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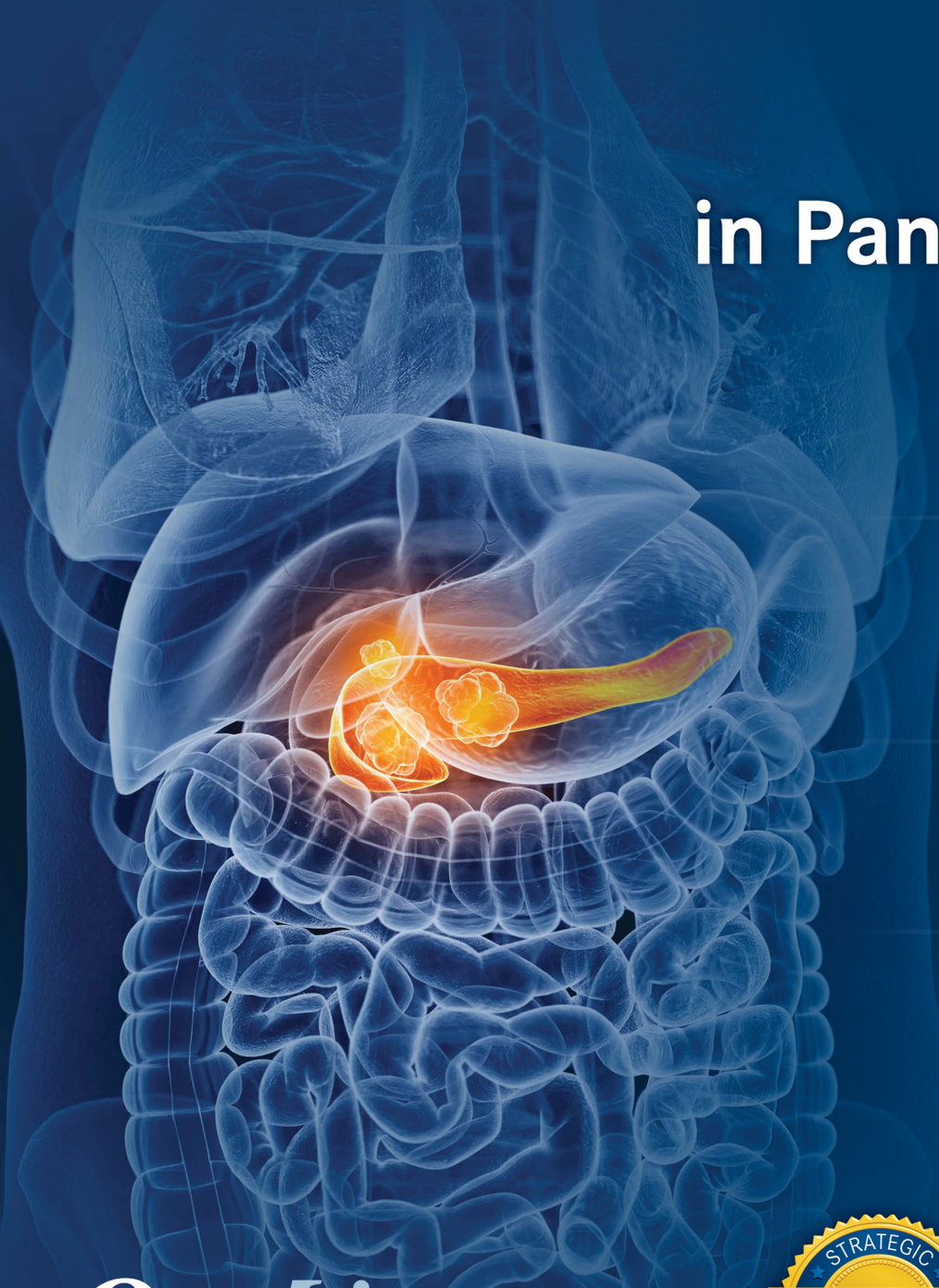

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Hidden Baseline Clinical Factors Often Influence Study Results

By Maurie Markman, MD

*Onc*Pathways®

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With Richard M. Stone, MD

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When Chemotherapy Fails: An Unmet Need in Metastatic CRC

Clinical Insights

Choosing Among Immunotherapies in Bladder Cancer

With Arjun V. Balar, MD

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Second Cancers Can Wield Greater Impact on Adolescent and Young Adult Survivors

By Theresa Keegan, PhD, MS

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Editorial Director, Oncology Specialty Group
Silas Inman

Associate Director, Print Editorial Managing Editor, *OncologyLive*
Anita T. Shaffer
ashaffer@onclive.com

Associate Director, Digital Editorial
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dlepping@mdmag.com

Vice President
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rgoldsmith@onclive.com

National Accounts Manager
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atierney@onclive.com

National Accounts Associates
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Morgan Michon

Sales & Marketing Coordinator
Christina McCollum
cmccollum@onclive.com

Strategic Partnership Coordinator
Nicholas D. Santoro
nsantoro@onclive.com

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CONTENTS

OncologyLive®
Volume 18 / Number 12 / 06.17
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18

Hopeful Signs in Pancreatic Cancer

Early Trials Show Promise for Improving Treatment Options

By Gina Battaglia, PhD

Although the prognosis for patients with pancreatic cancer is often grim, there have been noteworthy improvements in outcomes through the use of current chemotherapies. Several promising novel therapies are under investigation. Experts discuss challenges and emerging strategies.

From the Editor
9 **Hidden Baseline Clinical Factors Often Influence Study Results**
By Maurie Markman, MD

Medical World News®
14 **FDA Digest**
15 **Research Advance**
16 **New Drug Spotlight: Bavencio**

ONCOLOGY & BIOTECH NEWS®
Conference Coverage
2017 AUA Conference
22 **No Mortality Difference Between Prostatectomy, Observation in 20-Year Study**
By Ariela Katz

23 **Benefit Confirmed for ERBT Plus ADT in Locally Advanced Prostate Cancer**

24 **Study Examines High Rate of Burnout Among Urologists**

Clinical Trial In Focus
26 **2 Late-Stage Trials Test Novel PI3K Inhibitor in Non-Hodgkin Lymphoma**
By Ariela Katz

Clinical Insights
28 **Choosing Among Immunotherapies in Bladder Cancer**
By Danielle Bucco

30 **Update Supports Efficacy of Emerging Melanoma Combo**
By Jason Broderick

32 **Complete Metastasectomy Remains Vital RCC Option**
By Danielle Bucco

34 **Evolving Neoadjuvant and Adjuvant Approaches in RCC**
By Ariela Katz

Partner Perspectives
Vanderbilt-Ingram Cancer Center
36 **Making Strides Against a Rare Disease: Renal Medullary Carcinoma in Focus**
By W. Kimryn Rathmell, MD, PhD

UC Davis Comprehensive Cancer Center
37 **Second Cancers Can Wield Greater Impact on Adolescent and Young Adult Survivors**
By Theresa Keegan, PhD, MS

Precision Medicine in Oncology®
44 **Biomarkers Shift Treatment Paradigm in CLL**

*Onc*Pathways®
46 **Attacking *FLT3* Mutations Yields First Targeted Therapy in AML**
By Anita T. Shaffer and Jason Broderick

47 **Lead Researcher Discusses Midostaurin Approval**
By Shannon Connelly

OncLive Peer Exchange®
50 **When Chemotherapy Fails: An Unmet Need in Metastatic CRC**
By Christin Melton, ELS

61 **People in the News**

Investing in the Future

Although overall mortality rates have declined for most cancers, patients with certain malignancies unfortunately have not shared in the advancements that have helped deliver those improvements in the current era of discovery. In this issue of *OncologyLive*®, we focus on emerging trends for 2 of the most challenging cancers: pancreatic cancer and adult acute myeloid leukemia (AML).

In pancreatic cancer, optimism comes in small doses, as we report in our cover story, "Hopeful Signs in Pancreatic Cancer." In the absence of transformative treatments, researchers and clinicians are improving clinical outcomes with more effective chemotherapy regimens and are pondering the potential for more strategic use of these agents in presurgical settings. Novel therapies under study include agents that target a stem cell pathway and the tumor microenvironment.

Despite the positive nature of early research into these strategies, it is abundantly clear that more knowledge about the biology of pancreatic cancer is urgently needed. That is the type of research that is particularly important for government and industry to support–an investment that would pay dividends in future therapies. It also is clear we need a consensus on screening for pancreatic cancer. The rate of early detection for this cancer is abysmally low.

When it comes to adult AML, there also is a knowledge gap about the genomic underpinnings of the disease. The difficulty of targeting such a genomically complex cancer becomes sharply clear when one considers the various ways in which different mutations in the *FLT3* gene can affect oncogenic activity in AML.

After imatinib was approved for patients with chronic myeloid leukemia in 2001, researchers became excited about the prospect that a "magic bullet" could be found for AML. Investigators began focusing on FLT3 inhibitors in what would turn into a frustrating search for efficacy. That changed in April with the approval of midostaurin (Rydapt), as we report in our *Onc*Pathways® article, "Attacking *FLT3* Mutations Yields First Targeted Therapy in AML."

It has been more than 40 years since a new therapy has been introduced to the standard of care for AML, so the news of this drug approval has been greeted with enthusiasm. The hope is that the tide will turn to more targeted therapies for this malignancy. Again, investment in understanding the biology of the disease is of utmost importance.

As our contentious national debate over research funding continues, it is worth remembering the most pressing needs in the cancer field. As always, thank you for reading.

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By Maurie Markman, MD
@DrMaurieMarkman

Hidden Baseline Clinical Factors Often Influence Study Results

Great care is routinely taken in comparative trials to prevent imbalances in clinical trial arms for such factors as age, sex, tumor stage, or the number of prior treatment regimens. However, it is increasingly clear that additional clinical factors are potentially relevant.

There is an intense and seemingly growing debate within the clinical, research, and regulatory arenas regarding what should be appropriately required to declare that a new or novel strategy be considered an acceptable standard-of-care approach to cancer management within a particular setting. Traditionally, phase III randomized trials with overall survival, or more recently progression-free survival, have been the gold standards in this arena. However, due to the definition of progressively smaller patient subgroups for which a targeted therapeutic appears to be clinically relevant, the time, effort, and cost associated with the conduct of such studies is increasingly problematic. As a result, it is essential that alternative study designs continue to be developed and examined for clinical utility.

Although these questions have been widely discussed in clinical research circles, there is another important issue associated with the appropriate interpretation of randomized trials that unfortunately has not received adequate attention. That is the heterogeneity of relevant clinical features among participants in such studies that, in the past, would have been considered to be far more homogeneous. The concern is that this phenomenon has an impact on study outcomes independent of the specific question being addressed in the particular study.

Specifically, great care is routinely taken in comparative trials to prevent imbalances in what are suspected, or known to be, clinically relevant baseline factors that might influence survival, such as age, sex, tumor stage, or the number of prior treatment regimens. However, the concern is that there are additional clinical factors previously unknown to directly influence therapeutic outcomes that are potentially relevant and that imbalances of these features might interfere with the evaluation of an investigative strategy.

Examples Mount

A striking example of such a development was the outcome of a randomized phase II trial comparing a PARP inhibitor, olaparib, with single-agent pegylated liposomal doxorubicin (PEG) in the treatment of *BRCA* mutation–positive recurrent epithelial ovarian cancer.[1] At the time of initiation of this trial, PEG had well-known activity in this clinical setting, having been FDA approved years earlier as a single agent in second-line or later treatment of the malignancy. Similarly, single-agent phase II clinical trial data had provided strong evidence for the clinical activity of olaparib against ovarian cancers in the presence of a germline *BRCA* mutation. However, in the absence of data to the contrary, it was assumed that PEG would possess activity in tumors with a germline *BRCA* mutation similar to that observed in multiple clinical trials in patients unselected for mutation status.

The randomized study failed to reveal any difference in activity between PEG and olaparib, initially suggesting relatively limited utility for the PARP inhibitor in this setting. However, when the outcomes of the PEG-treated patients were more carefully analyzed, it became clear the study results were in fact not due to the lack of activity for the PARP inhibitor, but rather there was a surprising level of activity for PEG in the presence of a germline *BRCA* mutation. Further, these data raise the critical question of the clinical activity of other antineoplastic agents in *BRCA* mutation–positive ovarian cancer (versus *BRCA* wild-type) and suggest knowledge of *BRCA* status is highly relevant as an additional stratification factor in all drug therapy trials in this malignancy.

Another example of the relevance of a baseline clinical factor that may influence clinical outcomes is the documented presence or absence of direct peritoneal cavity involvement in metastatic colon cancer.[2] In a recently reported analysis of 14 phase III randomized trials conducted between 1997 and 2008, 13% of 10,553 patients exhibited evidence of peritoneal cavity involvement with the cancer. The finding of peritoneal metastasis and ≥1 other site of metastasis was associated with a statistically significant inferior overall survival compared with individuals with isolated nonperitoneal cavity metastatic disease (median 12.6 vs 20.0 months; HR, 1.79; P <.0001). In fact, based on these impressive data, it would be reasonable to conclude that any future comparative examination of the utility of a novel antineoplastic agent in colon cancer should ensure the absence of imbalances in the proportion of individuals with peritoneal cavity involvement between the study arms.

A final example of the impact of background clinical features on the results of an antineoplastic therapeutic comes from the experience with sorafenib in the management of hepatocellular carcinoma.[3] In a meta-analysis of 3 phase III trials that examined the utility of this agent versus an alternative drug, there was strong evidence for the utility of sorafenib in patients with hepatitis C as the etiologic agent in the disease process (median survival, 12.6 versus 10.2 months) but, unfortunately, no evidence of clinical benefit in individuals whose disease resulted from hepatitis B infection. These data support the hypothesis that future trials of novel agents in hepatocellular carcinoma need to consider the etiology of the disease process within the stratification factors in addition to other established clinical features.

These examples highlight increasingly recognized concerns about attempting to isolate the influence of a single relevant factor in cancer trials and, in fact, suggest a reason for challenging claims that an individual study has accomplished this goal. ■

Maurie Markman, MD, editor in chief, is president of Medicine & Science at Cancer Treatment Centers of America, and clinical professor of medicine, Drexel University College of Medicine. ***maurie.markman@ctca-hope.com.***

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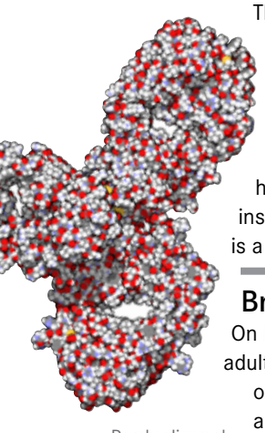
■ *FDA Digest*

Pembrolizumab Moves Forward in 3 Settings


Pembrolizumab

The PD-1 inhibitor pembrolizumab (Keytruda) continues its rapid progress in multiple tumor types, with the FDA taking action on 3 applications within a 6-day period in May. The decisions come on top of an expanded indication in non–small cell lung cancer earlier in May.

Pembrolizumab is now approved in 5 cancer types and across histologies in patients with solid tumors that are microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR). Here is a recap of the latest actions:

Breaking Ground in Biomarker-Based Therapy

On May 23, the FDA approved pembrolizumab for the treatment of adult and pediatric patients with unresectable or metastatic, MSI-H or dMMR solid tumors that have progressed after prior treatment and who have no satisfactory alternative treatment options, as well as for patients with MSI-H or dMMR colorectal cancer following progression on a fluoropyrimidine, oxaliplatin, and irinotecan regimen.

The decision marks the first time the agency has authorized a cancer drug without linking the indication to a primary body site. The approval was based on data from 149 patients with MSI-H or dMMR cancers enrolled across 5 single-arm clinical trials. Ninety patients had colorectal cancer and the remaining 59 had 1 of 14 other tumor types.

The approval for pembrolizumab in this setting was issued on an accelerated basis and is contingent upon the results of a confirmatory trial. **onclive.com/link/1189**

New Bladder Cancer Indication

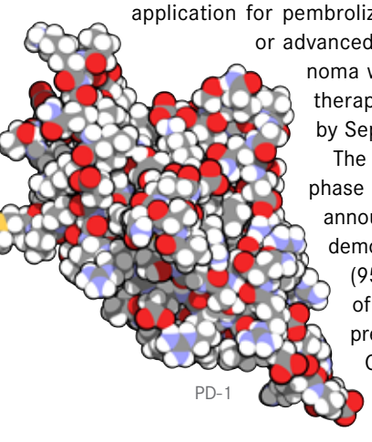
Pembrolizumab has gained FDA approval for patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

Additionally, the agency granted an accelerated approval to frontline pembrolizumab for patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy.

The decisions, issued May 18, were based on results from separate clinical trials. In the phase III KEYNOTE-045 study, single-agent pembrolizumab reduced the risk of death by 27% compared with chemotherapy in a second-line setting. In the phase II KEYNOTE-052 trial, pembrolizumab demonstrated a 28.6% overall response rate as first-line therapy for cisplatin-ineligible patients. **onclive.com/link/1190**

Ruling Pending in Gastric Cancer Setting

The FDA has granted a priority review for a supplemental biologics license application for pembrolizumab as a treatment for patients with recurrent or advanced gastric or gastroesophageal junction adenocarcinoma who have undergone at least 2 courses of chemotherapy. The agency is expected to announce a decision by September 22.


PD-1

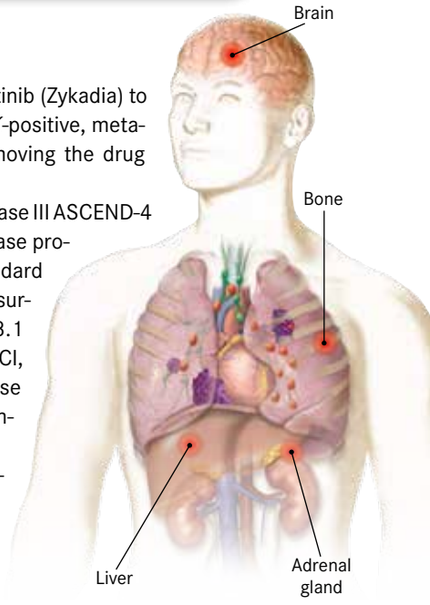
The application is based on data from cohort 1 of the phase II KEYNOTE-059 trial, the drug's developer, Merck, announced on May 24. Pembrolizumab monotherapy demonstrated an objective response rate (ORR) of 11.2% (95% CI, 7.6%-15.7%) and a median duration of response of 8.1 months, according to an abstract scheduled for presentation at the 2017 American Society of Clinical Oncology Annual Meeting. In PD-L1–positive patients, the ORR was 15.5%. **onclive.com/link/1187**

Frontline Indication for Ceritinib

The FDA has broadened the indication for ceritinib (Zykadia) to include previously untreated patients with *ALK*-positive, metastatic non–small cell lung cancer (NSCLC), moving the drug forward in the treatment timeline.

The approval is based on findings from the phase III ASCEND-4 trial, in which ceritinib reduced the risk of disease progression or death by 45% compared with standard chemotherapy. The median progression-free survival was 16.6 months with ceritinib versus 8.1 months with chemotherapy (HR, 0.55; 95% CI, 0.42-0.73; *P* <.0001). The objective response rate with ceritinib also was higher: 72.5% compared with 26.7% in the chemotherapy group.

Ceritinib initially was given an accelerated approval in April 2014 for patients with *ALK*-positive advanced NSCLC previously treated with crizotinib (Xalkori). The recent FDA action converts that second-line approval into a full approval and removes the requirement for prior treatment. **onclive.com/link/1181**



Stage IV NSCLC

ODAC Backs Neratinib in Breast Cancer

The Oncologic Drugs Advisory Committee (ODAC) has voted 12-4 in favor of recommending the approval of neratinib (Nerlynx) for the extended adjuvant treatment of patients with early stage, HER2-positive breast cancer following postoperative trastuzumab (Herceptin).

The FDA committee based its recommendation on data from the phase III ExteNET trial and the phase II CONTROL trial. In the primary analysis of the ExteNET trial, the invasive disease-free survival rate at 2 years was 94.2% with neratinib versus 91.9% with placebo (stratified HR, 0.66; 95% CI, 0.49-0.90; stratified log-rank *P*-value [2-sided] =.008).

Diarrhea was the primary safety concern with neratinib considered by the panel, as 95% of patients in the ExteNET trial who received the tyrosine kinase inhibitor experienced this adverse event, including grade 3 diarrhea in 40% of patients. Results from the ongoing CONTROL trial suggest that antidiarrheal prophylaxis can control the occurrence and severity of diarrhea among patients receiving neratinib.

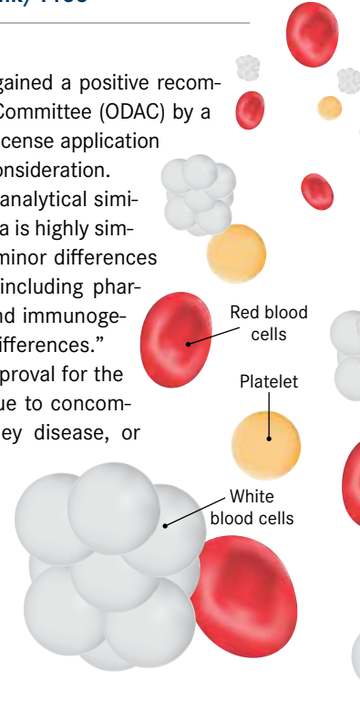
The FDA will now make its final decision on neratinib. The agency is not required to follow the ODAC recommendation. **onclive.com/link/1188**

Panel Approves Biosimilar Epoetin

A biosimilar version of epoetin alfa (Epogen/Procrit) gained a positive recommendation from the FDA's Oncologic Drugs Advisory Committee (ODAC) by a 14-1 margin after a hearing on May 25. The biologics license application for epoetin hospira (Retacrit) will now go the FDA for consideration.

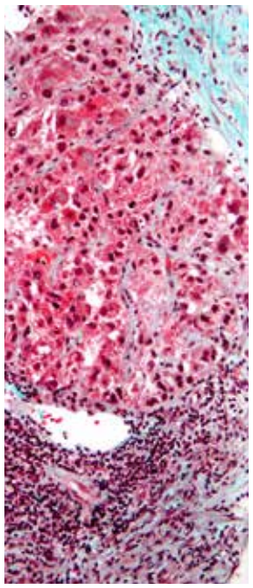
ODAC members concluded that "the totality of the analytical similarity data supports the conclusion that epoetin hospira is highly similar to US-licensed Epogen/Procrit, notwithstanding minor differences in clinically inactive components. The clinical data, including pharmacokinetics, pharmacodynamics, efficacy, safety, and immunogenicity data support a finding of no clinically relevant differences."

Hospira, a division of Pfizer, is seeking to obtain approval for the biosimilar as a treatment for patients with anemia due to concomitant myelosuppressive chemotherapy, chronic kidney disease, or zidovudine therapy for HIV infection, and for the reduction of allogeneic red blood transfusion in patients undergoing elective, noncardiac, nonvascular surgery. **onclive.com/link/1185**



Clockwise from top left: molekuul.be/fotolia | Illustration by Erin Moore | joshya/fotolia.com | molekuul.be/fotolia

■ *Research Advance*



Hepatocellular carcinoma.

Decision Date for Nivolumab in HCC

Nivolumab (Opdivo) will be assessed as a therapy for patients with hepatocellular carcinoma (HCC) following treatment with sorafenib (Nexavar) under the FDA's priority review program, with the agency scheduled to make a final decision by September 24.

The supplemental biologics license application for the PD-1 inhibitor is based upon safety and efficacy findings from the phase I/II CheckMate-040 trial, according to Bristol-Myers Squibb, which is developing the drug. The study included 48 patients in a dose-escalation phase and 214 individuals in a dose-expansion phase.

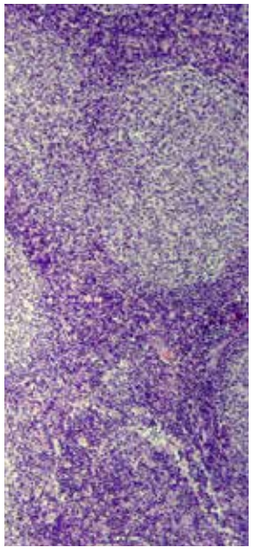
The objective response rate was 15% in the escalation phase, including 3 complete responses (CRs) and 4 partial responses (PRs), and 20% in the expansion group, including 3 CRs and 39 PRs. The 6- and 9-month overall survival rates were each 66% in the escalation phase, and 83% and 74%, respectively, in the expansion group. **onclive.com/link/1183**

Priority Review for CAR Therapy

Axicabtagene ciloleucel (axi-cel; formerly known as KTE-C19) will be evaluated under the FDA's priority review program as a treatment for transplant-ineligible patients with relapsed or refractory non-Hodgkin lymphoma (NHL), according to Kite Pharma, the developer of the chimeric antigen receptor (CAR) T-cell therapy.

The FDA granted the review status based on data from the phase II ZUMA-1 study in which axicabtagene ciloleucel demonstrated an objective response rate of 82% and a complete response (CR) rate of 54%. After 8.7 months of follow-up, 39% of patients continued to have a CR. Participants achieved these responses after receiving a single infusion of modified autologous T cells at a target dose of 2 x 10^6 CAR-positive T cells/kg.

Under the priority review program, the FDA will decide on the biologics license application for axicabtagene ciloleucel 4 months earlier than a standard review. The deadline for the approval, under the Prescription Drug User Fee Act, is November 29, according to Kite. **onclive.com/link/1182**



Follicular lymphoma.

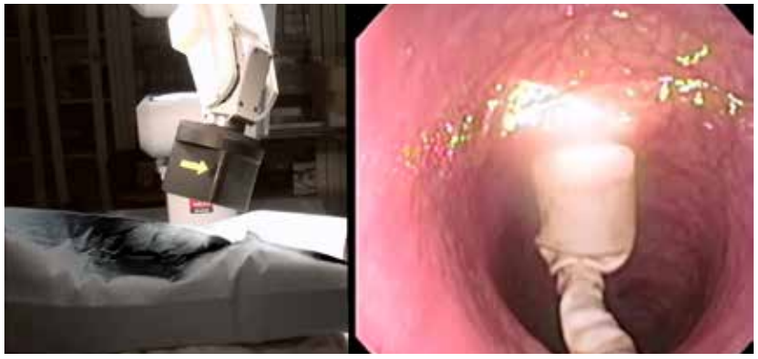
PI3K Inhibitor Advances

Copanlisib, a novel drug that inhibits PI3K, will be reviewed under the FDA's priority program as a treatment for patients with relapsed/refractory follicular lymphoma who have received at 2 least prior therapies, according to Bayer, the manufacturer of the drug.

The new drug application for copanlisib is based primarily on findings from the phase II CHRONOS-1 trial, which included patients with multiple types of lymphoma. In the study, 59% of patients achieved objective responses. These responses were durable, and the median progression-free survival approached 1 year.

Under the priority review program, the FDA is scheduled to decide on the application within 6 months, compared with the standard 10-month review. Copanlisib is an intravenous pan-class I PI3K inhibitor that has predominant activity against the PI3K-alpha and delta isoforms (**See story, page 26**). **onclive.com/link/1191**

First Robotic Colonoscopy Performed



A magnet-guided camera, left, performs a 180° retroflexion, right, on a pig without internal cables or the need to push off the colon wall.

Pietro Valdastri, PhD

Gastroenterologists may eventually be able to offer patients a sedation-free painless form of colonoscopy. Researchers at Vanderbilt University in Nashville, Tennessee, and the University of Leeds in northern England have developed a robotic soft-tethered capsule that can be maneuvered through the large intestine by means of an external magnetic robot arm. The device is smaller overall and can perform all the functions of an endoscope, according to the researchers, who presented their findings at Digestive Disease Week in Chicago in May.

The researchers successfully performed autonomous retroflexion of a robotic capsule during colonoscopy in a subject animal. Retroflexion is a process whereby the head of the capsule pivots 180 degrees to achieve a reverse view of the colon walls.

Pietro Valdastri, PhD, principal technical investigator, said the device being tested was controlled by the external magnetic robotic arm, which could pull and maneuver the tethered capsule without causing stress or damage to the walls of the colon. He said the test, which was performed 30 times in a pig, was 100% successful. "No leaks or histologic abnormalities were visualized on necropsy," according to a statement from the study's authors.

The significance of the achievement is that retroflexion to provide a better view of the colon can be performed at any point in the large intestine, painlessly, and without the need to push against a portion of the colon wall to help with the 180-degree turn performed by the instrument.

"With a traditional endoscope, that would not have been possible because we retroflected at positions where there was no wall to help the retroflection procedure," Valdastri, an assistant professor at Vanderbilt University School of Engineering and a professor at the University of Leeds, said in an interview with *OncologyLive*®.

Researchers said the procedure with the robotic capsule could be performed without sedation. This is important in cases where patients cannot be sedated because of their health problems. In addition, Valdastri said, monetary savings are possible by avoiding the use of anesthesiologists.

Currently, there are no robotic devices available for use in colonoscopy, although there is a system developed in Germany called an invendoscope, which still functions like a flexible endoscope. "The diameter is still large and the instrument is not soft and pliable," Valdastri said. The robotic capsule his group is designing is scheduled to move on to human trials in 2019 or 2020.

Valdastri said that artificial intelligence will one day make it possible to automate much of the activity of a colonoscopy and even such procedures as a polypectomy. "Nothing would prevent us from training our system to understand whether we are looking at a lesion or not. That's in the future—the soon-to-come future."

Medical World News®

New Drug Spotlight

Avelumab (Bavencio)

FDA Approvals

- March 23—Accelerated approval for the treatment of patients ≥12 years with metastatic Merkel cell carcinoma
- May 9—Accelerated approval for patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or with progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

Mechanism of Action: Monoclonal antibody that blocks programmed death ligand-1 (PD-L1). Avelumab binds PD-L1 and blocks the interaction between PD-L1 and its receptors PD-1 and B7.1.

How supplied: 200 mg/10 mL (20 mg/mL) single-dose vials

Dosage: 10 mg/kg via intravenous infusion over 60 minutes every 2 weeks. Premedicate patients with an antihistamine and acetaminophen prior to first 4 infusions and afterward based on clinical judgment and infusion reactions.

Companies: EMD Serono, Inc, and Pfizer, Inc

Pivotal Clinical Data for Merkel Cell Carcinoma Approval

- **JAVELIN Merkel 200 Trial**—Phase II single-arm, multicenter study of avelumab monotherapy in 88 patients with metastatic disease that progressed on or after chemotherapy

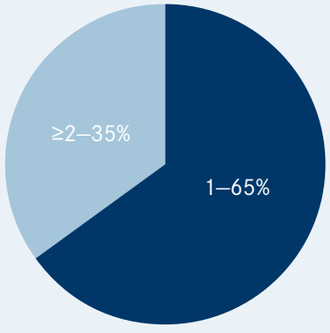
Efficacy Findings in Merkel Cell Carcinoma

Endpoints	Results
Response Rates, median, % (95% CI)	**(N = 88)**
ORR	33% (23.3%-43.8%)
CR	11.4% (6.6%-19.9%)
PR	21.6% (13.5%-31.7%)
Duration of Response, %	**N = 29**
Range in months	2.8-23.3
DOR ≥6 months	86%
DOR ≥12 months	45%

CR indicates complete response; CI, confidence interval; DOR, duration of response; ORR, overall response rate; PR, partial response.

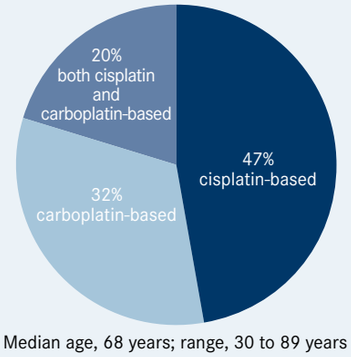
Patient Characteristics

Merkel Cell Carcinoma
Prior therapy for metastatic disease



Median age, 73 years; range, 33 to 88 years

Urothelial Carcinoma
Prior therapy



Median age, 68 years; range, 30 to 89 years

SOURCE

Bavencio [package insert]. Rockland, MA, and New York, NY: EMD Serono, Inc, and Pfizer, Inc. 2017.

Pivotal Clinical Data for Metastatic Urothelial Carcinoma

- **JAVELIN Solid Tumor Trial**—Phase Ib single-arm multicenter study of avelumab monotherapy in 242 patients with locally advanced or metastatic urothelial carcinoma with disease progression on, after, or within 12 months of platinum-containing chemotherapy

Efficacy Findings in Urothelial Carcinoma

Endpoints	≥13 Weeks Follow-Up (N = 226)	≥6 Months Follow-up (N = 161)
Response rates		
ORR, median, % (95% CI)	13.3% (9.1%-18.4%)	16.1% (10.8%-22.8%)
CR, %	4.0%	5.6%
PR, %	9.3%	10.6%
DOR, median, months (range)	NE (1.4-17.4)	NE (1.4-17.4)

CI indicates confidence interval; CR, conmplete response; DOR, duration of response; NE, not estimable; ORR, overall response rate; PR, partial response.

Warnings and Precautions—based on trials including 1738 patients

- Immune-mediated pneumonitis
- Immune-mediated hepatitis
- Immune-mediated colitis
- Immune-mediated endocrinopathies
- Immune-mediated nephritis and renal dysfunction
- Infusion-related reactions
- Embryo-fetal toxicity

Common Adverse Events, % Affected

	Merkel Cell Carcinoma N = 88		Urothelial Carcinoma[a] N = 242	
	All Grades, %	Grades 3-4, %	All Grades, %	Grades 3-4, %
Fatigue	50	2	41	7
Lymphopenia	49	19	n/a	11
Anemia	35	9	n/a	6
Musculoskeletal pain	32	2	25	3
Diarrhea	23	0	18	2
Nausea	22	0	24	1

n/a indicates not available.
[a]Number of patients with lab tests for lymphopenia and anemia varies between 188 and 235.

Image courtesy of EMD Serono and Pfizer

Hopeful Signs in Pancreatic Cancer

Early Trials Show Promise for Improving Treatment Outcomes

By Gina Battaglia, PhD

Despite improvements in the treatment of many formerly intractable cancers, the prognosis for pancreatic cancer remains dismal, with a 5-year survival rate of 8.2% (**Figure**).[1] Novel multimodal approaches that address the unique, aggressive biology of pancreatic cancer are needed, experts say.

Ronald Evans, MD

"It is a very challenging diagnosis, but there are new therapies coming along based on science. This kind of knowledge is what we need to crack open the problem," said Ronald Evans, MD, director of the Gene Expression Laboratory at the Salk Institute for Biological Studies in La Jolla, California.

In recent years, there have been significant developments in the management of pancreatic cancer, including neoadjuvant chemotherapy and radiation for patients with resectable disease and frontline use of multiagent cytotoxic therapy for metastatic disease. Several promising novel approaches that target the stem cell pathway and the tumor stroma are in the early stages of development and would be a big step forward for a subgroup of patients if they prove successful, according to Evans. Additionally, early-stage clinical trials are exploring the potential for immunotherapies including checkpoint blockade agents and chimeric antigen receptor therapies. However, much progress is still needed to improve toxicity with current chemotherapy regimens, standardization of molecular subtyping, utility of genomics testing, and screening recommendations for high-risk patients.

Optimizing Treatment Regimens

Neoadjuvant Chemotherapy

For the small percentage of patients with resectable disease, treatment has traditionally involved surgery followed by chemotherapy and radiation therapy. However, treatment in the neoadjuvant setting may improve outcomes for patients with resectable disease, according to Emma C. Fields, MD, radiation oncologist at the Virginia Commonwealth University Massey Cancer Center in Richmond, Virginia. A retrospective analysis[2] by Fields and colleagues showed that approximately 40% of patients had positive margins after resection; a positive margin was associated with shorter progression-free survival (PFS) than a negative margin.

Emma C. Fields, MD

According to Fields, maximizing tumor shrinkage with neoadjuvant therapy prior to surgery would help improve the likelihood of negative margins and thus survival outcomes. Furthermore, she stated that surgery for pancreatic cancer requires a lengthy recovery period during which the cancer could recur or metastasize. "Someone receives a pancreatic duodenectomy or Whipple [procedure], their recovery is 6 to 8 weeks, and then they have a CT scan showing development of disease elsewhere."

Furthermore, Fields noted that patients may be able to tolerate intense regimens of chemotherapy and radiation better prior to surgery, which is associated with high morbidity and incidence of postoperative complications. A retrospective analysis[3] showed completion of multimodality treatment in 83% of patients who received neoadjuvant therapy versus 58% of patients who received surgery first. Patients who completed multimodality therapy had better median overall survival (OS) at 36 months, compared with 11 months for those who received an incomplete regimen. Neoadjuvant treatment also tests the responsiveness of the tumor to chemotherapy and radiation, and patients unlikely to benefit from treatment could avoid unnecessary burdens from surgery and receive palliative care earlier.

According to Fields, providing radiation in the neoadjuvant setting also allows for a smaller volume of tissue to be treated. "Preoperatively, we can see the tumor and treat just around the tumor itself. Postoperatively, we treat a much larger volume because you're dealing with an operative bed and it's very hard to know where the tumor was with the reconstructed anatomy. So, we cover everywhere the surgeon potentially was and areas at risk." Fields also noted that the tissues and tumor regions have better blood flow and oxygenation before surgery, which likely improve the efficacy of chemotherapy and radiation.

Although the role of neoadjuvant radiation and chemotherapy for early-stage pancreatic cancer is promising, Fields said that prospective studies in specific categories of patients (eg, those with resectable, borderline resectable, or locally advanced disease) are currently ongoing to determine the benefits of neoadjuvant therapy and surgical eligibility at each stage of disease.

Chemotherapy for Metastatic Disease

Monotherapy with gemcitabine has fallen out of favor as the frontline treatment for metastatic pancreatic cancer, as the MPACT[4] and PRODIGE 4/ACCORD 11 trials[5] demonstrated improvements in survival with gemcitabine plus nab-paclitaxel (Abraxane) and the 4-drug combination of leucovorin, fluorouracil (5-FU), irinotecan, and oxaliplatin (FOLFIRINOX), respectively. In 2013, the FDA approved nab-paclitaxel in combination with gemcitabine for the first-line treatment of metastatic adenocarcinoma of the pancreas, which accounts for most pancreatic cancers, based on the MPACT data.

FOLFIRINOX and gemcitabine plus nab-paclitaxel have not been compared in a head-to-head trial, although many experts recommend FOLFIRINOX in patients with high performance status because the PRODIGE 4/ACCORD 1 trial results showed a longer OS with FOLFIRINOX (11.1 months) than the MPACT trial did with gemcitabine plus nab-paclitaxel (8.5 months).

However, Eileen M. O'Reilly, MD, stated during a recent *OncLive*® Peer Exchange® program[6] that patient

preferences may be worth considering in the absence of definitive data. "Some patients may have concerns about having a port and having infusion treatments with FOLFIRINOX," said O'Reilly, associate professor of medicine at Weill Medical College of Cornell University in New York City. "Other patients may have concerns about alopecia with nab-paclitaxel–based therapy."

Both regimens have substantial toxicity that often requires modification of the regimen. John L. Marshall, MD, chief of the Division of Hematology-Oncology at Georgetown University Hospital and director of the Otto J. Ruesch Center for the Cure of Gastrointestinal Cancer in Washington, DC, said during the Peer Exchange® that he usually modifies the FOLFIRINOX regimen up front by dropping the 5-FU bolus and reducing the dose of irinotecan.[6]

Many patients on gemcitabine plus nab-paclitaxel also require modified dosing, but may still be able to achieve acceptable survival outcomes. A retrospective analysis[7] presented at the 2015 Gastrointestinal Cancers Symposium showed that patients who received nab-paclitaxel and gemcitabine on days 1 and 15 of a 28-day cycle had comparable survival length and a better toxicity profile when compared historically with the results of the MPACT trial that dosed on days 1, 8, and 15 of a 28-day cycle. Although O'Reilly stated that the lower-frequency regimen may not be suitable for all patients and is not FDA approved, she indicated that the analysis should reassure patients and physicians that reduced dosing frequency can still yield survival outcomes close to those of the full regimen.

Although gemcitabine is frequently considered part of the therapeutic regimen, recent data suggest that it is less efficacious in patients with low expression of human equilibrative nucleoside transporter 1 (hENT1).[8] The randomized phase II GERCOR trial[9] results showed that nab-paclitaxel plus 5-FU/leucovorin exceeded the study goal of a 4-month PFS of 50% and yielded a 12-month survival of 48%, whereas gemcitabine plus nab-paclitaxel yielded a 41% survival at 12 months (the study was not designed to compare the 2 regimens). According to the study authors, the results suggest that nab-paclitaxel is safe and effective as part of a gemcitabine-free regimen and should be tested further in phase III trials.

Novel Approaches

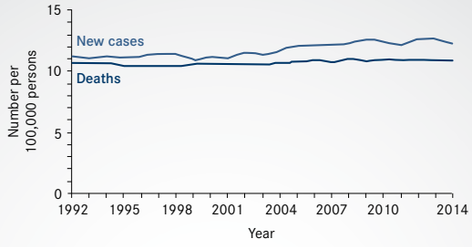
Stem Cell Pathways

Although they make up less than 1% of all pancreatic cancer cells, cancer stem cells are a major contributor to chemoresistance and tumor initiation, growth, and metastasis. Thus, developing treatments that inhibit these stem cell pathways is of interest to many researchers.

Figure. A Snapshot of Pancreatic Cancer

Diagnoses and Survival by Stage

Estimated new cases in 2017	53, 670
% of all new cancer cases	3.2%
Estimated deaths in 2017	43,090
% of all cancer deaths	7.2%



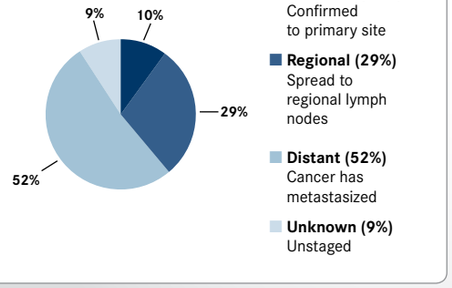
Percent surviving 5 years

8.2%

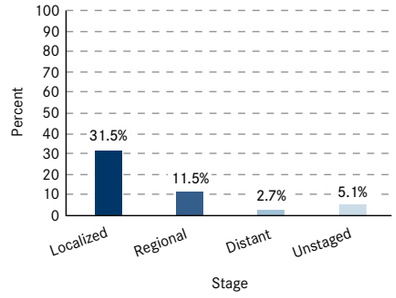
2007-2013

New Cases and Estimated Deaths

Percent of Cases by Stage



5-Year Relative Survival



This snapshot of pancreatic cancer is based on statistics from the Surveillance, Epidemiology, and End Results Program and the Centers for Disease Control and Prevention's National Center for Health Statistics, based on the most recently available data review conducted in November 2016.

SEER cancer stat facts: pancreas cancer. National Cancer Institute website. seer.cancer.gov/statfacts/html/pancreas.html. Published April 2017. Accessed May 29, 2017.

Napabucasin (BBI-608), developed by Boston Biomedical, inhibits transcription of cancer stemness genes mediated by STAT3, which is a transcription factor that is constituently active in cancer stem cells and is thought to promote cell stemness, suppress antitumor immunity, and drive tumor-promoting inflammation. At the 2016 Gastrointestinal Cancers Symposium, researchers from Boston Biomedical presented data from 2 pancreatic cancer trials. The phase Ib trial[10] showed that of the 7 evaluable patients with metastatic pancreatic ductal adenocarcinoma who received napabucasin, gemcitabine, and nab-paclitaxel, all had a partial response or stable disease and 6 had a sustained response (at least 24 weeks). The phase Ib/II study[11] showed disease control rates (sum of stable disease, partial response, and complete response rates) of 48% in patients with heavily pretreated pancreatic cancer and 68% in taxane-naïve patients.

"These studies continue to show napabucasin's safety and early efficacy across doses and in combination with a variety of established agents," said Chiang J. Li, MD, FACP, president, CEO, and chief medical officer of Boston Biomedical, in a press release.[12] "We plan to apply these findings as we advance and expand our clinical development program for this first-in-category cancer stemness inhibitor."

The phase III CanStem111P trial, launched in December 2016, is investigating the addition of napabucasin to the combination of nab-paclitaxel plus gemcitabine versus the 2 chemotherapeutic agents alone in patients with metastatic pancreatic adenocarcinoma who have not received prior systemic therapy for advanced disease (NCT02993731).

Vitamin D Receptor Therapy

Unlike many other cancers, immunotherapy has been largely unsuccessful in pancreatic cancer in part due to the dense desmoplastic stromal reaction that develops around the pancreatic tumor microenvironment, promoting angiogenesis and exclusion of immune cells and interacting with cancer cells to promote progression and invasion. Resetting genetic networks that promote this stromal reaction is among the goals of the Stand Up to Cancer (SU2C)-Cancer Research UK-Lustgarten Foundation Pancreatic Cancer's Dream Team. According to the researchers, restoring the normal function of these »


Eileen M. O'Reilly, MD

pathways weakens this barrier surrounding the tumor, improving sensitivity to chemotherapy and possibly enabling the efficacy of immunotherapy.

Evans, co-leader of the Dream Team, and his colleagues showed that vitamin D receptors are expressed in human pancreatic stellate cells. Treatment with calcipotriol, a vitamin D ligand, reduced markers of inflammation and fibrosis, induced remodeling in the cells, increased gemcitabine levels in the tumor, reduced tumor volume, and improved survival in a mouse model.[13] Paricalcitol, a modified form of vitamin D, showed similar effects in early human trials of pancreatic cancer in which it restored immune privilege, enabling entry of T cells into a tumor microenvironment that is typically void of T cells.

"Based on these findings, we might be able to take advantage of some of the advances in the immuno-oncology space for patients with pancreatic cancer," said Evans. A randomized pilot trial (NCT02030860) is currently ongoing to determine the effects of paricalcitol plus neoadjuvant therapy on cellular and imaging markers, tumor response, and pancreatic stellate cell gene expression program in patients with resectable pancreatic cancer.

The most notable adverse event with vitamin D therapy is a decrease in parathyroid hormone, but Evans stated that monitoring levels and correcting the problem with dose reductions is relatively easy. He said that the safety and benefits of the strategy are well recognized because paricalcitol is currently used for secondary hyperparathyroidism associated with chronic kidney disease.

PEGylated Human Recombinant Hyaluronidase

PEGylated human recombinant hyaluronidase (PEGPH20) has also shown promise in early trials. PEGPH20 disrupts the integrity of the pancreatic tumor stroma by reducing accumulation of hyaluronic acid, a component of the stroma that supports initiation and progression of cancer and impairs drug delivery to the tumor. Preclinical studies showed that the effects of PEGPH20 include depletion of stromal hyaluronic acid, re-expansion of tumor vessels, and enhanced effect of chemotherapeutic agents. A randomized phase II trial[14] showed that the addition of PEGPH20 to nab-paclitaxel plus gemcitabine led to a 46% overall response rate and improved outcomes compared with the 2 chemotherapy drugs alone in patients with pancreatic cancer with high hyaluronan (HA) accumulation in the extracellular matrix of the tumor surface, suggesting that the novel agent may be an effective component for this population. The PEGPH20-containing regimen demonstrated a statistically significant improvement in PFS over the 2 chemotherapy drugs alone (HR, 0.51; $P = .048$) and exploratory OS of 11.5 months versus 8.5 months, respectively. Clinical trials are currently underway to test the efficacy of PEGPH20 with nab-paclitaxel plus gemcitabine in patients with previously untreated HA-high pancreatic ductal adenocarcinoma in the phase III HALO-301 trial (NCT02715804) and with modified FOLFIRINOX in patients with newly diagnosed metastatic disease (NCT01959139).

Genomics and Molecular Subtyping

With the introduction of novel therapeutic approaches, the analysis of genomics and molecular subtypes to identify patients who may benefit from these targeted therapies is of increasing interest. In addition to the association between hENT expression and effectiveness of gemcitabine,[8] some data suggest that poly (ADP-ribose) polymerase (PARP) inhibitor-based and platinum-based therapies have clinical benefit in patients with genetic defects in the homologous recombination DNA repair pathway (HRD), particularly *BRCA* mutations. In a phase Ib trial, cisplatin, gemcitabine, and the PARP inhibitor veliparib (ABT-888) yielded a response rate of 66% in patients with a *BRCA1* or *BRCA2* mutations.[15]

However, the significance of many gene mutations detected through next-generation sequencing is not well known, which currently limits the clinical decision-making value of genomic tests. "In our institution, we routinely perform [molecular profiling] in patients with good performance status," said Caio S. Rocha Lima, MD, medical oncologist and associate director of translational research at the Gibbs Cancer Center and Research Institute in Spartanburg, South Carolina, during the Peer Exchange®.[6] "Most of those reports will come up with the *KRAS* mutation…and we do not have a way to really target *KRAS* today."

Although several researchers have begun to identify biological subgroups of pancreatic cancer, criteria for defining each subgroup is not well standardized and the ability of these characterizations to provide additional prognostic or predictive clinical information requires further investigation. However, George P. Kim, MD, a medical oncologist at 21st Century Oncology in Jacksonville, Florida, said during the Peer Exchange®[6] that regularly obtaining biopsies, and possibly repeat biopsies after a patient progresses, will help improve characterization of the dynamics of the cancer.

Screening Considerations

Lack of detection in early stages is a key contributor to the poor survival rates for patients with pancreatic cancer, but optimal procedures for screening such as the type of test, patient selection, and surveillance frequency are unclear. The US Preventive Services Task Force (USPSTF) states that population-based screening is not cost effective, but some experts suggest that screening high-risk individuals, particularly those with a strong family history of pancreatic cancer, may improve detection in the earlier stages, and thus survival outcomes. In 2012, the International Cancer of the Pancreas Screening Consortium[16] recommended screening with endoscopic ultrasonography and/or magnetic resonance imaging or magnetic resonance cholangiopancreatography for individuals with at least 2 relatives (and at least 1 first-degree relative) with pancreatic cancer; carriers of p16, *PALB2*, or *BRCA2* mutations with a first-degree relative with pancreatic cancer; individuals with Peutz-Jeghers syndrome; and individuals with Lynch syndrome and a first-degree relative with pancreatic cancer. However, the consortium did not reach a consensus on the age to initiate or stop surveillance, the most optimal screening modality, the intervals for follow-up imaging, and which screening abnormalities warranted consideration of surgery.


John L. Marshall, MD

A systematic review[17] showed that screening of familial high-risk individuals improved curative resection rate, median survival, and diagnosis of stage I pancreatic cancer, although it also increased perceived risk, patient anxiety, and economic burden. The USPSTF is currently composing a draft research plan to review predicted improvements in cancer morbidity and mortality with screening, the diagnostic accuracy of screening tests, potential harms of screening, and benefits and harms of treating screen-detected or asymptomatic pancreatic cancer.

Need for Collaboration Emphasized

Optimizing chemotherapy and radiation have led to incremental improvements in survival for pancreatic cancer, but experts agree that maintaining a durable treatment response and possibly achieving remission require development of novel therapies based on the unique biology of pancreatic cancer and tailored to the individual. Evans said that close collaborations between research scientists and clinical oncologists, such as those with the SU2C Dream Teams, will redefine the way to move forward with treatments for pancreatic cancer and other types of cancer. "By tackling the most lethal cancer, hopefully the lessons we learn will have widespread use for other cancers," Evans said. ■

For full list of references, see article on *OncLive*.com.

Oncology& Biotech News

Conference Highlights

2017 AUA Annual Meeting

Boston, Massachusetts

No Mortality Difference Between Prostatectomy, Observation in 20-Year Study

By Ariela Katz

Long-term follow-up results from the phase III Prostate Cancer Intervention Versus Observation Trial (PIVOT) indicated that radical prostatectomy does not significantly reduce all-cause or prostate cancer mortality compared with observation through nearly 20 years, according to findings presented at the 2017 American Urological Association Annual Meeting. The results demonstrated that there was not a statistically significant difference in all-cause mortality between patients who received surgery and those who were kept under observation ($P = .06$).

Timothy J. Wilt, MD, MPH

"We previously demonstrated no significant difference between surgery versus observation in all-cause or prostate cancer mortality through 12 years; however, treatment decisions often require information about very long-term mortality," Timothy J. Wilt, MD, MPH, professor of medicine at the University of Minnesota School of Medicine and core investigator at the Minneapolis VA Center for Chronic Disease Outcomes Research, said in his presentation at the conference, held May 12 to 16 in Boston.

The PIVOT study was a randomized controlled trial for patients with clinically localized prostate cancer that began recruitment in 1994. The follow-up analysis sought to determine whether radical prostatectomy reduced mortality compared with observation.

The primary endpoint was all-cause mortality, with prostate cancer mortality as the secondary endpoint assessed by a blinded committee. In the original follow-up, according to Wilt, investigators also addressed bone metastases, disease progression, patient-reported outcomes, and erectile, urinary, and bowel dysfunction.

The study sought to recruit men who were 75 years or younger, diagnosed within the previous 12 months, and who had a life expectancy of at least 10 years. Patients could have any grade of prostate cancer, including stage T1 to T2 and M0 disease, as long as they were viable candidates for radical prostatectomy. Their prostate-specific antigen (PSA) levels had to be less than 50 ng/mL.

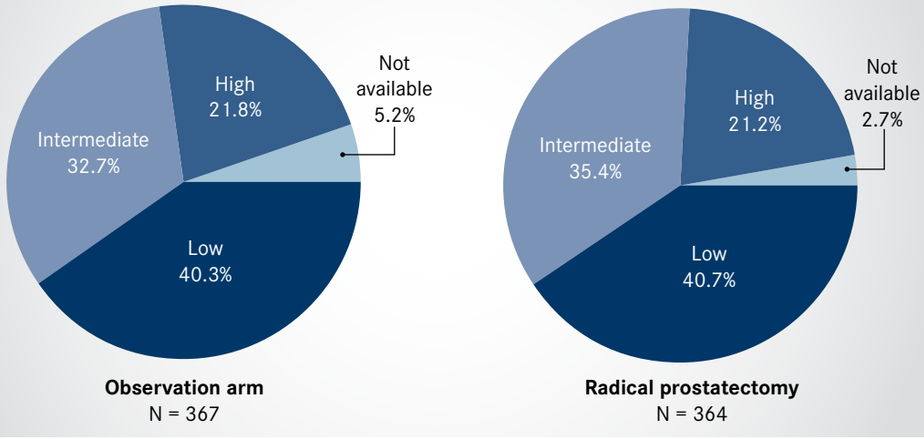
Based on these criteria, 731 patients were randomized to receive either a radical prostatectomy (n = 364) or observation (n = 367). Notably, Wilt said, observation in the PIVOT study included palliative therapy for symptomatic progression, which is different from commonly used PSA-based monitoring and biopsy-based active surveillance programs with delayed radical intervention. The patients in the observation group were offered palliative therapy or chemotherapy for symptomatic or metastatic disease progression.

The average age of the participants was 66.8 years with a mean PSA of 10.2 ng/mL in the observation arm and 67 years with a mean PSA of 10.1 ng/mL in the surgery arm. In terms of comorbidities, Wilt commented, "They were healthy; more than 50% had no comorbidities."

The investigators also factored in the patients' D'Amico tumor risk classifications at time of baseline biopsy (**Figure**), with the observation

(**PIVOT**, Continued on page 24)

Figure. Risk Categories of PIVOT Participants



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Benefit Confirmed for ERBT Plus ADT in Locally Advanced Prostate Cancer

The addition of external beam radiation therapy (EBRT) to androgen-deprivation therapy (ADT) reduced the risk of disease progression more than 70% compared with ADT alone among patients with locally advanced prostate cancer, according to long-term study results presented at the 2017 American Urological Association Annual Meeting.[1]

The 8-year progression-free survival (PFS) rate among patients who were treated with EBRT plus ADT was 47.9% versus 7.0% for participants who received ADT alone (HR, 0.27; log-rank P <.0001). The 8-year overall survival (OS) rate was 65.1% in the combination arm and 56.8% in the ADT arm; however, this difference was not determined to be statistically significant (P = .43). Metastasis-free survival (MFS) was also comparable between the arms, although locoregional PFS (LPFS) was statistically significant in favor of the combination arm compared with the ADT arm (P = .01).

The results confirm the clinical benefit of the combination strategy, said Paul Sargos, MD, a radiotherapy oncologist at the Institut Bergonié in Bordeaux, France, who presented the study results. "Achieving local control with radiotherapy in locally advanced prostate cancer has level 1 evidence, and alternatives to ADT combined with radiotherapy should only be considered in the context of a prospective randomized controlled trial," he said.

Sargos and colleagues said in their abstract that they launched the study because there is a paucity of data comparing ADT plus ERBT with ADT alone, unlike the survival benefit that has been demonstrated with the combination versus EBRT alone.

Key Findings in Study

The multicenter, phase III trial enrolled 273 patients who were randomly assigned to either receive ADT plus ERBT or ADT alone. Results were reported for 263 patents included in the intent-to-treat analysis, with 133 patients in the combination arm and 130 in the ADT arm.

To be eligible, participants were required to have biopsy-confirmed T3-4 prostate cancer with no metastases, a Karnofsky performance score ≥70, and be younger than 80 years old, Sargos said. Participants who had undergone transurethral resection of the prostate for obstructive syndrome were excluded.

For the ADT arm, the average age of the participants was approximately 70.5 years, and the mean Karnofsky performance status score was 96.1. Patients had a median prostate-specific antigen (PSA) score of 26.8 ng/mL. The Gleason scores were less than 7 for 67 patients (51.5%), equal to 7 for 41 patients (31.5%), and greater than 7 for 22 patients (16.9%). Additionally, 97.7% of patients had stage T3 disease.

Patient characteristics were similar in the combination arm, where the average age was 70.71 years and the mean Karnofsky score was 95.62%. The median PSA was 26.87 ng/mL. Gleason scores were less than 7 for 61 patients (45.9%); equal to 7 for 40 patients (30%); and greater than 7 for 32 patients (24%). Similar to the ADT arm, 96.2% of patients had stage T3 disease.

Participants were administered ADT consisting of 11.25 mg of subcutaneous leuprorelin, a luteinizing hormone-releasing hormone agonist, every 3 months for the duration of the 3-year study. Oral flutamide was administered at a dose of 750 mg per day for the first month of treatment. For those receiving radiotherapy, the whole pelvis was treated with EBRT at a dose of 46 Gy, and the prostate was treated with a boost from 20 Gy to 28 Gy.[1]

The primary objective of the study was 5-year PFS according to clinical or biochemical criteria. Secondary endpoints consisted of OS, disease-specific survival, LPFS, MFS, time to metastatic progression, biochemical PFS, and tolerance.

"For biological PFS, there was a statistically significant benefit, with 10.9% in the ADT arm and 50.4% in the combination arm," Sargos said. The risk of death from prostate cancer also was significantly reduced in the combination arm compared with the ADT arm.

Notably, patients who received the combination therapy experienced lower gastrointestinal and genitourinary tolerance. "Analysis of late toxicities revealed differences between arms, especially in the presence of grade ≥2 rectal toxicities in the ADT and [EBRT] arm 6 months after the end of radiotherapy," Sargos said. In the combination arm, gastrointestinal toxicities grade ≥2 were observed in 21 patients (16.7%), and genitourinary toxicities grade ≥2 were reported in 15 patients (11.9%).[1]

Although the study did not establish an OS benefit with the combination, prior research has demonstrated an improvement with the addition of radiation therapy to ADT in patients with locally advanced prostate cancer.[2]

From 1995 to 2005, 1205 patients were randomly assigned to receive either ADT alone (n = 602) or ADT combined with radiotherapy (n = 603), with OS as the primary endpoint at a median follow-up of 6 years. Radiotherapy was administered at 65 to 69 Gy to the prostate and seminal vesicles, and 45 Gy to the pelvic nodes.

At the time of analysis, 320 patients had died: 175 in the ADT arm and 145 in the combination arm. At 7 years, the OS rate was 74% in the combination arm and 66% in the ADT arm (HR, 0.77; 95% CI 0.61-0.98; P = .033).[2] ■

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New Data on Sipuleucel-T

Oliver Sartor, MD, discusses research comparing outcomes by race among patients with metastatic castration-resistant prostate cancer (mCRPC) who were treated with sipuleucel-T (Provenge) that was presented at the 2017 AUA Annual Meeting.

Investigators confirmed a greater overall survival benefit among African American men through a prospective analysis of the PROCEED registry, a database of more than 1900 patients with mCRPC who received sipuleucel-T between 2011 and 2013. The real-world data demonstrated a median overall survival benefit of 37.3 months for African American patients compared with 28.0 months for Caucasians, a statistically significant difference of 9.3 months (P <.001).

Sartor is the Laborde Professor of Cancer Research in the medicine and urology departments of Tulane School of Medicine, in New Orleans, Louisiana. **onclive.com/link/1202**

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(**PIVOT**, continued from page 22)

Table. Radical Prostatectomy Versus Observation

Outcome Category	Hazard Ratio	Absolute Risk Reduction
All-cause mortality		
Total population	0.84	5.5%
Low-risk prostate cancer	0.98	0.6%
Prostate cancer mortality		
Total population	0.63	4.0%
Low-risk prostate cancer	0.74	1.4%

arm having 40.3% of patients at low risk, 32.7% at intermediate risk, and 21.8% at high risk. The surgery arm had 40.7% of patients at low risk, 35.4% at intermediate risk, and 21.2% at high risk. "When using central histopathologic classification, two-thirds of men had intermediate or higher risk disease," Wilt noted.

In the surgery arm, 85.5% of patients underwent radical intervention, most within the first 6 months after randomization. In contrast, 20.4% of patients in the observation group underwent radical intervention, with radical intervention being rare 4 to 5 years after randomization. "We followed men for nearly 20 years, with a median of 12.7 years from randomization to death, or the end of the study," Wilt said.

The rate of all-cause mortality observed by the end of the study was 64% (468 patients). Particularly in patients with low-risk prostate cancer, treatment with radical prostatectomy did not reduce all-cause mortality, with an absolute risk difference of 0.6% (**Table**).

The observed prostate cancer mortality rate was 9.4% (69 patients total), which was deemed infrequent, and did not vary based on patient characteristics. However, prostate cancer mortality did vary based on tumor characteristics. Prostate cancer mortality was observed in 4.8% of low-risk patients, 12.2% of intermediate-risk patients, and 15.9% of high-risk patients. The absolute risk difference was 4.0% and was not statistically significant.

"Based on these findings, observation or PSA monitoring—not active surveillance with delayed radical intervention—is preferred for men with low-risk prostate cancer, and for many men with higher-risk disease when they are age 65 or older with life-limiting comorbidities, because it results in similar mortality with fewer treatment-related harms," Wilt said. "However, more effective and safer therapies are needed for younger men with higher-risk disease." ■

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Study Examines High Rate of Burnout Among Urologists

Nearly 40% of urologists who participated in a recent survey reported suffering from burnout as measured by the Maslach Burnout Inventory (MBI) scale. The finding is of importance for not just the health of professional urologists in general, but also for the state of the profession itself, according to lead author Amanda C. North, MD, who presented the results at the 2017 American Urological Association (AUA) Annual Meeting.

Amanda C. North, MD

"Although physician burnout in urology is less than previously reported, it is still a serious issue that impacts workforce issues. There are projected physician shortages in all areas of medicine. Urology had one of the largest projected shortages and we cannot lose more urologists to burnout," said North.

In all, 38.8% of the 1126 urologists participating in the survey said they were feeling burned out. The survey was conducted from May to September 2016 as part of the 2016 AUA Census. Investigators randomly assigned MBI questions to census participants to determine how many urologists met the criteria for burnout.

Whereas many physicians and urologists can experience burnout, it is more likely to occur in urologic oncologists, who often see patients with aggressive and even incurable disease. Physician burnout is linked to decreased job performance, increased medical errors, interpersonal conflicts, and depression, according to North, an assistant professor of pediatric urology at Montefiore Medical Center.[1] She noted that burnout is an accepted medical condition for which there is an ICD 10 billing code.

North said there are 3 categories of burnout in MBI. The first is emotional exhaustion, which includes a feeling of being overextended, fatigue, and a lack of enthusiasm for work. The second is depersonalization, which encompasses objectification of patients and a less-caring attitude toward them. The third is a decreased sense of personal accomplishment and a feeling that work has lost meaning.

A 2015 study that also used the MBI scale found that urology had the highest rate of physician burnout among all specialties. In addition, that rate was rising: from 41.2% in 2011 to 63.6% in 2014.[2] "This made urologists the most burnt-out specialty of medicine," North commented. That study was limited in its relevance, however, due to the small sample sizes for urologists. Thus, North pursued further clarity on the prevalence of urologist burnout and the factors associated with it.

In the AUA study, the burnout rate among urologists aged 29 to 65 years was 41.3%. The authors of the study said 17.2% scored high for emotional exhaustion and 37.1% scored high for depersonalization.[1] No significant differences between male and female urologists were reported.

The authors said there are several risk factors for burnout. Major work-related stressors are administrative duties and work hours, which are linked to early retirement and job changes. Urologists seeing more patients than average or working longer hours are at risk for burnout. Other risk factors include being in a younger age group, practicing in a subspecialty other than pediatrics or oncology, being part of an independent or multispecialty practice, and having a practice size greater than 2 urologists.

Although North's findings on burnout rates for urologists are lower than previously reported, burnout remains a serious problem, and North recommended that practices make mitigation a priority. Understanding the causes of burnout will help to guide future intervention. She also recommended creating and considering use of resources to address physician burnout, such as the American Medical Association's STEPS Forward program. This program provides a methodology for identifying at-risk physicians and ways to facilitate access to care. ■

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2 Late-Stage Trials Test Novel PI3K Inhibitor in Non-Hodgkin Lymphoma

By Ariela Katz

Copanlisib (BAY 80-6946), a novel PI3K inhibitor, is being combined with standard rituximab (Rituxan)-based regimens in patients with relapsed, indolent non-Hodgkin lymphoma (NHL) in 2 phase III clinical trials that investigators hope will expand treatment options in refractory disease settings, particularly with less toxic alternatives.

The clinical trials are continuing while the FDA reviews a new drug application for copanlisib as a treatment for patients with relapsed/refractory follicular lymphoma (FL), which is among several subtypes of CD20-positive NHL included in the late-stage trials. FL is the most common subtype of indolent NHL, accounting for about 22% of newly diagnosed cases.[1]

The FDA agreed on May 17 to review the application based on earlier clinical trial data under its priority review program, in which the agency is scheduled to decide within 6 months versus the standard 10-month review, according to Bayer, which is developing the drug.

The CHRONOS-3 trial is comparing the combination of copanlisib plus rituximab with rituximab plus placebo in patients with relapsed indolent B-cell NHL (**Figure 1**). The CHRONOS-4 trial is evaluating copanlisib with either rituximab plus bendamustine (Treanda) or with R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; **Figure 2**) in a similar patient population.

"The trials are designed to give clear data about what will improve upon standards for treatment in these patient populations," said John F. Gerecitano, MD, PhD, who is the global co-principal investigator for both CHRONOS trials.

John F. Gerecitano, MD, PhD

Although advances in immunochemotherapy have led to improvement in the prognosis for patients with NHL, relapsed and refractory disease is still a challenge to treat successfully. "These patients require lifelong intermittent therapies for their disease, since these are incurable diagnoses, and we're trying to develop more targeted agents that will be less toxic than traditional cytotoxic chemotherapies," said Gerecitano, clinical director of Outpatient Lymphoma Services at Memorial Sloan Kettering Cancer Center and assistant professor of medicine at Cornell Weill Medical College, both in New York City.

The PI3K pathway, which regulates proliferation and survival in various cell types, has emerged as a promising target for anticancer therapy, particularly in hematologic malignancies.[2] Copanlisib is a highly selective and potent pan-class I PI3K inhibitor, preferentially active against the alpha and delta isoforms.[2] PI3K-delta is expressed only in hematopoietic cells and has been shown to play a critical role in B-cell function, while expression of the alpha isoform is increased upon relapse and may be a factor in tumor escape mechanisms.[2,3]

CHRONOS Trial Details

The CHRONOS-3 and CHRONOS-4 trials are both open to patients with the indolent NHL subtypes of FL grades 1 to 3a, small lymphocytic leukemia (SLL), lymphoplasmacytoid lymphoma (LHL)/Waldenström macroglobulinemia (WM), and marginal zone lymphoma (MZL). Patients with a histologically confirmed diagnosis of FL grade 3b, disease transformation, or chronic lymphocytic leukemia are excluded.

In CHRONOS-3 trial (NCT02367040), investigators are seeking to determine whether copanlisib in combination with rituximab is superior to rituximab with placebo in patients who have relapsed after 1 or more prior lines of rituximab-containing therapy. An estimated 567 patients will be randomized in a 2:1 ratio to either the combination copanlisib and rituximab arm, or the rituximab and placebo arm.

The trial is enrolling patients with a histologically confirmed diagnosis of relapsed, CD20-positive indolent B-cell NHL and an Eastern Cooperative Oncology Group performance status less than or equal to 2. There can be no known lymphomatous involvement of the central nervous system. Patients cannot have documented evidence of resistance to prior treatment with idelalisib or other PI3K inhibitors.

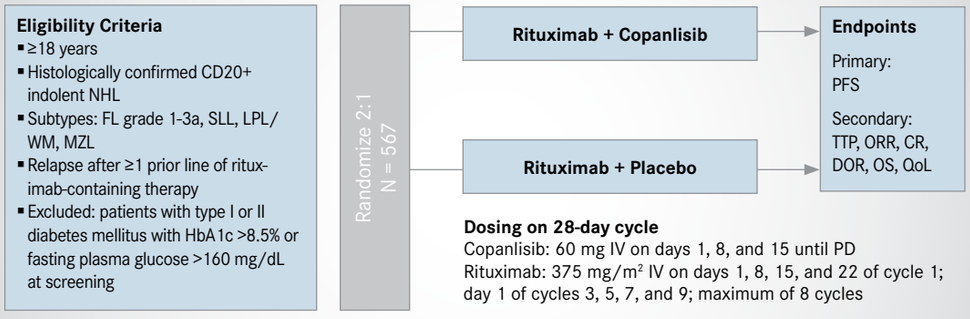
Prior to treatment, blood samples will be collected for safety and pharmacokinetic analyses. Archival tumor tissue and blood samples will also be collected for biomarker analysis and central pathology review. The primary endpoint is progression-free survival (PFS); secondary endpoints are objective tumor response, duration of response (DOR), overall survival (OS), complete response, and time to disease progression. The investigators will also be assessing the safety and tolerability of the combination.

The CHRONOS-4 trial (NCT02626455) is investigating whether copanlisib in combination with standard immunochemotherapy is effective and safe compared with placebo in combination with standard immunochemotherapy.

An estimated 676 patients will be stratified into 2 groups based on prior treatment, with the first group consisting of patients who have previously received R-CHOP or R-CVP (rituximab plus cyclophosphamide, vincristine, and prednisone) and the second group made up of participants who have received rituximab plus bendamustine (R-B). Patients also will be stratified based on NHL histology (FL vs other indolent NHL), and duration of treatment-free interval (6-12 months vs >12 months).

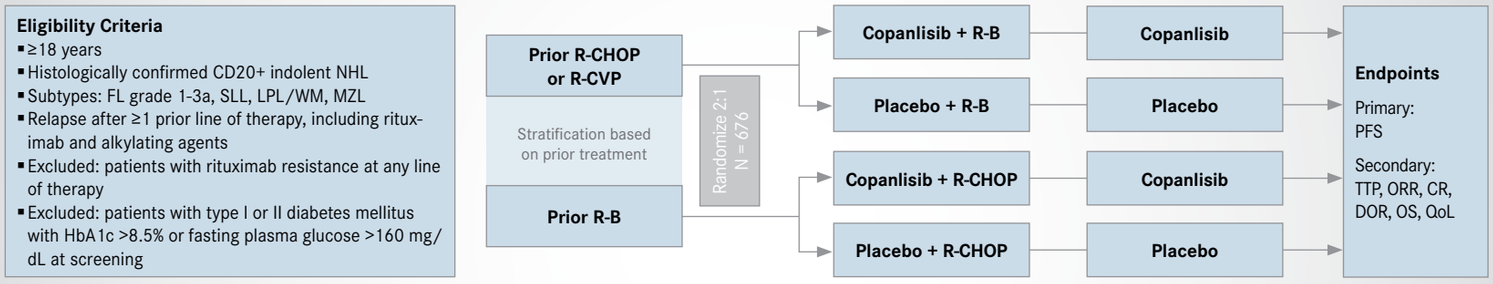
Participants in the first group will then be randomized 1:1 to receive either copanlisib plus R-B or placebo plus R-B. Those in the second group will be randomized to either copanlisib plus R-CHOP or placebo plus R-CHOP.

Figure 1. CHRONOS-3 Trial: Copanlisib Versus Rituximab



CR indicates complete response; DOR, duration of response; FL, follicular lymphoma; LHL, lymphoplasmacytoid lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; QoL, quality of life; SLL, small lymphocytic leukemia; TTP, time to progression; and WM, Waldenström macroglobulinemia.

Figure 2. CHRONOS-4 Trial: Copanlisib Versus Immunochemotherapy



Dosing after safety run-in to determine DL toxicities
Copanlisib: 60 mg IV on days 1, 8, and 15 of each 28-day cycle
R: 375 mg/m^2 IV on day 1 of each 28-day cycle for R-B group and day 2 of each 21-day cycle for R-CHOP group
B: 90 mg/m^2 IV on days 1 and 2
C: 750 mg/m^2 IV on day 2 of 21-day cycle
H: doxorubicin at 50 mg/m^2 IV on day 2 of 21-day cycle
O: vincristine at 1.4 mg/m^2 IV (maximum dose 2.0 mg) on day 2 of each 21-day cycle
P: 100 mg orally daily on days 2 through 6

B indicates bendamustine; CR, complete response; DL, dose-limiting; DOR, duration of response; FL, follicular lymphoma; LHL, lymphoplasmacytoid lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; QoL, quality of life; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CVP, rituximab, cyclophosphamide, vincristine, and prednisone; SLL, small lymphocytic leukemia; TTP, time to progression; and WM, Waldenström macroglobulinemia.

The trial is open to patients who have relapsed after 1 or more prior lines of therapy, including those who have received rituximab and alkylating agents. Notably, patients who may have had previous exposure to PI3K inhibitors also are eligible, provided there is no documented resistance. There must also be no evidence of resistance to rituximab at any line of therapy.

Prior to the full phase III trial, there will be a safety run-in phase for CHRONOS-4 to assess a dose escalation for the chemotherapy combinations, according to Gerecitano. During this phase, copanlisib will be given at 45 mg or 60 mg in the R-CHOP arm on days 1 and 8 over a 21-day cycle, and in the R-B arm, copanlisib will be given on days 1, 8, and 15 over a 28-day cycle. For cycles 1 through 6, R-CHOP and R-B will be given at the standard doses for lymphoma for 6 cycles. After 6 cycles, copanlisib maintenance will be given on days 1, 8, and 15 of a 28-day cycle.

The primary endpoint of CHRONOS-4 also is PFS; secondary endpoints are objective tumor response, DOR, OS, complete response, time to tumor progression, and safety and tolerability.

Prior Research Into Copanlisib

The new drug application for copanlisib is based primarily on findings from the phase II CHRONOS-1 trial, which included patients with multiple types of lymphoma. In the study, 59% of patients achieved objective responses to the intravenously administered copanlisib. Responses were durable, and the median PFS approached 1 year.[4]

Martin Dreyling, MD, PhD

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Lymphoma subtypes included in the CHRONOS-1 study were FL grades 1-3a, MZL, SLL, and LHL/WM. Eligible patients had relapsed or refractory disease and failure of at least 2 prior lines of therapy.

Data analysis included 142 patients who had a median age of 63. The median time since the most recent disease progression was 8.3 months, and the study population had received a median of 3 prior regimens. All patients had prior exposure to rituximab and 1 or more alkylating agents, and 60.6% had disease that was refractory to the last regimen received.

Across the lymphoma subgroups, 80.3% of the patients had advanced disease (stage III or IV) at enrollment. FL was the dominant lymphoma subtype, accounting for 73.2% of the study population.

The 59.2% overall response rate included complete responses in 12.0% of patients and partial responses in 47.2% of patients. An additional 29.6% of patients had stable disease, resulting in a disease control rate of 85.9%. Objective response rates were 59% or higher across all lymphoma subtypes except LHL/WM, wherein 1 of 6 patients with the subtype achieved an objective response with copanlisib.

The study population had a median PFS of 11.2 months (95% CI, 8.1-24.2). In the FL subgroup, the median PFS was also 11.2 months.

The most common adverse events (all grades) were hyperglycemia (48.6%), hypertension (28.9%), and decreased neutrophil count (24.6%). Grade 3 hyperglycemia occurred in 33.1% of patients and grade 4 in 7.0%. Grade 3 hypertension occurred in 22.5%. Grade 3 decreased neutrophil count occurred in 6.3% and grade 4 in 12.7% of the patients. The most common laboratory abnormalities were elevated liver enzymes, which was grade 1/2 in all but a few cases.

"Copanlisib demonstrated significant efficacy, and the safety profile was manageable and distinct, compared with that of oral PI3K inhibitors, possibly due to the intermittent schedule and intravenous route of administration," said Martin Dreyling, MD, PhD, head of the lymphoma program at University Hospital–Grosshadern in Munich, Germany, who presented the data at the 2017 American Association for Cancer Research Annual Meeting in April.

Gerecitano said the intravenous route of administration with copanlisib offers an improved toxicity profile compared with orally administered PI3K inhibitors in its class. "Although, like other drugs in its class that inhibit the alpha isoform of PI3K, copanlisib does lead to hyperglycemia and hypertension, there is an advantage to giving this intravenously instead of orally," he said. "Some of the oral PI3K-alpha inhibitors cause chronic hyperglycemia much like diabetes and chronic hypertension, but this agent causes just transient hyperglycemia and hypertension, which does not require diabetic-like treatment in most patients."

Both phase III trials exclude patients with type I or II diabetes mellitus with HbA1c >8.5% or fasting plasma glucose >160 mg/dL at screening. ■

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Choosing Among Immunotherapies in Bladder Cancer

By Danielle Bucco

The FDA's approval of pembrolizumab (Keytruda) for first-line and second-line settings has delivered yet another new immunotherapy option for patients with metastatic urothelial carcinoma (mUC).

In decisions announced May 18, the agency approved the PD-1 inhibitor in the second-line setting for the treatment of patients with locally advanced or mUC who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. The ruling was based on the phase III KEYNOTE-045 study in which single-agent pembrolizumab reduced the risk of death by 27% in patients with advanced, progressive mUC.

In the frontline setting, the FDA granted an accelerated approval for pembrolizumab as a treatment for patients with locally advanced or mUC who are not eligible for cisplatin-containing chemotherapy, based on an overall response rate of 29% to pembrolizumab monotherapy in the phase II KEYNOTE-052 study. The accelerated approval for frontline pembrolizumab in mUC is contingent upon the results of a confirmatory trial.

The approvals make pembrolizumab the fifth checkpoint blockade immunotherapy agent that the FDA has approved for mUC, the most common form of bladder cancer, since May 2016. It joins the PD-1 inhibitor nivolumab (Opdivo) and the PD-L1 antibodies avelumab (Bavencio), durvalumab (Imfinzi), and atezolizumab (Tecentriq). (**Timeline**)

All of these drugs are approved in second-line settings; only pembrolizumab and atezolizumab carry frontline indications for patients who are not eligible for cisplatin-containing chemotherapy. In May, Genentech, which is developing atezolizumab, announced that the drug did not meet its primary endpoint of improving overall survival over platinum-based chemotherapy for patients with locally advanced, progressive mUC in the phase III IMvigor211 study. The trial was designed to convert atezolizumab's accelerated approval status in the second-line setting into a full approval. It is not clear what impact, if any, these results will have on that process. Other studies of atezolizumab are ongoing.

Timeline. Big Year for FDA Approvals In Advanced/Metastatic Urothelial Carcinoma

May 18, 2016	Atezolizumab (Tecentriq)
February 2, 2017	Nivolumab (Opdivo)
May 1, 2017	Durvalumab (Imfinzi)
May 9, 2017	Avelumab (Bavencio)
May 18, 2017	Pembrolizumab (Keytruda)

In an interview with *OncologyLive®*, Arjun V. Balar, MD, a lead investigator on pivotal pembrolizumab research in bladder cancer, and an assistant professor in the Department of Medicine and director of the Genitourinary Medical Oncology Program at New York University's Perlmutter Cancer Center in New York City, discussed the impact of immunotherapy agents in urothelial carcinoma, as well as the next steps with these treatments.

Arjun V. Balar, MD

Q: What does the FDA's approval of pembrolizumab in bladder cancer mean for patients?

It comes down to which approval we're talking about, whether it is the second line or the first line. For the second line, at that point, pembrolizumab becomes the fifth drug approved for the second-line treatment of bladder cancer. From that perspective, it adds to our armamentarium in terms of options that we can provide our patients. It's similar in terms of the class of drug. It's a PD-1 antibody, allowing it to work on the PD-1 axis, making the response and safety very similar to other agents in its class.

What's unique about pembrolizumab in the second-line setting is that it was approved on the basis of a randomized phase III trial that definitively demonstrated its improved survival versus standard-of-care chemotherapy, which no other agent in this class has been able to do. In my opinion, that is probably the strongest level of evidence for any of the drugs.

In terms of the frontline setting, pembrolizumab is now just 1 of 2 drugs approved for patients who are ineligible for cisplatin. In this case, both pembrolizumab and atezolizumab are accelerated approvals, whereas pembrolizumab's second-line approval is a full approval. Both accelerated approvals are on the basis of response and durability of responses in the first-line setting.

What is particularly unique about atezolizumab and pembrolizumab in the frontline setting is that these are the first FDA-approved drugs for a population of patients who have never had an FDA-approved drug. These are the first treatments that have ever been approved for patients who are ineligible for cisplatin. About 50% to 70% of our patients with metastatic bladder cancer are cisplatin ineligible. This means these approvals greatly impact a majority of patients with metastatic bladder cancer, which is quite exciting.

Q: Now that we have more options for immunotherapy treatments, how do you determine which drug to use?

I think that is the main challenge right now. Within 1 year, we've had 5 different drugs that have been approved in various settings. It's been difficult for the research community and the bladder cancer community to parse out the differences between these agents. The response rates, the durability of responses, and the survival rates appear to be very similar. However, again, the caveat is it's a mix of phase I, phase II, and now a phase III study.

I don't think we can make any comparisons about survival because survival between phase I, II, and III studies can be marginally different for a variety of reasons. In terms of the response, durability of responses, and the safety of the drugs, I think they are quite comparable and that is probably the most we can say at this point.

Q: What other questions regarding these agents still need to be addressed?

From these drugs so far, I think what we need to see concerns the frontline setting. The major unanswered question is whether pembrolizumab and atezolizumab are better than standard-of- care chemotherapy. We need a randomized phase III trial. There are 2 notable studies that are currently ongoing: the atezolizumab study, which is IMvigor130 (NCT02807636), and then the pembrolizumab phase III study where it is compared with chemotherapy, which is KEYNOTE-361 (NCT02853305). Both of those trials will answer the question of whether PD-1 [pathway] blockade improves survival versus chemotherapy in the frontline setting.

Q: What do you anticipate for the future of these agents?

Now that we have these approvals, the challenge is that, based on pembrolizumab and atezolizumab, up to 25% of patients are responding to treatment. What that means is the next generation of trials needs to improve on that response rate.

We need to use immunotherapy as a backbone and to develop novel combinations. Perhaps those combinations are with radiation, chemotherapy, targeted therapy, or other immuno-oncology drugs to increase that response rate in terms of immune responses. ■

Update Supports Efficacy of Emerging Melanoma Combo

By Jason M. Broderick

The combination of the BRAF inhibitor encorafenib and the MEK inhibitor binimetinib reduced the risk of disease progression or death by 23% compared with single-agent encorafenib for patients with *BRAF*-mutant melanoma, according to findings from part 2 of the phase III COLUMBUS trial.

The median progression-free survival (PFS) for patients treated with the combination was 12.9 months compared with 9.2 months for patients receiving encorafenib alone (HR, 0.77; 95% CI, 0.61-0.97; *P* = .029).

Based on these data, along with previously reported findings from part 1 of the COLUMBUS trial, Array BioPharma, the developer of the combination, anticipates filing a new drug application with the FDA in June or July.

If approved, the combination would be the latest such pairing of a BRAF and a MEK inhibitor to gain acceptance in melanoma. The strategy was first established with the combination of trametinib (Mekinist), a MEK inhibitor, and dabrafenib (Tafinlar), a BRAF inhibitor, which the FDA approved in January 2014 for patients with unresectable or advanced melanoma with a *BRAF* V600E or V600K mutation. In November 2015, the FDA approved the MEK inhibitor cobimetinib (Cotellic) in combination with vemurafenib (Zelboraf), a BRAF inhibitor, for a similar patient population.

In announcing the latest data in May, Array said the results of the COLUMBUS trial confirm the benefit of the encorafenib plus binimetinib regimen.

"The totality of the COLUMBUS results, including estimated progression-free survival, objective response rate, dose intensity, and tolerability of the combination, provide a strong and consistent theme across multiple endpoints, underscoring the promise of binimetinib plus encorafenib as an attractive treatment option for patients diagnosed with *BRAF*-mutant melanoma," Keith T. Flaherty, MD, director of the Termeer Center for Targeted Therapy, Massachusetts General Hospital, and professor of medicine, Harvard Medical School, said in a statement.

Keith T. Flaherty, MD

Encorafenib Plus Binimetinib Findings

The COLUMBUS trial included 921 patients with locally advanced, unresectable, or metastatic *BRAF* V600-mutant melanoma. Prior treatment with immunotherapy was allowed. Those with untreated central nervous system lesions, leptomeningeal metastases, uveal melanoma, and mucosal melanoma were excluded from the trial.

In part 1 of the study, 577 patients were randomized in a 1:1:1 ratio to receive encorafenib plus binimetinib, encorafenib alone, or vemurafenib alone. In the combination arm, encorafenib was administered at 450 mg daily and binimetinib was administered at 45 mg twice daily. Single-agent encorafenib was given at 300 mg daily and vemurafenib was administered at 960 mg twice daily.

Part 2 of the study randomized 344 patients in a 3:1 ratio to receive encorafenib plus binimetinib at 45 mg twice daily or encorafenib alone. Encorafenib was given at 300 mg daily.

"Part 2 was designed specifically to assess the contribution of binimetinib to the combination of binimetinib and encorafenib by reducing the dose of encorafenib to 300 mg in the combination arm to allow for a comparison of equal doses across arms," Array said in a press release.

Array also noted that the part 2 combination dose was well tolerated, with adverse events (AEs) consistent with the reported side effects for the combination in part 1. Additional data from part 2 will be presented at an upcoming medical meeting this year.

In part 1 of the study, the median PFS was 14.9 months with the combination of encorafenib and binimetinib compared with 7.3 months for vemurafenib alone. The improvement in PFS represented a 46% reduction in the risk of progression or death (HR, 0.54; 95% CI, 0.41-0.71; *P* <.001).

When single-agent encorafenib was compared with the combination arm, the difference between the groups did not reach statistical significance (HR, 0.75; 95% CI, 0.56-1.00; *P* = .051). However, median PFS with encorafenib was statistically superior to vemurafenib (HR, 0.68; 95% CI, 0.52-0.90; *P* = .007). Findings for overall survival (OS) were not yet available.

The objective response rate (ORR) with the combination was 63% versus 40% with vemurafenib. With single-agent encorafenib, the ORR was 51%. The complete response rate was 8% with the combination versus 5% and 6% with encorafenib and vemurafenib, respectively. The median duration of response was 16.6 months with the combination versus 14.9 months with encorafenib and 12.5 months with vemurafenib.

By local review, median PFS with the combination was 14.8 versus 7.3 months with vemurafenib (HR, 0.49; 95% CI, 0.37-0.64; *P* <.001). The ORRs by local review were 75% for the combination versus 49% and 58% for vemurafenib and encorafenib monotherapy, respectively.

In this assessment, the combination was superior to single-agent encorafenib (HR, 0.68; 95% CI, 0.52-0.90; *P* = .006). The median PFS with encorafenib was 9.2 months, which was also superior to single-agent vemurafenib (HR, 0.70; 95% CI, 0.54-0.91; *P* = .008).

All-grade AEs with the most variability between the 2 arms for the combination, single-agent encorafenib, and vemurafenib, respectively, were arthralgia (26%, 44%, 45%), pyrexia (18%, 15%, 28%), alopecia (14%, 56%, 37%), hyperkeratosis (14%, 38%, 29%), dry skin (14%, 30%, 23%), rash (14%, 21%, 29%), palmoplantar keratoderma (9%, 26%, 16%), and palmar-plantar erythrodysesthesia syndrome (7%, 51%, 14%). All-grade AEs of special interest with the combination included rash (23%), pyrexia (18%), retinal pigment epithelial detachment (13%), and photosensitivity (5%).

Grade 3/4 AEs were experienced by 58% of patients treated with the combination versus 66% and 63% with encorafenib and vemurafenib, respectively. The most common grade 3/4 AEs with the combination were gamma-glutamyltransferase, increased blood creatine phosphokinase, and hypertension. Time to first grade 3/4 AE was long with the combination: at 2.5 months versus 0.4 months for encorafenib and 1.3 months for vemurafenib.

In March, Array withdrew its FDA new drug application for single-agent binimetinib as a treatment for patients with *NRAS*-mutant advanced melanoma, based on feedback from the FDA during a preplanned review meeting.

The application for binimetinib was based on data from the phase III NEMO study, which was presented at the 2016 American Society of Clinical Oncology Annual Meeting. In the open-label study, the PFS with binimetinib was 2.8 months versus 1.5 months with dacarbazine, representing a 38% reduction in the risk of progression or death (HR, 0.62; 95% CI, 0.47-0.80; *P* <.0001); however, OS did not improve with the MEK inhibitor alone. ■

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Complete Metastasectomy Remains Vital RCC Option

By Danielle Bucco

Complete metastasectomy can more than double life expectancy for many patients with metastatic renal cell carcinoma (mRCC), according to the results of a meta-analysis of observational data published in *The Journal of Urology*.

The analysis looked at 8 published cohort studies with a total of 2267 patients with mRCC. The median overall survival range for patients who underwent a complete surgical metastasectomy was 36.5 months to 142 months compared with 8.4 months to 27 months for those who received an incomplete surgical metastasectomy.


Bradley C. Leibovich, MD

"When we pooled the data from these multiple studies, it appears that complete surgical removal of metastatic disease is very beneficial for patients," said Bradley C. Leibovich, MD, an author on the trial.

In an interview with *OncologyLive*®, Leibovich, a professor of Urology at Mayo Clinic in Rochester, Minnesota, discussed the benefits of surgery and the need for more effective drug treatments for patients with mRCC.

Q: What was the impetus for this research?

Many patients with kidney cancer have a tumor that is found when it is localized. Surgery in those patients is curative the majority of the time without the need for any additional treatment. Some patients don't need surgery at all. However, a portion of patients have disease that has already spread to other areas of the body.

Unlike other cancers, traditional chemotherapy drugs don't work for kidney cancer. The drugs that we have help extend a patient's life but they don't usually cure the disease. These drugs are most beneficial at holding things steady or causing a tumor to shrink modestly and then holding it steady. Sooner or later, the cancer starts to outsmart these drugs and when that happens, we switch from drug to drug, but eventually the patient is likely to succumb to mRCC.

We have had about 10 drugs approved by the FDA since 2005. Prior to 2005, there was only 1 drug ever approved by the FDA, which was approved in 1992. Prior to 1992, there was nothing. Over the years, our group at Mayo Clinic has had an interest in removing the disease to the fullest extent possible in patients who have metastatic disease. We have seen that some of these patients are durably cured. Patients who aren't cured seem to live much longer than patients who don't have surgery to remove all their metastatic disease.

The problem is that it's a very small subset of patients who can have all their disease surgically removed. Therefore, many kidney cancer experts would argue that we are simply operating on patients who are going to do well no matter how you treat them. If there is so little disease that you can feasibly surgically remove it all, nihilists would say that those patients are likely to do well with other options of treatment.

Over the years, there have been publications trying to address that concern by comparing patients who have had disease completely removed with those who have not and to adjust for other factors that might be significant in terms of those patients' prognosis. When we adjust for disease factors to make a fair and balanced comparison, it seems like complete removal of metastatic disease is beneficial for patients with metastatic renal cell carcinoma.

The purpose of this research was to pool the data from multiple studies that have been done in this area and attempt to eliminate the bias that's inherent in looking backward over time rather than doing this as a prospective clinical trial. In fact, when we pooled the data from these multiple studies, it does still appear that complete surgical removal of metastatic disease is beneficial for patients.

Our hope and expectation is that this paper will continue to keep people aware of the potential benefit of completely removing metastatic disease and to assure that doctors in the community who are using these new drugs don't forget that surgical removal of metastatic sites is potentially additive to the drug treatment in extending survival.

Q: What other challenges in RCC need to be addressed?

We would like more effective drug treatments. Around the globe, we are working hard to come up with better regimens to treat patients with these medications. There is additional work that needs to be done to determine if there are other ways to approach this problem.

Regarding the impact of surgery, we need to determine if treating patients with drugs prior to complete surgical resection would work even better. Would giving a limited period of drug treatment after complete surgical resection make things better? Our data so far would indicate that it is not the case. We've been doing genetic analyses on these patients looking at the genetics of the primary tumor and the metastatic disease to determine if we can better predict which patients will do well with these treatments, and which drugs to give if and when they do have recurrent disease after resection. The challenges and need for additional work are seemingly endless.

Q: Are there any clinical trials looking at those challenges?

We have an ongoing trial of complete surgical resection with drug treatment afterward. There are multiple trials of new drug therapies. We have a program now where we take out the metastatic disease and grow it in an animal model and test various drugs to determine the best form of treatment for the patient.

Q: Please summarize the message you would give to practicing oncologists.

I think the take-home message is, despite the fact that we have many new drugs for treating kidney cancer, they are unfortunately rarely curative. The data seem to indicate that surgical removal of disease remains an integral portion of providing those patients with maximum extension of life. We don't want people to forget about the potential positive impact of surgery and the overall improvements that we're making in the care of these patients. ■

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Hereditary Kidney Cancers Studied

W. Marston Linehan, MD, discusses the mutational landscape of hereditary kidney cancer, for which investigators have identified 16 genes that cause more than a dozen subtypes.

Linehan is chief of the Urologic Oncology Branch at the National Cancer Institute in Bethesda, Maryland.

onclive.com/link/1204

Robotic Surgery Outcomes

Ketan K. Badani, MD, describes the benefits of robotic surgery for partial nephrectomy for patients with kidney cancer, which include the ability to conduct minimally invasive procedures and to shorten the time the kidney is without blood flow.

Badani is a professor of urology at the Icahn School of Medicine at Mount Sinai Hospital and vice chairman of urology and robotic operations at Mount Sinai Health System in New York City.

onclive.com/link/1205

Evolving Neoadjuvant and Adjuvant Therapeutic Approaches in RCC

By Ariela Katz

Surgical resection, including cytoreductive nephrectomy, remains the standard of care for most patients with renal cell carcinoma (RCC). However, many patients will have a recurrence, and could benefit from additional therapy. Much research has been conducted to define the role of neoadjuvant and adjuvant therapies for patients with RCC, but the standard of care has not changed significantly in the past several years.

Role of Neoadjuvant Therapy


David M. Nanus, MD

"The [benefit] of giving therapy, like a TKI for instance, would be to start systemic therapy right away, have the tumor shrink, so the nephrectomy will be easier," said David M. Nanus, MD, during a presentation at the New York GU™: *10th Annual* Interdisciplinary Prostate Cancer Congress® and Other Genitourinary Malignancies that Physicians' Education Resource® (PER®) hosted March 18 in New York City.

Nanus said that rapid initiation of systemic therapy prior to surgery could also decrease cancer-related mortality, and could eliminate these risks in patients who would not benefit from a nephrectomy. "The contrast to that is that it may add to the morbidity or mortality of surgery if you give the drug; there may be wound-healing issues, and you may 'decondition' the patient and [then] they can't get systemic therapy. And it hasn't been proven that it improves survival, so why should we do it," commented Nanus, a Mark W. Pasmantier Professor of Hematology and Oncology in Medicine, Weill Cornell Medicine.

Previously there were several prospective clinical trials in the neoadjuvant setting prior to cytoreductive nephrectomy (**Table 1**), but such investigations have become less frequent due to the recent push for developing immunotherapies. One such study Nanus mentioned was a phase II study of pazopanib (Votrient) in patients with localized RCC to optimize preservation of the renal parenchyma.[1] Of the13 patients originally unable to undergo a partial nephrectomy, 6 underwent surgery. Significant decrease in the size of the tumors occured in the patients. "Keeping a patient from going on dialysis by shrinking the tumor preoperatively should be done," Nanus commented.

In another phase II study assessing the safety and efficacy of pazopanib therapy prior to a planned nephrectomy in patients with metastatic clear cell RCC (ccRCC), investigators discovered that a nephrectomy could be performed safely after upfront treatment with pazopanib and was associated with good outcomes in patients with intermediate-risk disease.[2] A significant size reduction in the primary tumor was observed, with a median reduction of 14.4% (range, 1.4%-21.1%).

"However, when you look at progression-free survival, in this study it was about 7 months, so it's not very clear that giving preoperative [pazopanib] in the metastatic setting made a big difference," Nanus said. "I think giving cytoreductive neoadjuvant therapy should be restricted to select patients."

Table 1. Selected Prospective Neoadjuvant Trials in RCC

Agent	Trial Description	Sample Size (n)
Bevacizumab	Phase II presurgical feasibility study in untreated patients with metastatic RCC	50
Sorafenib	Sorafenib in patients with metastatic RCC refractory to either sunitinib or bevacizumab	30
Sunitinib	Feasibility and efficacy of neoadjuvant sunitinib before nephron-sparing surgery	12
	Prospective clinical trial of preoperative sunitinib in patients with RCC	20
	Assessment of the outcome of patients with metastatic clear cell RCC who receive sunitinib prior to planned nephrectomy	66
	Phase I dose-escalation trial of tremelimumab plus sunitinib in patients with metastatic RCC	28
Pazopanib	Phase II study of the safety and efficacy of pazopanib prior to planned nephrectomy in metastatic clear cell RCC	34
	Phase II study of pazopanib in patients with localized RCC to enable partial nephrectomy	23
Axitinib	Phase II trial of neoadjuvant axitinib in patients with locally advanced nonmetastatic clear cell RCC	24

Role of Adjuvant Therapy

"There was no prospective randomized trial in the cytokine era that clearly demonstrated a benefit with adjuvant therapy," Nanus said. "But obviously, there's still a need for adjuvant therapy studies." Nanus further explained that patients tend to relapse at high rates, with a tendency toward mortality for those who progress to metastatic disease. Patients in these populations could benefit from an adjuvant treatment if one were proven effective (**Table 2**), but investigations into adjuvant treatments have had several trials leading to negative results.

Another such trial, the phase III ARISER trial, assessed adjuvant girentuximab (Rencarex) in patients with non-metastatic RCC. Girentuximab is an antibody to the RCC-associated G250 antigen, which is especially overexpressed in ccRCC. The investigators determined that girentuximab had no clinical benefit as an adjuvant treatment for patients with high-risk ccRCC, based on a median disease-free survival (DFS) of 71.4 months for the girentuximab arm (n = 433), whereas the DFS was not reached in the placebo arm (n = 431). A median overall survival (OS) was not reached for either arm.4

In another completed study, the phase III ASSURE trial, compared adjuvant sorafenib (Nexavar) or sunitinib (Sutent) to placebo for patients with unfavorable RCC. There was no difference observed in 5-year DFS or OS between the 3 arms.5 A preplanned ccRCC subset analysis also revealed that there was no significant difference among the 3 arms of the trial.

Recently updated data from the ccRCC subset of the phase III ASSURE trial assessing sunitinib or sorafenib versus placebo in treating patients with RCC removed by surgery that there was no improvement in DFS and OS.6 In the secondary analysis, the 5-year DFS rates were 47.7%, 49.9%, and 50.0% for sunitinib, sorafenib, and a placebo, respectively. Additionally, dose intensity did not affect outcomes. Ultimately, there was no benefit observed from adjuvant sunitinib or sorafenib therapy in the high-risk ccRCC population.

From the phase III S-TRAC study, which compared the efficacy and safety of sunitinib versus placebo for patients at a high risk for

Table 2. Selected Phase III Clinical Trials for Agents in the Adjuvant Setting for RCC

Mechanism of Action	Trial Name	Trial Description	ClinicalTrials.gov ID	Recruitment Status
Anti-VEGF	ASSURE	Sunitinib malate or sorafenib tosylate in treating patients with RCC removed by surgery	NCT00326898	Completed
	SORCE	Sorafenib in treating patients at risk of relapse after undergoing surgery for RCC	NCT00492258	Completed
	S-TRAC	Trial comparing efficacy and safety of sunitinib vs placebo for treating patients at high risk of recurrent RCC after surgery	NCT00375674	Active, not recruiting
	ATLAS	Adjuvant axitinib for RCC in high-risk patients	NCT01599754	Active, not recruiting
	PROTECT	Evaluation of pazopanib as an adjuvant treatment for localized RCC	NCT01235962	Active, not recruiting
mTOR Inhibitor	EVEREST	Everolimus in treating patients with RCC who have undergone surgery	NCT01120249	Active, not recruiting
Tumor Antigen Antibody	ARISER	Girentuximab monoclonal antibody therapy in treating patients with nonmetastatic RCC who have undergone surgery	NCT00087022	Completed
Immunotherapy	IMmotion010	Study of atezolizumab as adjuvant therapy in participants with RCC at high risk of developing metastasis following nephrectomy	NCT03024996	Recruiting
	PROSPER	Study of nivolumab in treating patients with localized RCC undergoing nephrectomy	NCT03055013	Recruiting

recurrent RCC, early data show that DFS was longer in the sunitinib group than in the placebo group (6.8 years vs 5.6 years), although at the cost of a higher rate of AEs.7 However, the results were only just statistically significant (HR, 0.76; 95% CI, 0.59-0.98; P = .03).

Looking to the Future

There are many challenges in assessing treatments in the neoadjuvant and adjuvant settings for patients with RCC. One of the issues with many of these studies is that their primary endpoints are set to DFS, and this endpoint may or may not read out for OS as more data points in that direction, according to Nanus. Additionally, the median follow-up for these studies, about 5 years, may or may not be long enough to assess the drugs for their true efficacy. The imaging review and frequency also makes a difference in these trials, like in the S-TRAC study.

There are also eligibility factors in play for each patient, depending on their tumor size and histology. The duration of therapy for any of these agents may yet be an unexplored area of concern, since there are no data on how many months of treatment is most effective for these patients in either the neoadjuvant or adjuvant setting.

Additionally, there are issues pertaining to varying therapies. "Not only is it different therapies, one drug versus another, but there's a lot of dose reductions, treatment discontinuations, and grade 3 to 5 toxicities, so it makes it tricky to compare across trials, but it also makes it difficult to keep patients on studies," Nanus commented.

Conversely, there are a lot of opportunities in these settings. There is a clinical need to improve survival in these patients. "This is a patient population that we've really let down; a lot of these patients go through surgery, and then they relapse," Nanus said.

With large datasets incoming, there will be an opportunity to validate or even develop prognostic and molecular models to determine which patients are at the highest risk for recurrence, and which would benefit from certain therapies. According to Nanus, these models would lead to a better way for clinicians to determine which of their patients would be candidates for certain trials or conventional therapies.

There is also a need to refine surveillance guidelines for this patient population, particularly since these patients tend to have high rates of relapse or recurrence of their disease after surgery. It would also be beneficial to have more trials accruing data to understand the effectiveness of second-line therapy after relapse with adjuvant therapy.

"There is a high bar to achieve out there, and I think we will achieve it. There's a lot of effort in this area, and I look forward to the day when we can find something that will help our patients after surgery," Nanus said. ■

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Making Strides Against a Rare Disease: Renal Medullary Carcinoma in Focus

By W. Kimryn Rathmell, MD, PhD

Director, Division of Hematology and Oncology
Cornelius A. Craig Professor of Medicine
Professor, Medicine, Cancer Biology, and Biochemistry
Vanderbilt-Ingram Cancer Center
Nashville, TN

Renal medullary carcinoma (RMC) is a rare but devastating tumor type almost exclusively affecting young adults carrying 1 copy of hemoglobin beta (*HBB*) harboring the A17T mutation (HbS). The pathophysiology of the association to HbS, or sickle cell trait, remains unknown. This is a highly aggressive neoplasm, for which there are no established guidelines to direct standards of care.[1]

Similarly, the diagnosis of these cancers can be difficult, unless the urologic oncologist, pathologist, and/or medical oncologist is alert to the possibility. RMC management can also be challenged by the unique age distribution, which overlaps pediatric and adult oncology. The exact incidence of the disease in the United States is unknown, but it is reasonable to think that there are fewer than 500 cases annually diagnosed, such that an individual oncologist might only encounter 1 of these cases in their career.

Multiple case reports have suggested these cancers can be responsive to multiagent platinum regimens, which are the current mainstay of treatment for this cancer.[2] It is critical to be alert to the rare patient who presents with this cancer, because the diagnosis may be delayed by the uncertainties of histology and chemotherapy is not typically considered in patients with renal neoplasms. A case report of a patient responding to bortezomib has led to interest in this drug class[3], and recently combination chemotherapy with bortezomib has been reported with good response in 2 pediatric patients.[4]

Recent studies have shed light on the biological underpinnings of RMC, namely a clear association with *SMARCB1* (also known as *INI1*) mutations, implicating chromatin reprogramming and epigenetics in the development of this cancer.[5,6] This finding is critical to sealing the diagnosis, since a loss of *SMARCB1* staining can confirm a diagnosis of RMC.

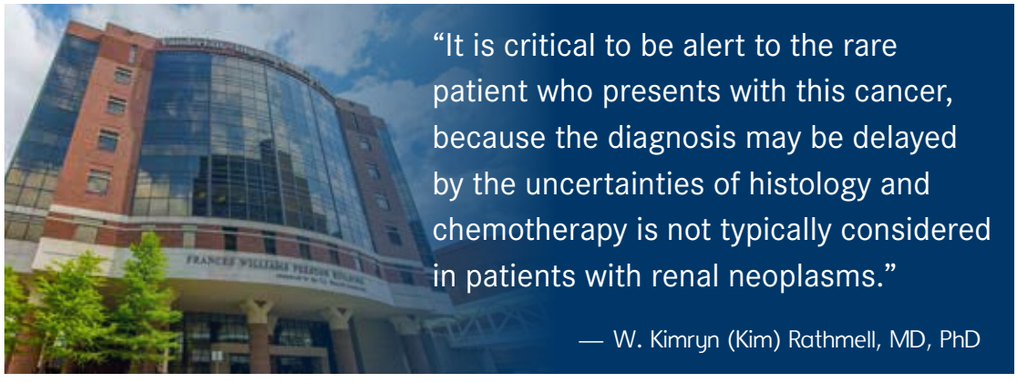
This finding also suggests a possible role for therapeutics targeting the epigenetic program, of which a number are currently undergoing evaluation. Ongoing slinical trials are testing EZH2 inhibitors at The University of Texas MD Anderson Cancer Center in Houston, under the supervision of Nizar M. Tannir, MD, a long-time champion for studying rare kidney tumors, and at a growing number of centers across the country. This interest is based on findings linking sensitivity to inhibition of EZH2, an epigenetic regulator, with *SMARCB1* loss.[7]

Little is known about the responsiveness of these cancers to checkpoint immunotherapy strategies. Researchers from Vanderbilt University and colleagues recently reported on a single case of a patient who had biopsy-confirmed progression after chemotherapy and was treated with nivolumab.[8] This patient remains in complete response and disease free 2 years later. The range of responses, however, is not known.

In an attempt to reach some consensus on the diagnosis and treatment of RMC, the William Guy Forbeck Foundation has provided support for an international meeting of experts with experience dealing with sickle cell trait manifestations and RMC. This meeting, held in April 2016 in Nashville, Tennessee, resulted in a consensus manuscript, in press in the *Journal of Oncology Practice*. In addition to developing consensus guidelines regarding diagnosis and treatment algorithms, the group concluded that the most pressing need going forward was to raise awareness among at-risk patient groups and physicians about the specific features of RMC.

Collectively, we have partnered to develop the RMC Alliance, with a goal to increase visibility and awareness of this cancer type as distinct from other more common renal cell carcinomas, and to enhance communications between groups with a mission to accelerate advances in the care of these patients.

Equally important in raising public awareness is the role of advocacy, with efforts led by a group of remarkably dedicated advocates. Information is available from the group R.M.C. at RMCsupport.org and the Chris Johnson Foundation at chrisjohnsonfoundation.org. Other efforts are underway to engage and educate at-risk groups. A second meeting of the RMC Alliance, open to all interested parties, is scheduled to be held in conjunction with the 49th Congress of the International Society of Paediatric Oncology on October 12 in Washington, DC. ■



> "It is critical to be alert to the rare patient who presents with this cancer, because the diagnosis may be delayed by the uncertainties of histology and chemotherapy is not typically considered in patients with renal neoplasms."
>
> — W. Kimryn (Kim) Rathmell, MD, PhD

More than 300 researchers and physician-scientists are engaged in research at the Vanderbilt-Ingram Cancer Center.

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Second Cancers Can Wield Greater Impact on Adolescent and Young Adult Survivors

By Theresa Keegan, PhD, MS

Associate Professor
Cancer Epidemiology and Survivorship
Division of Hematology and Oncology
UC Davis Comprehensive Cancer Center
Sacramento, CA

Advances in treatment and supportive care have resulted in substantial improvements in cancer survival and a growing number of cancer survivors in the United States. These survivors, however, are at an increased risk of developing a second cancer due to genetic factors, the carcinogenic effects of cancer treatment, common exposures (eg, tobacco), and other as yet unknown factors. The risk of developing a second cancer also varies by age, with those diagnosed with their first cancer during childhood having the highest risk. The burden of second cancers in survivors of adolescent and young adult (AYA) cancers (15-39 years) is also high; they have a higher risk of developing a second cancer than older cancer survivors and have the highest absolute excess risk of a second cancer, or excess cancers per 10,000 person-years, among all age groups.

A number of studies have noted the increased late mortality after specific second cancers among young cancer survivors, but no studies have systematically assessed whether second cancers have a similar detrimental impact on survival for children, AYAs, and older adults. As progress in improving the survival of AYA patients with cancer has lagged behind that of younger and older cancer patients, it is important to determine whether the impact of second cancers on survival is disproportionate in the AYA population.

Our study, based on an analysis of more than 1 million patients with cancer of all ages from throughout the United States, compared survival by age after a second cancer to survival of the same cancer that occurs as a first cancer. We identified all patients diagnosed with only 1 or a first and second cancer during 1992 through 2008 using Surveillance, Epidemiology and End Results program data from 13 cancer registries (**Figure**). We collected data on the 14 most common cancer types that affect AYAs: female breast, thyroid, testicular, Hodgkin lymphoma, non-Hodgkin lymphoma, acute lymphoblastic leukemia, acute myeloid leukemia, soft tissue sarcoma, bone sarcoma, colorectal, central nervous system, cervical, melanoma, and ovarian.

In this large population-based study published in *JAMA Oncology*, the impact of a second cancer on survival was most pronounced in AYAs and the relatively few second cancers that occurred in children compared with older adults. We found that survival after almost all types of cancers is much higher when the cancer occurs as a first cancer than if it is a second cancer, and that for the most common second cancers in AYAs, the absolute differences in survival were substantial. Overall, children and AYAs had an 80% chance of surviving 5 years after a diagnosis of a first cancer. However, if the same cancer occurred as a second cancer, 5-year survival dropped to 47% for children and 60% for the AYA population. The differences in survival were not nearly as marked in the older adult population, who had a 70% chance of surviving 5 years overall for a first cancer and 61% for a new, second cancer.

When we looked at 5-year survival by age and individual cancer type, we found striking differences depending on whether it was a first or second cancer in all but 2 of the 14 cancer types: testes and melanoma. For the most common second cancers in AYAs, the absolute difference in 5-year survival was 42% lower for second non-Hodgkin lymphoma, 19% lower for second breast cancer, 15% lower for second thyroid cancer, and 13% lower for second soft tissue sarcoma.

In multivariable survival models, almost every cancer conferred a higher risk of death than that of the same first cancer, and the impact on survival was significantly greater in younger patients compared with older patients. What struck us was that the second cancer caused such an increased risk of death. For example, second Hodgkin lymphoma and thyroid cancer had a more than 3-fold greater risk and second breast, testicular, soft tissue sarcoma, and bone sarcoma had a more than 2-fold greater risk of cancer-specific death than each cancer occurring as a first cancer.

Worse survival after second cancers may result from the second cancers being more biologically aggressive or patients with a second cancer having a worse response to treatment, limitations on the types or doses of treatments that they can receive as a result of their prior cancer treatment, or impaired physiologic reserves that impact their ability to tolerate treatment for their second cancer.

Why younger patients tend to fare worse than older patients with the same second cancers is not fully understood or an aspect we could specifically address in this study. We next plan to examine how the time between getting a first and second cancer affects survival and whether the types of treatments for the first cancer influence the outcome of a second cancer. We hope these findings help guide clinicians in providing age-specific recommendations on cancer prevention, screening, treatment, and survivorship, especially among the AYA population for whom survival rates have not improved to the same extent as they have for children and older adults. ■

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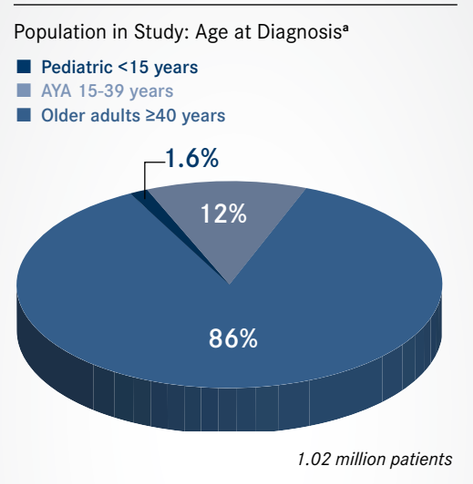
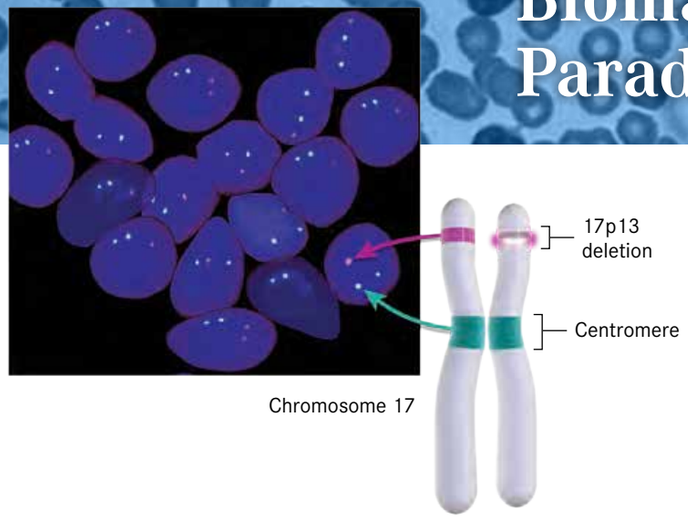
Figure. Second Primary Malignancies



[a]Percentages have been rounded.

AYA indicates adolescents and young adults.

Biomarkers Shift Treatment Paradigm in CLL



Based on improved insight into chronic lymphocytic leukemia (CLL) biology and pathophysiology, approaches to identify patients who are at higher risk for disease progression have been refined, as have strategies to select therapies that maximize treatment outcomes due to their selectivity for distinctive phenotypic or physiological features of the respective CLL cells.[1]

With changing treatment paradigms, particularly the use of oral targeted agents, predictive value and use of prognostic factors to determine treatment choice are shifting. Traditional risk factors, including disease stage and lymphocyte doubling time, are becoming less relevant for treatment selection, and the predictive value of cytogenetic and molecular markers on response to treatment with novel agents is being redefined based on the outcomes of recent trials.[2-5]

Disease Characteristics Affecting Prognosis and Therapy

The presence of a deletion of chromosome 17p [del(17p)] and mutated *TP53* represent the most relevant disease characteristics that guide the choice of therapy in patients with CLL.[6] Del(17p) causes the loss of 1 *TP53* allele and is associated with mutations in the remaining *TP53* allele in more than 80% of patients, resulting in loss or dysfunction of *TP53*. Both del(17p) and mutated *TP53* are associated with poor response to chemotherapy-based regimens, short progression-free survival (PFS), and poor overall survival (OS), independently of *IGHV* mutation status **(Table)**.[1,7,8]

Recent trials have demonstrated activity of novel targeted agents in patients with del(17p)/*TP53*-mutant CLL, who are considered a distinct subgroup who require a specific therapeutic approach.[1,9] This has significantly changed outcomes for this subgroup for whom previous options to increase the duration of response were largely limited to stem cell transplant in eligible patients.[1]

Ibrutinib (Imbruvica), a first-in-class oral covalent inhibitor of Bruton tyrosine kinase (BTK), blocks an essential component of the B-cell receptor cascade, inhibiting survival signaling between CLL cells and the tumor microenvironment. The agent was first approved by the FDA in 2014 for the treatment of patients with relapsed/refractory CLL, supported by outcomes of phase II and III studies demonstrating high response rates (71%),[10] higher objective response rates (ORR; 43% vs 4%), and significantly improved PFS compared with treatment with ofatumumab (Arzerra; not reached vs 8.1 months at median follow-up of 9.4 months), and OS benefit [1-year OS, 90% vs 81%; HR for death, 0.43; $P = .005$].[3] Importantly, the phase III RESONATE study showed that efficacy differences were retained in patients carrying del(17p) and in those resistant to purine analogues.[2]

The CLL indication of ibrutinib has recently been expanded to include frontline therapy, in part based on outcomes from the phase III RESONATE-2 study comparing ibrutinib with chlorambucil in 260 elderly treatment-naïve patients with CLL.[11] Ibrutinib induced a significantly higher ORR (86% vs 35%), longer median PFS (not reached vs 18.9 months), and a longer OS (98% vs 85% at 2 years).[11] This study specifically excluded patients with known del(17p) CLL; however, a recently published single-arm phase II study also demonstrated activity in previously untreated patients and in those with relapsed/refractory CLL with del(17p) or *TP53*-mutant disease, with an objective response rate of 97% among untreated patients and 80% among relapsed/refractory patients after a median follow-up of 2 years.[12]

Ibrutinib is considered the preferred first-line therapy for patients with del(17p)/*TP53*-mutant CLL, and is a category 1 recommendation for patients with CLL without del(17p)/*TP53* mutation who are frail, or are ≥65 years of age, or younger with significant comorbidities, according to the National Comprehensive Cancer Network (NCCN) guidelines on CLL.[1]

With the availability of targeted therapies, which also include idelalisib (Zydelig) and venetoclax (Venclexta) for the treatment of patients with relapsed/refractory CLL, the question how to optimally sequence agents has become highly pertinent. Findings of a retrospective study evaluating outcomes with targeted therapies suggest better outcomes with ibrutinib as the first kinase inhibitor compared with idelalisib, superior outcomes with an alternate kinase inhibitor or venetoclax than with chemoimmunotherapy combinations after kinase inhibitor failure, and possibly better outcomes with venetoclax after ibrutinib failure.[13] Consequently, the authors emphasized the need for clinical trials testing sequencing strategies to optimize treatment algorithms.

Del(11q) and Response to Ibrutinib

The del(11q22.3) cytogenetic abnormality, which is detected in up to 20% of patients with CLL at diagnosis and at a higher frequency in relapsed/refractory CLL, has traditionally been considered an unfavorable cytogenetic alteration associated with extensive lymphadenopathy, disease progression, and shorter median survival (79 months).[7]

The presence of del(11q) predicts poor response to chlorambucil-, fludarabine-, or FCR (fludarabine, chlorambucil, rituximab [Rituxan])-based regimens, with shorter duration of remission and OS compared with other cytogenetic groups.[7,14] Previous findings have shown that adding an alkylating agent such as cyclophosphamide to

fludarabine-based chemoimmunotherapy can improve outcomes.[1]

A recent study has now investigated whether the presence or absence of del(11q) was associated with clinical outcomes following treatment with the BTK inhibitor ibrutinib in phase III studies. Lead investigator Thomas J. Kipps, MD, PhD, from the University of California Moores Cancer Center, and colleagues presented these findings at the 2016 American Society of Hematology Annual Meeting.[3]

The study was based on patient data from 3 phase III studies that had demonstrated superiority of single-agent ibrutinib to treatment with ofatumumab in relapsed/refractory CLL (RESONATE),[3] to chlorambucil in treatment-naïve CLL (RESONATE-2),[11] and of ibrutinib in combination with bendamustine and rituximab (BR) to treatment with BR in relapsed CLL (HELIOS).[15]

Analyses of pooled data of 1210 patients with available data on del(11q) revealed that the presence of del(11q) was not an adverse prognostic factor for PFS in patients who received ibrutinib-based treatment (n = 609 patients; 179 with del(11q), 430 without) but was in those who received the respective comparator treatment (n = 601; 149 with del(11q), 452 without).[3]

The presence versus absence of del(11q) was associated with prolonged PFS (24-month, 82% vs 75%) and OS (30-month, 93% vs 86%) in ibrutinib-treated patients, but shorter PFS (9% vs 19%) in comparator-treated patients. Furthermore, treatment with ibrutinib was associated with superior clinical outcomes versus comparators regardless of del(11q) status.[3]

IGHV Mutational Status

Mutational status of the immunoglobulin heavy chain variable region gene (*IGHV*) in the CLL clone has been increasingly considered as a parameter when determining treatment choice, whereas del(11q) is no longer considered a marker with relevance for treatment selection in current guidelines by NCCN.[1] CLL cells expressing unmutated *IGHV* originate from B cells that have not undergone somatic hypermutation, which has been associated with a more aggressive disease course and poor outcomes with standard chemotherapy-based regimens.[16]

Long-term follow-up from the CALGB 9712 study of first-line therapy with concurrent versus sequential fludarabine and rituximab found unmutated *IGHV* a significant independent predictor for shorter PFS and OS, and del(17p) or del(11q) independent predictors for shorter survival.[5]

Recently updated results from the phase III CLL8 study found *TP53* mutation, del(17p) and unmutated *IGHV* the strongest predictors of shorter PFS and OS.[5] Study findings further confirmed survival benefits of FCR versus FC in physically fit previously untreated patients with CLL <65 years (5-year OS, 80.9% vs 69.2%; $P = .002$).[1] In patients with mutated *IGHV,* FCR was associated with improved survival in all cytogenetic groups except del(17p) compared with FC (median PFS not reached vs 41.9 months, $P < .001$; 5-year OS, 86.3% vs 79.8%).

In contrast, *IGHV* mutational status does not predict response to ibrutinib, according to an integrated analysis of data from the phase III RESONATE, RESONATE-2, and HELIOS studies presented at the 2017 American Association for Cancer Research Annual Meeting.[17] According to Kipps et al, "*IGHV*-unmutated CLL was an adverse predictor of outcome for comparator-treated, but not for ibrutinib-treated patients."[17]

The pooled analysis was comprised of data from 985 CLL/SLL participants in the 3 studies, including 494 patients who received ibrutinib (351 with *IGHV*-unmutated disease and 143 with mutated *IGHV*) and 491 patients who received the respective control treatment ofatumumab, chlorambucil, and/or BR (366 with *IGHV*-unmutated CLL and 125 with *IGHV* mutations). At a median follow-up of 21.4 months for patients receiving ibrutinib and 20.6 months for those on control treatment, PFS and OS were similar among ibrutinib-treated patients ($P = .93$ for ibrutinib vs control), regardless of *IGHV* mutation status (2-year OS, 88% vs 89% for *IGHV*-unmutated and mutated disease, respectively; $P = .86$).

In patients receiving control treatments, *IGHV*-unmutated disease was associated with shorter survival than *IGHV*-mutation–harboring disease, also in multivariate analyses that adjusted for age, sex, baseline ECOG performance status, del(11q) and del(17p) status, prior lines of therapy, and other prognostic variables (2-year OS, 78% vs 87%; adjusted $P = .01$).[17]

Table. Disease Characteristics and Prognostic Outcomes

Characteristics	Outcomes
TP53 mutations	Resistance to fludarabine-based chemotherapy, short PFS, poor OS
Del(17p)	Poor response to chemotherapy, short PFS, poor OS
Del(11q)	Extensive lymphadenopathy, disease progression, and shorter median survival; poor response to fludarabine-based chemotherapy
IGHV unmutated	Significantly decreased PFS and OS vs mutated *IGHV* with standard chemotherapy-based regimens; poor prognosis

OS indicates overall survival; PFS, progression-free survival.

Evolving Basis For Treatment Decisions In CLL

Treatment decisions in CLL are generally based on the distinct molecular profile of their disease and age as well as the fitness of the patient.[1,6]

However, current NCCN guideline recommendations for the group of patients with CLL who have del(17p)/*TP53* mutations are universal and not stratified by patient age or condition.[1] Recommended frontline therapy options in order of preference are ibrutinib, dose-dense high-dose methylprednisolone (HDMP) plus rituximab, obinutuzumab (Gazyva) plus chlorambucil (category 3), and the anti-CD52 antibody alemtuzumab (Lemtrada) alone or in combination with rituximab.

Ibrutinib also leads the list of preferred regimens for relapsed/refractory disease, followed by venetoclax with or without rituximab, idelalisib plus rituximab, single-agent idelalisib, and other rituximab and ofatumumab-based therapies. Suggested post–first- and second-line maintenance therapies include lenalidomide (Revlimid) in high-risk patients, and lenalidomide or ofatumumab, respectively.[1]

In patients with CLL without del(17p)/*TP53* mutations, the most important features directing treatment choices are advanced age of >65 years, the presence of medical comorbidities, and the objectives of treatment.[6]

Preferred first-line therapies for frail patients are obinutuzumab plus chlorambucil, followed by ibrutinib (both category 1 recommendations), ofatumumab plus chlorambucil, rituximab plus chlorambucil, single-agent obinutuzumab, rituximab, and chlorambucil. The same treatment options are available for patients ≥65 years of age and younger patients with significant comorbidities, with the inclusion of bendamustine with rituximab following rituximab and chlorambucil in preference.[1]

For patients younger than 65 years without comorbidities, chemoimmunotherapy remains the standard frontline treatment, with FCR as category 1, FR, and PCR, and bendamustine plus rituximab, as well as ibrutinib (category 2A).[1]

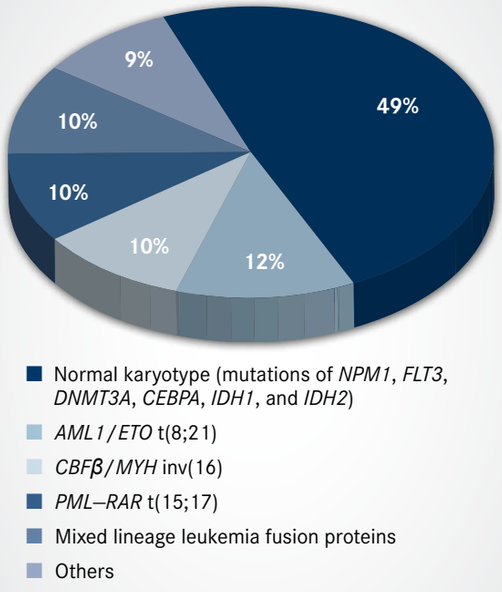
For the treatment of relapsed/refractory CLL without del(17p)/*TP53* mutations, ibrutinib is the preferred regimen in patients of all performance groups, followed by idelalisib plus rituximab, venetoclax with or without rituximab, chemoimmunotherapy regimens that are again guided by patient performance, and various CD20 monoclonal antibody-based regimens. Lenalidomide or ofatumumab can be considered for post–second-line maintenance therapy.[1] With accumulation of data from clinical trials, these recommendations are likely going to evolve in the near future. ■

For full references, see article on *OncLive*.com

Attacking *FLT3* Mutations Yields First Targeted Therapy in AML

By Anita T. Shaffer and Jason M. Broderick

Figure. Drivers for epigenetic alterations in acute myeloid leukemia



Source: Mehdipour P, Santoro F, Minucci S. Epigenetic alterations in acute myeloid leukemias. *FEBS Journal*. 2015;282:1786–1800.

Although *FLT3* mutations are well established as a prognostic marker in patients with acute myeloid leukemia (AML), efforts to target the aberration therapeutically were underway for more than 15 years before yielding success. That happened in April, when the FDA approved midostaurin (Rydapt), the first new therapy for AML in about 40 years.

Midostaurin is approved for the treatment of adult patients with newly diagnosed *FLT3*-positive AML in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation. The drug has also been approved for patients with advanced systemic mastocytosis (SM), including aggressive systemic mastocytosis (ASM), SM with associated hematological neoplasm (SM-AHN), and mast cell leukemia.

AML is a genetically complex disease that researchers are still seeking to elucidate. Researchers believe that AML is driven by somatic alterations in a "2 hit" process: a proliferative mutation in a class I gene such as *FLT3* and an aberration in a class II gene that prevents cells from maturing.[1]

FLT3 mutations are among the epigenetic drivers of AML in normal karyotypes (**Figure**).[2] Investigators have found somatic mutations in *FLT3* genes in several spots, notably in 27% to 34% of samples in the internal tandem duplication (ITD) domain in various studies.[1] The presence of an *FLT3*-ITD mutation confers a poor risk for patients with AML, with worse outcomes in disease-free and overall survival.[3]

In recently updated joint guidelines, the College of American Pathologists and the American Society of Hematology strongly recommend testing all pediatric and adult patients with suspected or confirmed AML for *FLT3*-ITD mutations.[3] Midostaurin was approved along with a companion diagnostic, the LeukoStrat CDx FLT3 Mutation Assay, to test for *FLT3* mutations in DNA extracted from mononuclear cells obtained from peripheral blood or bone marrow aspirates.

Although it was approved for patients with *FLT3* mutations, midostaurin is a small molecule that inhibits multiple receptor tyrosine kinases; in vitro biochemical and cellular assays also have suggested that it can inhibit wild-type *FLT3* activity.[4] In reference to aberrant *FLT3* activity, the drug inhibits FLT3 receptor signaling and cell proliferation, and induces apoptosis in leukemic cells expressing ITD and tyrosine kinase domain mutant FLT3 receptors.[4]

The midostaurin approval has generated much excitement in the field. Several other FLT3 inhibitors have entered the later-stages of clinical development (**Table**) and the prospects for more targeted agents are building.

"Use of next-generation sequencing technology has generated a plethora of novel insights into the genetics of AML, providing important information about dysregulated signaling involved in leukemic transformation and leading to new therapeutic targets," said Elias Jabbour, MD, an associate professor at The University of Texas MD Anderson Cancer Center in Houston, during a recent *OncLive*® Peer Exchange® program.[5] "After a dearth of new therapies available for acute myeloid leukemia over the last few decades, we are transitioning into a new era with several promising strategies in late-stage development."

Pivotal Midostaurin Findings

The midostaurin approval is based on the phase III RATIFY trial in AML and 2 single-arm, open-label studies of patients with SM. In RATIFY, the addition of midostaurin to standard chemotherapy reduced the risk of death by 23% compared with chemotherapy alone in patients with *FLT3*-mutant AML. After censoring for patients who received stem cell transplants, the overall survival (OS) benefit with midostaurin remained steady at 25%.

In the phase II trial considered for the SM approvals, among patients receiving 6 cycles of midostaurin, the rates of confirmed complete remission (CR) plus incomplete remission (ICR) by modified Valent criteria were 38% for ASM and 16% for SM-AHN. One patient with mast cell leukemia had a CR.

In the phase III RATIFY trial, also known as CALGB 10603, 717 patients with newly diagnosed *FLT3*-mutant AML were randomized to standard induction and consolidation chemotherapy plus midostaurin (n = 360) or placebo (n = 357). Hydroxyurea was allowed for up to 5 days prior to beginning therapy, while *FLT3* test results were obtained.

During induction therapy, daunorubicin was given at 60 mg/m^2 on days 1 to 3 with cytarabine at 200 mg/m^2 on days 1 to 7. Oral midostaurin was administered at 50 mg twice daily on days 8 to 22. If patients achieved a complete remission, consolidation therapy was given with cytarabine at 3 g/m^2 for 3 hours every 12 hours on days 1, 3, and 5 plus either placebo or midostaurin. After 4 cycles of consolidation, maintenance therapy with either midostaurin or placebo was administered for up to 1 year.

The 2 treatment arms were well balanced for age (median, 48 years), race, *FLT3* subtype, and baseline complete blood counts. There were more males in the midostaurin arm versus placebo (48.2% vs 40.6%). The primary endpoint of the study was OS, with secondary outcome measures such as event-free survival (EFS) and safety.

In uncensored data, median OS was 74.7 months with midostaurin versus 25.6 months with chemotherapy alone (HR, 0.77; 95% CI, 0.63-0.95; P = .016). The 5-year OS rate for patients in the midostaurin arm was 50.9% versus 43.9% with placebo. Median EFS with midostaurin was 8.2 months versus 3.0 months with placebo (HR, 0.78; 95% CI, 0.66-0.93; P = .004). The 5-year EFS with midostaurin was 27.5% versus 19.3% with placebo.

Median OS seen in the midostaurin arm was well beyond investigator expectations of 20.9 months.

A possible explanation for this could be the rates of stem cell transplantation or incomplete data. The confidence intervals for OS were not fully attained for the midostaurin arm (95% CI, 31.7-not attained).

Overall, 57% of patients received an allogeneic stem cell transplant at some time during the trial, more commonly in the midostaurin arm versus placebo (58% vs 54%). Median time to transplant was 5.0 months with midostaurin and 4.5 months with placebo. Twenty-five percent of transplants occurred during the first complete remission. Overall, 59% of patients in the midostaurin arm and 54% in the placebo group experienced a complete remission (P = .18).

Median OS data were not obtained in the censored population. Overall, the 4-year censored OS rate with midostaurin was 63.8% versus 55.7% for placebo (HR, 0.75; P = .04). In those censored for transplant, median EFS with midostaurin was 8.2 months versus 3.0 months with placebo (HR, 0.84; P = .025).

Grade ≥3 AEs were similar between the midostaurin and placebo arms. Overall, 37 grade 5 AEs occurred in the study, which were similar between the 2 arms, at 5.3% with midostaurin versus 5.0% with placebo. A statistically significant difference was not observed for treatment-related grade 5 AEs (P = .82). ■

Table. Selected Later-Stage Clinical Trials of FLT3 Inhibitors in AML

Agent (Industry Developer)	Phase/Clinical Setting (www.ClinicalTrials.gov identifier)
Gilteritinib (ASP2215) (Astellas Pharma)	Phase III • Maintenance therapy post induction/consolidation in *FLT3*+ AML after first remission (NCT02927262) • Relapsed/refractory *FLT3*+ AML (NCT02421939) • Maintenance therapy post-allogeneic transplant in *FLT3*-ITD+ AML (NCT02997202) Phase II/III • Plus azacitidine in newly diagnosed *FLT3*+ AML not eligible for intensive induction chemotherapy (NCT02752035)
Midostaurin (Rydapt) (Novartis)	Phase II • Plus decitabine in newly diagnosed older patients with *FLT3*+ AML (NCT02634827)
Pacritinib (Cti Biopharma)	Phase II • Plus decitabine or cytarabine in older patients with AML (NCT02532010)[a]
Quizartinib (Daiichi Sankyo)	Phase III • Refractory/relapsed *FLT3*-ITD+ AML (NCT02039726) • Plus standard chemotherapy and as maintenance therapy in newly diagnosed *FLT3*-ITD+ AML (NCT02668653)
E6201 (Strategia Therapeutics)	Phase I/II • *FLT3*+ advanced hematologic malignancies (NCT02418000)

[a]Study is ongoing but not recruiting participants.

AML indicates acute myeloid leukemia; FLT, FMS-like tyrosine kinase 3; ITD, internal tandem duplication.

For a list of references, see article on *OncLive.com*

Lead Researcher Discusses Midostaurin Approval

By Shannon Connelly

The recent FDA approval of midostaurin (Rydapt) has generated much excitement in the field of acute myeloid leukemia (AML), where the orally administered drug is the first targeted therapy for patients with the cancer type. Midostaurin is approved for adult patients with newly diagnosed *FLT3*-positive AML in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation.


Richard M. Stone, MD

Richard M. Stone, MD, the lead author of the RATIFY trial that led to the drug's approval, discussed the implications of the decision in an interview with *OncologyLive*®. Stone is the director of the Adult Leukemia Program at the Dana-Farber Cancer Institute and a professor of medicine at Harvard Medical School, both in Boston.

Q: What impact do you see midostaurin making in the AML community?

AML is a devastating disease that affects about 15,000 people in the United States annually. Unfortunately, about 40% to 50% of the people who get this disease die of it. It is particularly difficult for older adults who get this disease, and the median age is about 68 to 70. Even in young people, a lot of patients die of it.

We have not really done much to change or improve the care of people between the ages of 18 and 60 who have AML, and we have done even less, frankly, for those with AML who are over the age of 60 over the last few years. There have not been any drug approvals for AML in several decades, so any new drug in AML that is going to improve the cure rate is going to be heralded with some degree of excitement.

With midostaurin, when added to chemotherapy, one has a better outcome in the long run, and in the short run, for that matter, than if one added placebo to chemotherapy. That is why we are excited about this.

Q: Which patients will benefit from midostaurin?

People between the ages of 18 and 60 who had a *FLT3* mutation in the leukemic cells at the time of diagnosis. Those are the ones who would get chemotherapy plus midostaurin—that represents about 30% or 35% of all patients with AML.

It is important to note that more than half of the patients on the trial were transplanted at some point. About a quarter of the patients were transplanted during the first remission, and about a quarter of the patients were transplanted later after they had relapsed or had not gone into remission. I think the positive total outcome that we saw was due, at least in part, to the fairly high transplant rate. As it turns out, compared with when the trial started, we learned that it was a good idea to transplant people who had this type of mutation.

For a patient with AML and a *FLT3* mutation who was between 18 and 60, I would give them midostaurin. If they were a transplant candidate, I would give them 1 cycle of consolidation, or whenever the transplant was ready; I would then transplant them. That is going to lead to a pretty good outcome. If you look at the curve of patients who had midostaurin and were transplanted in first remission, the 5-year survival rate was about 60%.

Q: Do you think this agent could open the door for other targeted agents in AML?

Absolutely. There is a lot of research with targeted therapies, which is either ongoing or soon to start, specifically of FLT3 inhibitors that are being tested in different situations. There's also IDH1 and IDH2 inhibitors that are being tested in patients with *IDH1* and *IDH2* mutations.

The good news is that AML might be dealt with in a better way than we have done in the past by using targeted therapies. The challenge is that you're subdividing a relatively rare disease into even more rare subtypes, each of which might require a different targeted therapy. ■

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PROGRAM TITLE
"The Divide and Conquer of Advanced Colorectal Cancer"

Moderator
John L. Marshall, MD
Professor and Chief, Division of Hematology/Oncology
Georgetown University Hospital
Director, Ruesch Center for the Cure of Gastrointestinal Cancers
Washington, DC

Panelists
Johanna C. Bendell, MD
Director, GI Cancer Research Program
Associate Director, Drug Development Program
Sarah Cannon Research Institute
Nashville, Tennessee

Tanios S. Bekaii-Saab, MD
Co-Leader, Gastrointestinal Cancer Program
Mayo Clinic Cancer Center
Phoenix, Arizona

Alan P. Venook, MD
Shorenstein Associate Director for Program Development
Helen Diller Family Comprehensive Cancer Center
Professor, Division of Hematology/Oncology
University California-San Francisco
San Francisco, California

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When Chemotherapy Fails: An Unmet Need in Metastatic CRC

By Christin Melton, ELS

As precision medicine moves to the forefront in disease management, targeted agents have supplanted cytotoxics as first-line treatment for many types of cancer. That is not the case with colorectal cancer (CRC), however, for which standard care starts with systemic chemotherapy.

Patients whose CRC progresses after multiple lines of chemotherapy have few alternatives. As with most cancers, CRC progression corresponds with a sharp decline in the 5-year survival rate. For stage IIIA CRC, which remains localized, the relative 5-year survival rate is 89%.[1] Once CRC has metastasized to distant sites, the 5-year survival rate drops to approximately 11%.[1] A recent *OncLive*® Peer Exchange® program featured a panel of leaders in CRC research discussing how they manage patients with metastatic CRC after chemotherapy has failed. The panelists also shared their optimism about immunotherapy agents, such as checkpoint inhibitors, which are emerging as a viable alternative for the subset of patients with CRC who have microsatellite instability (MSI).

Regorafenib and TAS-102

Patients with CRC typically endure many lines of therapy, including fluoropyrimidine-, oxaliplatin, and irinotecan-based chemotherapy; VEGF inhibitors; and, if genetic testing shows the patient does not have a *KRAS* mutation, an EGFR inhibitor.


Tanios S. Bekaii-Saab, MD

According to panel member **Tanios S. Bekaii-Saab, MD,** patients with CRC who have exhausted all these options are left with 2 choices: regorafenib (Stivarga) or TAS-102 (Lonsurf). "TAS-102 is a more traditional cytotoxic agent, which belongs to that super family of fluoropyrimidines," he said. Bekaii-Saab noted that despite belonging to the same family as 5-fluorouracil (5-FU), TAS-102 is very different and has shown efficacy in patients after failure of 5-FU. Unlike TAS-102, regorafenib is a tyrosine kinase inhibitor, he said. Its targets include VEGFR1, VEGFR2, VEGFR3, TIE2, KIT, RET, RAF1, BRAF, PDGFR, and FGFR.[2] Regorafenib inhibits angiogenesis and induces apoptosis in cancer cells.

"Both have been looked at in the refractory setting versus placebo, and they have both shown benefits," Bekaii-Saab said. Regorafenib and TAS-102 are oral drugs that can be given sequentially but not in combination. The drugs have never been compared prospectively in a head-to-head clinical trial, and colon cancer guidelines from the National Comprehensive Cancer Network (NCCN) say data are insufficient to determine which one to use first.[3] Bekaii-Saab said although a few patients benefit greatly from regorafenib or TAS-102, most derive little to no benefit.

John L. Marshall, MD, who moderated the panel, agreed. He said neither regorafenib nor TAS-102 produces much of a response in refractory patients. In the phase III CORRECT trial, which randomly assigned patients with metastatic CRC to regorafenib or placebo, only 1% of regorafenib users achieved an objective response and none had a complete response.[2] The pivotal phase III trial that compared TAS-102 with placebo reported a similar response rate of 1.6% for patients randomly assigned to TAS-102, with no complete responses in the treatment arm.[4] Patients in both trials were heavily pretreated, and Marshall suggested such low response rates are common with second-line therapies in metastatic CRC.

"When I talk to patients about both of these therapies, [I tell them] we're hopefully going to see it stop your disease from growing," said **Johanna C. Bendell, MD.** She said she tries to convince her patients that stable disease is not hurting them.

She also tells them clinical trials have found both regorafenib and TAS-102 prolong overall survival (OS). In CORRECT, median OS was 6.4 months in the regorafenib arm versus 5.0 months in the placebo arm (HR, 0.77; 95% CI, 0.64-0.94; $P = .0052$).[2] In the TAS-102 trial, OS was 5.7 months in the TAS-102 arm versus 4.0 months in the placebo arm (HR, 0.66; 95% CI, 0.56-0.78; $P < .001$).[4] Bendell said she reminds patients that the data reflect averages, and their survival could be longer or shorter.

Dosing of both oral drugs can be complicated. TAS-102 is taken twice daily for 5 days, skipped for 2 days, taken for 5 more days, skipped for 2 days, and then discontinued for 2 weeks. Bendell advises her patients to take the pills Monday through Friday for the first 2 weeks and then to take 2 weeks off.

TAS-102 may cause severe myelosuppression. Neutropenia, which is the drug's most common adverse effect, occurs in approximately two-thirds of patients.[4] Although neutropenia can be life threatening, Bendell said its severity appears to correspond to a greater probability of response. Instead of reducing the dose of TAS-102 for patients with neutropenia, Bendell prefers to extend the 4-week treatment cycle to 5 weeks.

The recommended daily dose for regorafenib is 160 mg for 21 days followed by 7 days off.[5] **Alan P. Venook, MD,** said he "errs on the side

of undertreating patients with regorafenib" to reduce the risk of hand-foot skin reactions, which are the most common safety concern. "I tend to start lower and then build my way up…you can go up much easier than you can go down," he said. Venook said he has patients check in weekly in the initial weeks after starting regorafenib and escalates the dose if they have no adverse reactions. He will increase the dose to 160 mg by the third week "if everything is squeaky clean."


Alan P. Venook, MD

Bekaii-Saab said he starts patients at 160 mg. "You have to have a discussion with the patient; it's all about quality of life…if it seems to be affecting their daily living, I definitely would go down," he said. Bekaii-Saab said his institution is involved in a randomized trial that is comparing a regimen of escalating regorafenib to 160 mg as tolerated versus starting at the 160-mg dose. "I'm hoping we'll have the results of this study presented somewhere in the fall of this year," he said.

The panel agreed on the importance of seeing patients weekly in those first weeks after starting regorafenib, as Venook mentioned, to perform complete blood cell counts and liver function tests. Marshall added that the weekly visits also help with compliance.

The group talked about strategies for patients whose disease progresses while taking TAS-102 or regorafenib. They concurred that it was rare to be able to give patients the drugs in sequence. They also discussed the possibility of rechallenging patients with chemotherapy but did not reach a consensus. The experts unanimously agreed on the need to encourage patients to participate in clinical trials.

Checkpoint Inhibitors

On May 23, the FDA granted an accelerated approval to pembrolizumab (Keytruda) for the treatment of adult and pediatric patients with unresectable or metastatic, MSI-high or deficient mismatch repair (dMMR) solid tumors that have progressed after prior treatment and who have no satisfactory alternative treatment options, as well as for patients with CRC that is MSI-high or dMMR following progression on a fluoropyrimidine, oxaliplatin, and irinotecan regimen. The decision marked the first FDA approval of an immunotherapy for patients with CRC.

The approval was based on data from 149 patients with MSI-H or dMMR cancers enrolled across 5 single-arm clinical trials. Ninety patients had CRC and the remaining 59 patients had 1 of 14 other tumor types. The objective response rate (ORR) with pembrolizumab was 39.6% (95% CI, 31.7-47.9), including 11 (7.4%) complete responses and 48 (32.2%) partial responses. The ORR was 36% in patients with CRC and 46% in patients with other tumor types.[6]

The panelists discussed the potential for PD-1 checkpoint blockade immunotherapy during the program, which took place before the FDA's decision. NCCN guidelines recommend pembrolizumab or nivolumab (Opdivo) as options for patients with MSI-high metastatic disease based on promising clinical trial data.[3] Venook said NCCN guidelines also recommend testing all patients with CRC for MSI. Bendell mentioned that nivolumab and pembrolizumab are listed in the compendia for the 5% of CRC patients she said have MSI; the drugs were included before the FDA's decision on pembrolizumab.

Marshall questioned whether it made sense to administer checkpoint inhibitors in the frontline. "We don't know the answer to that yet," Bendell said. "If you have a patient who's asymptomatic with a relatively low burden of disease in the first line, maybe that's the person whom you would give a checkpoint inhibitor to right away, because you have a little time to see if it will work. But if the person is symptomatic, maybe you should do chemotherapy first," she said, noting that chemotherapy can be rapidly effective.


John L. Marshall, MD

Bekaii-Saab said he would use a PD-1 inhibitor in the frontline. "I've had more than just anecdotal experiences with patients who were very symptomatic, with a high tumor burden, who had significant responses to PD-1 inhibitors," he said. He contended that patients can always restart chemotherapy. "I don't think there's a right or wrong answer…but we need to study this further," Bekaii-Saab said.

Bendell said she and others are evaluating what can be done for the 95% of patients with CRC who do not have MSI-high disease. Researchers are trying to find drugs to encourage the immune system of patients without MSI to mount a response to checkpoint inhibitors.


Johanna C. Bendell, MD

The panel agreed that progress will depend on identifying more targetable biomarkers. Currently, targeted therapies approved for CRC operate on exclusion—patients undergo genetic testing and are excluded from using certain drugs if they have certain mutations. Studies are needed to discover genetic targets that allow patients to receive agents highly effective against those targets.

Bendell said the "future is bright" but that clinicians need to profile their patients to aid the progress being made. "Let's learn as much about them as we can, both for their current treatment and for treatments to come," she said.

Marshall expressed optimism that finding other novel targets would lead to breakthroughs and bring the field closer "to a precision medicine model." ■

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On the Move

Four Neuro Experts to Lead New Glioblastoma Research Center

NewYork-Presbyterian in New York City has established the William Rhodes and Louise Tilzer-Rhodes Center for Glioblastoma, to be led by 4 experts in the field of neuro-oncology from Columbia University Medical Center and Weill Cornell Medicine: **Jeffrey N. Bruce, MD,** co-director of the Brain Tumor Center; **Andrew B. Lassman, MD,** chief of the Division of Neuro-oncology in the Department of Neurology and co-director of the Brain Tumor Center; **Howard A. Fine, MD,** founding director of the Brain Tumor Center and associate director for Translational Research at the Sandra and Edward Meyer Cancer Center at Weill Cornell Medicine; and **Rohan Ramakrishna, MD,** a surgical neuro-oncologist in the Brain Tumor Center.


Jeffrey N. Bruce, MD


Andrew B. Lassman, MD


Howard A. Fine, MD


Rohan Ramakrishna, MD

The new center for glioblastoma was created in honor of Louise Tilzer-Rhodes, who died of glioblastoma in June 2016. The center aims to advance care for patients with glioblastoma and other deadly brain cancers by providing multidisciplinary, research-driven care, with a focus on genomics and precision medicine; emphasizing translational research to rapidly bring promising new therapies from the bench to the bedside; and educating the next generation of clinicians and scientists.

Department leaders in neurology and neurosurgery will also play a guiding role at the center: **Richard P. Mayeux, MD, MSc,** neurologist-in-chief at NewYork-Presbyterian/Columbia University Medical Center and co-director of the Taub Institute for Research on Alzheimer's Disease and the Aging Brain; **Robert A. Solomon, MD, FACS,** neurosurgeon-in-chief at NewYork-Presbyterian/Columbia University Medical Center and the Byron Stookey Professor of Neurological Surger; **Matthew E. Fink, MD,** neurologist-in-chief at NewYork-Presbyterian/Weill Cornell Medical Center, and the Louis and Gertrude Feil Professor in Clinical Neurology and chairman of the Department of Neurology at Weill Cornell Medicine; and **Philip E. Stieg, PhD, MD,** neurosurgeon-in-chief at NewYork-Presbyterian/Weill Cornell Medical Center and professor and chair of the Department of Neurological Surgery at Weill Cornell Medicine.

Marshall Appointed Chief Medical Officer of Caris

John L. Marshall, MD, of Georgetown Lombardi Comprehensive Cancer Center and MedStar Georgetown University Hospital in Washington, DC, has been appointed chief medical officer of Caris Life Sciences.


John L. Marshall, MD

Marshall has more than 20 years of experience as a medical oncologist and clinical trial investigator, most recently serving as associate director for clinical care at Georgetown Lombardi and the chief of the Division of Hematology-Oncology at MedStar Georgetown University Hospital. Marshall is also the founding director of Georgetown Lombardi's Otto J. Ruesch Center for the Cure of Gastrointestinal Cancer.

In his new role, Marshall will direct the Caris Life Science's oncology research efforts through the Caris Research Institute and guide clinical strategies for innovative precision medicine tools and tumor profiling services. As part of the collaboration, network members are actively developing consensus guidelines for tumor profiling and precision medicine, while also participating in research and outcome-tracking initiatives for patients who have received tumor profiling. In addition, Marshall will continue to serve as chairman of the Caris Centers of Excellence for Precision Medicine Network on behalf of the Georgetown Lombardi Comprehensive Cancer Center.

Chesney Tapped as Director of James Graham Cancer Center

Jason Chesney, MD, PhD, has been appointed director of the University of Louisville's James Graham Brown Cancer Center. Chesney joined the university in 2003 as an assistant professor, and became associate professor with tenure in 2008 and a full professor in 2014. He holds joint appointments with the departments of biochemistry and molecular biology, and pharmacology and toxicology.


Jason Chesney, MD, PhD

In addition to his new role, Chesney will serve as an associate vice president for health affairs and will continue to hold the Brinkley Endowed Chair in Lung Cancer Research. He succeeds Donald Miller, MD, PhD, who has served as director of the center since 1999 and is returning to the faculty.

In 2014, Chesney's clinical research team was one of the top 2 clinical groups to find that the combination of ipilimumab (Yervoy) and nivolumab (Opdivo) is an effective immunotherapy regimen for patients with cancer. His research group has also discovered the roles of several metabolic enzymes in the development and progression of lung cancer, including 6-phosphofructo-2-kinase 3, choline kinase, and cytochrome c oxidase. Chesney also has been at the forefront of understanding the metabolic effects of cancer-driving genes including *RAS*, the estrogen receptor, and the epidermal growth factor receptor.

Shalabi Joins Cancer Research Institute

Aiman Shalabi, PharmD, MBA, BCOP, has been appointed chief medical officer of the Cancer Research Institute (CRI), a nonprofit organization with the goal of developing lifesaving immunotherapies for all forms of cancer.


Aiman Shalabi, PharmaD, MBA, BCOP

Shalabi has more than 17 years of experience developing transformative medicines, most recently as vice president and head of Immuno-Oncology Global Medical Affairs at AstraZeneca, where he served in leadership roles to develop an immunotherapy program from preclinical stage to FDA submission. He also has managed a portfolio of oncology agents at the National Cancer Institute's Cancer Therapy Evaluation Program and the compassionate use program that provides patients with access to new anticancer medicines prior to regulatory approval.

In his new role, Shalabi will provide strategic direction and integrated oversight for CRI's cancer immunotherapy clinical trial program, the CRI Ann-Maria Kellen Clinical Accelerator. He will also be working with a comprehensive set of nonprofit resources that includes a global network of more than 60 leading scientists, clinical trials management capabilities, venture philanthropy funding, and operational, reagent access, and co-funding partnerships with more than 20 nonprofit and industry organizations. ■