telehealth-specific equipment, the government should allow the purchase of that equipment to be a reimbursable event.

Q: Ten years from now, what do you think telehealth will look like? How widespread do you think it will be?

CONROY: I think we're going to get it right, and I think it will have a global impact, too. A lot of companies are working on it. I can see telehealth being provided to other countries through the United States. With the technologies in the pipeline, you're into some pretty exciting things. Besides having telehealth, you should have a fully automated home that fully embraces somebody who is disabled, and you should have the ability to send medical information anytime and anywhere that they need it. And I'm talking about physicians who need it. Then, finally, there is artificial intelligence (AI). There are not enough nurses out there, not enough doctors. So, what are you going to do? You should have AI be a part of your system, which would enable a doctor to get a full preevaluation before they talk to the patient. I think AI is going to be absolutely critical to anybody's road map. ■

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CONTINUING MEDICAL EDUCATION (CME)

Individualizing Treatment Plans and Optimizing Outcomes for Patients With MF and PV

FACULTY

Srdan Verstovsek, MD, PhD
United Energy Resources, Inc.
Professor of Medicine
Chief, Section for Myeloproliferative Neoplasms (MPNs)
Director, Hanns A. Pielenz Clinical Research Center for MPNs
Department of Leukemia
The University of Texas MD Anderson Cancer Center
Houston, TX

Claire Harrison, DM, FRCPath
Professor
Guy's and St Thomas' NHS Trust
London UK

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Local: 609-378-3701
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info@gotoper.com

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- Explain current clinical treatment strategies for patients with MF and PV
- Summarize the latest data reported from ongoing clinical trials and their potential impacts to the treatment landscape of MF and PV

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Diagnosis and Risk Stratification of Myelofibrosis and Polycythemia Vera.

The myeloproliferative neoplasms (MPN) are malignancies characterized by chronic proliferation of differentiated hematopoietic cells.¹ The main MPNs include polycythemia vera (PV), essential thrombocythemia (ET), and myelofibrosis (MF), presenting primarily as erythrocytosis, thrombocytosis, and bone marrow fibrosis due to myeloproliferation, respectively.^{1,2} The pathogenesis for MPNs includes a phenotypic driver mutation involving constitutive activation of the JAK-STAT pathway, which is physiologically responsible for numerous hematopoietic processes.

Suspicion of PV in patients presenting with erythrocytosis involves an initial work-up that includes testing for *JAK2* V617F mutations and serum erythropoietin (EPO).³ The presence of a *JAK2* V617F mutation accompanied by subnormal serum EPO levels strongly suggests PV and warrants further work up to confirm diagnosis (**Table 1**). Major criterion number 2, as detected by a bone marrow biopsy, may not be required in cases with sustained absolute erythrocytosis if major criterion number 3 and the minor criterion are present. However, initial fibrosis can only be detected by performing a bone marrow biopsy; this finding may predict a more rapid progression to overt myelofibrosis. In cases of negative *JAK2* V617F mutation

TABLE 1. WHO Diagnostic Criteria for PV and ET

Polycythemia vera (PV) ^a		Essential thrombocythemia (ET) ^b
Major criteria		
1	One of the following: <ul style="list-style-type: none"> ▪ Hb > 16.5 g/dL in men; > 16.0 g/dL in women ▪ Hct > 49% in men; > 48% in women ▪ Increased red cell mass (RCM)^c 	Platelets ≥ 450 × 10 ⁹ /L
2	Hypercellular bone marrow with panmyelosis	Proliferation mainly of megakaryocyte lineage including enlarged, mature megakaryocytes with hyperlobulated nuclei. No significant increase or left shift in neutrophil granulopoiesis or erythropoiesis
3	Presence of <i>JAK2</i> V617F or <i>JAK2</i> exon 12 mutation	Not meeting WHO criteria for other myeloid neoplasms
4		Presence of <i>JAK2</i> , <i>CALR</i> , or <i>MPL</i> mutation
Minor criterion		
1	Serum EPO below normal reference range	Presence of a clonal marker or absence of evidence for reactive thrombocytosis

EPO, erythropoietin; Hb, hemoglobin; Hct, hematocrit.

^aDiagnosis of PV requires meeting all 3 major criteria or the first 2 major criteria and the minor criterion

^bDiagnosis of ET requires meeting all 4 major criteria or the first 3 major criteria and the minor criterion

^cRCM > 25% above mean normal predicted value.

accompanied by subnormal or normal serum EPO levels, further testing for the presence of *JAK2* exon 12 mutations as well as a bone marrow biopsy are required to establish PV diagnosis.

The 2016 WHO diagnostic criteria distinguishes a new entity, prefibrotic MF, which is distinct from PMF and does not share the same poor prognosis (**Table 2**).⁴ The classification of prefibrotic primary MF allows its distinction from true essential thrombocythemia by morphologic findings from bone marrow biopsy, which has significant prognostic implications for patients. Current NCCN guidelines for MPN recommend that prognostic risk primarily determine the clinical approach

to patients with MF.⁵ Several prognostic scoring methods are available, all of which have been modified from the initial International Prognostic Scoring System (IPSS). The preferred prognostic scoring systems recommended by NCCN guidelines for patients with primary MF (which does not apply to pre-fibrotic MF or secondary MF) include the Mutation-Enhanced IPSS (MIPSS-70; for patients age ≤ 70 years) and the mutation and karyotype-enhanced IPSS (MIPSS-70+ Version 2.0) as shown in **Table 3**. The Dynamic IPSS (DIPSS)-Plus is the recommended scoring tool when molecular testing is unavailable. The recommended prognostic scoring tool for patients with post-

PV or post-ET MF is the Myelofibrosis Secondary to PV and ET-Prognostic Model (MYSEC-PM).

Evolving Management of Polycythemia Vera

Current NCCN guidelines recommend that patients with PV undergo risk stratification prior to treatment based on risk factors for thrombosis to guide treatment planning.⁵ Patients younger than 60 years of age with no history of thrombosis are classified as having low-risk PV, whereas those aged 60 years and older or who have a history of thrombosis are classified as high risk. Patients with low- and high-risk PV should be managed with therapeutic phlebotomy to maintain a

hematocrit lower than 45%.¹¹ Cyto-reductive therapy is indicated for patients with high-risk disease and select patients with low-risk disease (eg, requiring frequent phlebotomy, severe disease-related symptoms, platelet count greater than $1500 \times 10^9/L$, and progressive leukocytosis). First-line cytoreductive therapy options for patients include hydroxyurea and peginterferon alfa-2a. The use of an interferon is generally reserved for younger patients, due to the risk of toxicity. In older adults, busulfan is an additional therapy option for cytoreduction.⁹ Regardless of risk, all patients with PV should be managed for cardiovascular risk factors, and unless contraindicated, receive acetylsalicylic acid 81 mg to 100 mg daily.

Ropeginterferon alfa-2b is an investigational agent that was evaluated in the phase 3 randomized, controlled PROUD-PV trial and its extension study, CONTINUATION-PV. A total of 257 patients with low-risk PV were randomized 1:1 to receive either ropeginterferon alfa-2b or hydroxyurea. In PROUD-PV the composite primary end point of complete hematological response with normal spleen size was achieved in 21% of patients receiving ropeginterferon versus 28% of those receiving best available therapy, which demonstrated ropeginterferon noninferiority to hydroxyurea.¹² Recently published 5-year follow-up data from CONTINUATION-PV reported that hematocrit less than

TABLE 2. WHO Diagnostic Criteria for Prefibrotic PMF and PMF

Prefibrotic PMF ^a	
Major criteria	
1	Megakaryocyte proliferation and atypia without reticulin fibrosis > grade 1, plus age-adjusted BM cellularity, granulocytic hyperplasia, often decreased erythropoiesis
2	Not meeting WHO criteria for other myeloid neoplasms
3	Presence of <i>JAK2</i> , <i>CALR</i> , or <i>MPL</i> mutation or in the absence, the presence of another clonal marker ^b or absence of evidence for reactive BM fibrosis
Minor criterion	
1	One or more of the following: <ul style="list-style-type: none"> ▪ Anemia not attributed to comorbid condition ▪ Leukocytosis $\geq 11 \times 10^9/L$ ▪ Palpable splenomegaly ▪ LDH > ULN
Overt PMF ^a	
Major criteria	
1	Megakaryocyte proliferation and atypia accompanied by either reticulin and/or collagen fibrosis
2	Not meeting WHO criteria for other myeloid neoplasms
3	Presence of <i>JAK2</i> , <i>CALR</i> , or <i>MPL</i> mutation or in the absence, the presence of another clonal marker ^b or absence of evidence for reactive BM fibrosis
Minor criterion	
1	One or more of the following: <ul style="list-style-type: none"> ▪ Anemia not attributed to comorbid condition ▪ Leukocytosis $\geq 11 \times 10^9/L$ ▪ Palpable splenomegaly ▪ LDH > ULN ▪ Leukoerythroblastosis

BM, bone marrow; LDH, lactate dehydrogenase; ULN, upper limit of normal.

^aDiagnosis of prefibrotic and overt PMF requires all 3 major criteria and 1 minor criterion confirmed in 2 consecutive determinations

^bMutations in *ASXL1*, *EZH2*, *TET2*, *IDH1/IDH2*, *SRSF2*, or *SF3B1*

45% without phlebotomy was maintained in 81.8% of patients (n = 70) in the ropeginterferon arm versus 63.2% (n = 57) in the best available therapy arm (*P* = .01).¹³ Molecular response at 5 years was achieved in 69.1% of patients in the ropeginterferon arm versus 21.6% of patients in the control arm (RR, 3.2; 95% CI, 2.1-4.9; *P* < .0001). In the ropeginterferon arm, the median *JAK2* V617F allele burden was reduced

from 37.3% at baseline to 7.3%, whereas the control arm median allele burden increased from 38.1% to 42.6% (*P* < .0001). The most common adverse events in the ropeginterferon (n = 127) versus best available therapy (n = 127) arms included thrombocytopenia (22% vs 29%), leukopenia (20% vs 23%), increased gamma-glutamyltransferase (19% vs 3%), fatigue (13% vs 14%), increased alanine aminotrans-

ferase (13% vs 2%), anemia (13% vs 25%), and increased aspartate aminotransferase (10% vs 2%).¹²

Response to PV treatment is assessed using the European LeukemiaNet (ELN) criteria, represented in **Table 4**.¹⁴ Inadequate response to first-line cytoreduction (eg, hydroxyurea) warrants switching the cytoreductive agent. Second-line therapies recommended by NCCN guidelines include ruxolitinib

TABLE 3. Prognostic Scoring Systems for MF

	Prognostic variable (points)	Risk group
MIPSS-70⁶	Hb < 10 g/dL (1)	0-1 = Low 2-4 = Intermediate ≥ 5 = High
	WBC > 25 x 10 ⁹ /L (2)	
	Circulating blasts ≥ 2% (1)	
	Constitutional symptoms (1)	
	Platelets < 100 x 10 ⁹ /L (2)	
	Bone marrow fibrosis grade ≥ 2 (1)	
	1 HMR mutation (1)	
	≥ 2 HMR mutations (2)	
	Type 1/like <i>CALR</i> absent (1)	
MIPSS-70+ v2.0⁷	VHR karyotype (4)	0 = Very low 1-2 = Low 3-4 = Intermediate 5-8 = High ≥ 9 = Very high
	Unfavorable karyotype (3)	
	≥ 2 HMR mutations (3)	
	1 HMR mutations (2)	
	Type 1/like <i>CALR</i> absent (2)	
	Severe anemia (2)	
	Moderate anemia (1)	
	Circulating blasts ≥ 2% (1)	
	Constitutional symptoms (2)	
DIPSS⁸	Age > 65 years (1)	0 = Low 1-2 = Intermediate-1 3-4 = Intermediate-2 5-6 = High
	Hb < 10 g/dL (2)	
	WBC > 25 x 10 ⁹ /L (1)	
	Circulating blasts ≥ 1% (1)	
	Constitutional symptoms (1)	
DIPSS-Plus⁹	DIPSS low (0)	0 = Low 1 = Intermediate-1 2-3 = Intermediate-2 4-6 = High
	DIPSS int-1 (1)	
	DIPSS int-2 (2)	
	DIPSS high (3)	
	Unfavorable karyotype (1)	
	Red cell transfusion need (1)	
	Platelets < 100 x 10 ⁹ /L (1)	
MYSEC-PM¹⁰	Age (years x 0.15)	< 11 = Low 11-13 = Intermediate-1 14-16 = Intermediate-2 > 16 = High
	Hb < 11 g/dL (2)	
	Platelets < 150 x 10 ⁹ /L (1)	
	Circulating blasts ≥ 3% (2)	
	<i>CALR</i> absent (2)	
	Constitutional symptoms (1)	

(preferred), which is indicated for the treatment of patients with PV who have had an inadequate response to or are intolerant of hydroxyurea, and the first-line cytoreductive therapy options not previously received.⁹

Ruxolitinib was evaluated for the treatment of patients with PV who were resistant or intolerant to hydroxyurea in the RESPONSE and RESPONSE-2 studies. The 5-year follow-up data from the RESPONSE study of 222 patients with baseline splenomegaly revealed that 74% of patients had a durable primary composite response (hematocrit control and ≥ 35% spleen volume reduction).¹⁵ Recent 5-year follow-up data from the RESPONSE-2 study of 149 patients without baseline splenomegaly revealed that durable hematocrit control was achieved in 21.6% of patients (n = 74) and complete hematocrit response was achieved in 24.3% of patients.^{16,17}

Selected Emerging Treatment Options for Myelofibrosis

In asymptomatic patients with lower-risk MF, NCCN guidelines recommend observation and clinical trial.⁹ In patients with lower-risk MF who are symptomatic, recommended therapy options additionally include ruxolitinib, interferon, or hydroxyurea. In patients with higher-risk MF, initial treatment is dependent on transplant eligibility of the patient. Transplant candidates are recommended to proceed to allogeneic hemo-

poietic cell transplantation (HCT). Transplant-ineligible patients with higher-risk MF and platelets less than $50 \times 10^9/L$ may consider clinical trial enrollment. In those with platelets greater than or equal to $50 \times 10^9/L$, therapy options include ruxolitinib (category 2A) and fedratinib (category 2B). Patients who inadequately respond to ruxolitinib may receive second-line therapy with fedratinib (category 2A). The use of fedratinib for the second-line treatment of MF following inadequate response to ruxolitinib was evaluated in the JAKARTA-2 study. A reanalysis of JAKARTA-2 data evaluated 79 of 97 patients (81%) who met a more stringent definition of ruxolitinib failure.¹⁸ The primary end point of spleen volume response rate (ie, $\geq 35\%$ spleen volume reduction) was 30% (95% CI, 21-42) in this cohort of patients, whereas symptom response rate was 27%. Safety findings were consistent with previously reported JAKARTA-2 data.

Patients with MF presenting with anemia should undergo a comprehensive work-up to exclude other potential causes of anemia (eg, iron, B12, folate deficiency).⁹ Serum erythropoietin (EPO) measurements help guide optimal therapy selection. In patients with serum EPO less than 500 mU/L, NCCN guidelines recommend erythropoiesis-stimulating agents (ESAs) including darbepoetin alfa or epoetin alfa (or an FDA-approved biosimilar). In Europe, this threshold is lower (less than 250 mU/mL). Treat-

TABLE 4. ELN Response Criteria for PV

Complete remission	All of the following: <ul style="list-style-type: none"> ▪ Durable (≥ 12 weeks) resolution of disease-related signs, including palpable hepatosplenomegaly and symptom improvement ▪ Durable (≥ 12 weeks) peripheral blood count remission defined as: hematocrit $< 45\%$; platelets $\leq 400 \times 10^9/L$; WBC $< 10 \times 10^9/L$ ▪ Absence of progressive disease and any hemorrhagic or thrombotic event ▪ Bone marrow histologic remission defined as: presence of normo-cellularity; absence of trilineage hyperplasia; absence of grade > 1 reticulin fibrosis
Partial remission	All of the following: <ul style="list-style-type: none"> ▪ Durable (≥ 12 weeks) resolution of disease-related signs, including palpable hepatosplenomegaly and symptoms improvement ▪ Durable (≥ 12 weeks) peripheral blood count remission defined as: hematocrit $< 45\%$; platelets $\leq 400 \times 10^9/L$; WBC $< 10 \times 10^9/L$ ▪ Absence of progressive disease and any hemorrhagic or thrombotic event ▪ Absence of bone marrow histologic remission defined as persistence of trilineage hyperplasia
No response	Any response not meeting criteria for partial remission
Progressive disease	Transformation into myelofibrosis, MDS, or acute leukemia

MDS myelodysplastic syndrome; WBC, white blood cells.

ment options for patients with serum EPO greater than or equal to 500 mU/L and those with inadequate response to ESA therapy include clinical trial (preferred), danazol, and lenalidomide or thalidomide with or without prednisone.

Luspatercept is an investigational novel erythroid maturation agent currently undergoing evaluation for the treatment of patients with MF-associated anemia. In an ongoing open-label phase 2 study, 74 patients with MF-associated anemia received treatment with luspatercept, for which interim data has been reported.^{19,20} In the subset of patients who were not transfusion dependent, the primary end point of an increase of greater than or equal to 1.5 g/dL hemoglo-

bin at each visit for at least 12 consecutive weeks in the first 24 weeks was achieved in 2 of 21 patients (10%) not receiving concomitant ruxolitinib and in 6 of 22 patients (27%) who were receiving concomitant ruxolitinib. In the subset of patients with transfusion-dependence, the primary end point of red blood cell transfusion independence for greater than or equal to 12 consecutive weeks in the first 24 weeks was achieved in 2 of 20 patients (10%) not receiving concomitant ruxolitinib and in 6 of 19 (32%) patients receiving concomitant ruxolitinib. The most common treatment-related adverse events included hypertension (11%), bone pain (8%), and diarrhea (4%).

CPI-0610 is an investiga-

tional BET inhibitor being evaluated in the ongoing phase 2 MANIFEST study for the treatment of patients with MF. In arm 1 of the study, patients with MF who had inadequate response to prior ruxolitinib were treated with second-line CPI-0610.²¹ Among patients who were not transfusion dependent ($n = 27$), the primary end point of a reduction of greater than or equal to 35% of the spleen volume at week 24 was achieved in 20% of evaluable patients ($n = 10$) and median change in spleen volume from baseline was -26.8% (range, -51.9 to 4.7). In arm 2 of the MANIFEST study, patients with MF who had a suboptimal response to ruxolitinib received CPI-0610 in addition to ruxolitinib.²² Among patients who were

transfusion dependent ($n = 36$), the primary end point of transfusion independence for 12 weeks was achieved 36.8% of evaluable patients ($n = 19$), with a median duration of transfusion independence of 14.1 weeks. In a third arm of MANIFEST, patients with JAK inhibitor-naïve disease were treated with the combination of CPI-0610 and ruxolitinib.²³ The primary end point of a reduction of greater than or equal to 35% of the spleen volume at 12 weeks was achieved in 72.5% of patients, with a median reduction of 50.8%.

Pacritinib is an investigational agent undergoing evaluation for the treatment of patients with MF. In the randomized phase 3 PERSIST-1 study, patients with higher-risk MF were randomized 2:1 to receive treatment with either pacritinib ($n = 220$) or best available therapy excluding JAK2 inhibitors ($n = 107$).²⁴ The primary end point of a reduction of greater than or equal to 35% of the spleen volume at week 24 was achieved in 19% of patients receiving pacritinib versus 5% of those receiving best available therapy. The most common grade 3-4 adverse events in patients receiving pacritinib versus best available therapy included anemia (17% vs 15%) and thrombocytopenia (12% vs 11%). In the phase 3 PERSIST-2 study, patients with MF and thrombocytopenia were randomized 1:1:1 to receive treatment with pacritinib 400 mg once daily ($n = 75$), pacritinib 200 mg twice daily ($n = 74$), or best

available therapy, including ruxolitinib ($n = 72$). The coprimary end points were a reduction of greater than or equal to 35% spleen volume and a reduction of greater than or equal to 50% of the total symptom score at week 24.²⁵ Among patients receiving pacritinib twice daily, a reduction of greater than or equal to 35% of the spleen volume was achieved by 22% versus 3% of those receiving best available therapy ($P = .001$); a reduction of greater than or equal to 50% of the total symptom score was achieved in 32% of patients receiving pacritinib twice daily versus 14% in those receiving best available therapy ($P = .01$). ■

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