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ONCOLOGY recently spoke to Andre Goy, MD, MS about the advances that will be discussed at the 24th Annual International Congress on Hematologic Malignancies: Focus on Leukemias, Lymphomas, and Myeloma.

Q: There’s a heavy focus on chimeric antigen receptor (CAR) T-cell therapies on the agenda for the conference. Why is this therapy important to put center stage at this time?

Dr. Goy: Over the last few years, we had dedicated a pre-symposium conference that was focused on CAR T-cells and cell therapy. CAR T-cells are a game changing treatment in a population of patients that really has an unmet need. We know patients with refractory/relapsed Chronic Lymphocytic Leukemia (CLL) do very poorly even with allogeneic transplant. Patients with refractory/relapsed large cell lymphoma and aggressive lymphomas can sometimes survive with long-term disease control from an allogenic transplant. However, they may have cardiac failure and they can’t be put into remission.

We have seen some patients who had an excess of 10 prior therapies who have had very durable responses to CAR T-cells, and potentially some of these patients may be cured. What we found in aggressive lymphoma, in both clinical trials and in real-world settings, is that patients who received approved CAR T-cell therapy with axi-cel have superimposable results. We see that, long-term, the survival rate without progression is close to 40%. That’s quite a remarkable result. There are still challenges, but that presents us with an opportunity to learn more.

A number of different platforms of CAR T and different drugs have been approved now. There are over 800 cell therapies in the pipeline, more than half of which are CAR T-cells. This provides a real opportunity. There will be other forms of cell therapy, including dual CAR T, newer constructions of CAR T, third generations of CAR T-cells. Potentially, NK cells will also be important in that setting. This is not only a game changer, but something that offers a new platform for patients who have no options with standard therapy.
Key Could you discuss the long-term safety and efficacy of axi-cel from the ZUMA-1 trial?

Dr. Goy: Research confirms the early impression that when patients have achieved a complete response (CR) and have not relapsed within the first 6 months, typically these patients have somewhat of a plateau with, only very rarely with late relapses.[1] It brings up the question of whether we might discover factors that could predict response. We’ve seen that about 25% to 30% of patients who have a partial response captured by standard/functional imaging can convert into a CR over time, which is very important. The other question that arises is why this happens. Do they have persistent CAR T more than other patients? This is debated in the CAR T community, depending on the construct itself but also depending on the aforementioned potential combinations.

I am not convinced that the persistence of the CAR T is really essential. It’s obviously a good thing, but we have about 1/3 of patients who did not have detectable CAR T who still have been in a durable response. That’s very promising. What is also interesting about the plateau is that the responses and the duration of response was seen regardless of the number of prior therapies, refractory, bulky, and so on. This is consistent with the consensus that this is a completely novel and different form of therapy that overcomes chemoresistance in those patients.

Q: Are you working with axi-cel exclusively or other CAR T cells?
Dr. Goy: We are working with a number of different CAR T constructs besides axi-cel, in multiple myeloma, large cell lymphoma, follicular lymphoma, and now in marginal zone lymphoma. We will also have studies opening up in Hodgkin lymphoma. Hopefully, we’ll soon open trials evaluating cell therapy and CAR T in adult acute myeloid leukemia (AML), as well as, hopefully, in solid tumors.

Q: Could you talk about some trends in the CAR T space and some of the biggest unanswered questions?
Dr. Goy: The results are quite spectacular for a subset of patients. The next big question is how to build upon this. How do you predict or understand that the patient is going to do well versus trying to improve the patient who still has a failure? We see quite a few patients who respond well but who have a partial response but actually progress afterwards. Few patients who achieve a complete response then relapse, but there’s still an opportunity to improve the depth of response early on. There are some data suggesting that a combination of checkpoint inhibitors, as in the ZUMA-6 trial, might induce higher expansion of T-cells and a more prolonged duration of those CAR T-cells. We have seen some case reports, and now this is being explored as part of the clinical trial of combining CAR T-cell therapy with checkpoint inhibitors at the time of relapse.

For some patients who had further expansion and durable responses, there are a number of different concepts looking at CAR T-cell combinations of small molecules, including Ibrutinib in CLL, combinations with lenalidomide in aggressive lymphoma, and there will be others. The second aspect that needs to be answered is how we can mitigate toxicity and try to make the treatment more feasible. We know this is a therapy that is extremely impressive when it works, but it has toxicities. Cytokine release syndrome (CRS) is present across the board to some degree, with some variation, depending on the CAR T construct. The neurotoxicity is really the issue. It is something that tends to be more delayed from the CRS and we can predict that neurotoxicity. The CRS tends to occur in most patients with variable degrees, but durable toxicity doesn’t occur across all patients. Typically, neurotoxicity correlates with the degree of expansion of CAR T-cells. We would like to see an expansion of CAR T cells because I do believe that the CAR T-cell expansion early on is really what translates into a better outcome. Although neurotoxicity can be significant, it’s manageable. We now have therapies targeting IL-6 to control this neurotoxicity. What is also important in ongoing studies is the preemptive, early use of steroids and prophylactic use of steroids to mitigate these effects.

Q: Do you have to find the right dose of CAR T?
Dr. Goy: Finding the right dose is important, yes. We also consider questions such as whether several infusions of low-dose CAR T could work. Could we also use CAR T when patients have been less heavily pretreated? There’s an ongoing study in double hit lymphoma where these patients typically relapse after induction therapy; allogeneic transplant doesn’t really work, and when they relapse, they typically can’t make it to the allogeneic transplant. Could this population get CAR T-cells much earlier? That presents an opportunity to try to treat these patients.

Q: Are there other areas of hematology/oncology that you want to focus on at this year’s conference?
Dr. Goy: There is an estimate of 10,000 new drugs in the pipeline of medicine, and 2/3 are in oncology. The other remarkable thing is a better understanding of the molecular diversity of cancer across diseases. As we see over the years there’s further classification and re-stratifiation of patients, pushing the field towards precision medicine. This is an opportunity at this conference to see what’s
A s Dr. Goy enthusiastically points out, cell therapy, Car-T, and Immunotherapies have allowed us to move beyond chemotherapy for the treatment of resistant, aggressive lymphomas, and for patients who relapse. When these new therapies work, they offer spectacular results particularly in patients who are chemo resistant, or have relapsed. Fifty percent of these patients have no other options and do not qualify for clinical trials, and yet close to 40% of those treated have sustained clinical response with CAR T therapy.

Car-T therapies are evolving at a rapid pace. Although treatment comes with toxicities, third generation CAR T may also offer fewer toxicities, particularly when combined with other modalities. What is clear is that clinical response does not correlate with the degree of toxicity. The goal is to find out what will predict a patient’s individual risk.

We are at an exciting time in the field of oncology with over 10,000 therapies in the pipeline from cell therapies, CAR-T, immunotherapy, small molecules and combinations of therapies. The biology of cancer is extremely diverse, which allows for the differentiation and certification of patients based on their molecular and genetic makeup. This has pioneered personalized treatment plans based on these characteristics, which in turn has improved survival rates.

The charge of modern oncologists is to find the proper therapies, in the proper sequence, given for the proper period of time, and to make value based treatment decisions that maximize the chance for a durable response, and minimize toxicity while paying attention to cost. Oncologists are exposed to such a dizzying array of treatment options, and in such a rapidly changing landscape. Clinicians need to understand what is relevant to patients today and tomorrow. It is essential to keep learning, in order to clarify the issues essential to patient quality of life and survival.

FINANCIAL DISCLOSURES: The author has no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.
Q: Could you talk about irbritinib?

Dr. Goy: Ibrutinib was the first Bruton’s tyrosine kinase (BTK) inhibitor that has had an enormous impact in CLL and a number of diseases; mantle cell lymphoma (MCL) obviously. We recently published our data with R2 ibrutinib in patients who are not candidates for high-dose therapy, salvage therapy, and stem cell transplant in refractory/relapsed large cell lymphoma.[2] Building on the success of the ibrutinib story, the combination of R2 and ibrutinib has been very impressive with a response rate over 60% and close to 40% CR. Some patients are in remission for more than 3 years. This is very promising. Ibrutinib has provided multiple subtypes of lymphoma with truly targeted therapy that has really changed the field. It provides a first backbone, particularly in combination with rituximab, with which we can build up non-chemotherapy options, even in aggressive large cell lymphoma.

Q: What are the implications of ibrutinib and lenalidomide?

Dr. Goy: In practice, with CLL, the combination of an anti-CD20 antibody has been debated based on the data recently published where ibrutinib itself did as well as ibrutinib/rituximab. In lymphoma, typically the CR rate is better in MCL. We talked about the window of opportunity in patients with p53 abnormalities. For example, the CR rate with the combination of ibrutinib/rituximab in patients with MCL is very impressive in the frontline setting. This provides an opportunity for consolidation with chemotherapy. The data have been used across the board. Ibrutinib/rituximab has also shown very impressive activity in marginal zone lymphoma (MZL), offering an opportunity for these patients who are often more elderly. Even with high-dose therapy and stem cell transplantation we’re talking about less than a year, year and a half versus close to 10 years. This was something that was really important and provided a rationale for those patients, particularly in MCL when they have abnormalities, to not start with chemotherapy. We start with R2 ibrutinib or ibrutinib/rituximab and bring them into remission, followed by shorter chemotherapy.

DISCLOSURE: Dr. Goy has consulted for; received research funding or honoraria from, and/or served on the boards of Kite/Gilead, Janssen, Celgene, Acerta, AstraZeneca, COTA, Genentech, HackensackUMC, Pharmacyclics, and University of Nebraska. He has equity ownership in COTA.

References
A 67-year-old African American male presents with an elevated prostate-specific antigen (PSA), which had risen from 6.6 ng/mL two years ago to 8.4 ng/mL four months ago. Two prior prostate biopsies were negative. A SelectMDx test one year ago showed a 50% risk of cancer, and a 23% risk of high-grade cancer. A recent prostate biopsy had a cellular myxoid cell neoplasm involving 20% of a core in the left-mid prostate. Tumor cells had 0.1% nuclear staining with Ki-67, no mitotic activity, and were focally positive for estrogen receptors. Due to the patient’s body habitus (body mass index 46), he was unable to obtain magnetic resonance imaging (MRI). Other medical problems include hypertension and type 2 diabetes. His father had prostate cancer. He has a 15-pack year smoking history but quit in 1984. Imaging is relevant for a CT with stable subcentimeter pulmonary nodules obtained six months prior. The diagnosis was likely benign tumor of the prostate but stromal tumor of uncertain malignant potential (STUMP) could not be excluded.

Discussion
Mesenchymal neoplasms account for <1% of all cancer found in the prostate and are predominantly prostatic stromal proliferations. Other tumors found in

What is the next step in clinical management of this patient?
A. Radical prostatectomy
B. Obtain chest CT and attempt MRI of the pelvis
C. Repeat prostate biopsy in six months
D. Focal cryoablation
E. Active surveillance with yearly PSA and biannual prostate needle biopsy

FIGURE 1 Axial T2 weighted image showing the 0.8x0.8 cm lesion (arrow). A second-level review of the pathology was obtained, which decided that this was a stromal hyperplasia without malignant features rather than STUMP. The patient chose surveillance of the tumor and is scheduled for a repeat prostate biopsy and MRI in six months.
prostate needle biopsy specimens include myofibroblastic proliferations, smooth muscle neoplasms, gastrointestinal stromal tumors, schwannomas, rhabdomyosarcomas, prostration sarcomas, and mixed epithelial stromal tumors of the seminal vesicle.[1] The World Health Organization classifies prostatic stromal proliferations into two categories – STUMP and stromal sarcoma.[2]

STUMP tumors have much overlap with the stromal hyperplasia of benign prostatic hyperplasia (BPH) as well as variable degrees of epithelial proliferation. [3-5] Four histologic patterns have been described – a cellular spindled, eosinophilic pattern, a pattern with scattered atypical stromal cells, a phyllodes-like pattern, and a myxoid pattern[6] – with the recent addition of a “round-cell” pattern in a recent review.[7] They all have minimal mitotic activity and minimal necrosis.

STUMP have a range of clinical outcomes, and the histologic subtype has not been linked to a specific clinical outcome. [8] The clinical course of the disease is uncertain in part because there have been few published case series on STUMP. [6,8-9] The majority remain stable for years without intervention and do not recur if resected, some recur locally after repeated resections, and some develop concurrently or subsequently characteristics of stromal sarcoma, which can lead to widespread metastasis and death.

Unfortunately, a prostate biopsy finding STUMP without any degree of sarcoma does not guarantee a stable disease course. In the largest case series, one STUMP preceded the development of stromal sarcoma by 9 years. In another patient, an initial needle biopsy yielded STUMP, but a subsequent radical prostatectomy (RP) showed STUMP and high-grade sarcoma. The clinical presentation is also non-specific. The mean age of presentation was 58 years. The most common presenting symptoms were lower urinary tract symptoms (LUTS), abnormal digital rectal exam, and hematuria, with a significant subset of patients biopsied due to a rising PSA.[8]

Treatment of STUMP ranges from observation to RP with chemoradiation, and outcomes are related to the degree of sarcoma present in the tissue. A case series of 21 patients with prostatic sarcoma (including rhabdomyosarcoma and leiomyosarcoma) who were treated with RP and chemoradiation yielded a survival rate of 38% at 5 years.[11] In a series of 23 patients with phyllodes tumor, 12 were treated with prostatectomy; of those, 4 had recurrent or persistent disease.[9] In one large case series, 50 patients were split between those with prostatic STUMP (n=36) and patients with partial or complete sarcoma (n=14). Of the pure STUMP tumors, 14 were watched without evidence of disease progression, 5 required repeated trans-urethral resections, and 14 undercut immediate RP without evidence of recurrence (3 were lost to follow up). The patients with sarcoma present all underwent RP. Of those, 4 had disease recurrence, 8 had no evidence of disease recurrence, and 2 were lost to follow up.[8] A different case series of 18 patients with “stromal hyperplasia with atypia” showed no development of sarcomatous differentiation or malignancy on follow-up.[13] These data suggest that RP should be seriously considered for patients with features of sarcoma at initial diagnosis. For all others, the benefits of RP as initial treatment are less clear; at the very least, these patients should undergo surveillance to watch for disease progression.

Very little is known about imaging STUMP. One case report of an MRI taken of a STUMP showed that the lesion had homogenous low-signal on T1 weighted image, but was diffusely heterogeneous on T2 weighted image, with layered cysts located in areas of the tumor. Its appearance was quite different from ad-
While prostate adenocarcinoma is the predominant malignant histology of the prostate, practicing clinicians, especially urologists and pathologists, should be aware of less common prostate histology. Prostatic stromal proliferations, classified by the WHO into either stromal tumor of uncertain malignant potential (STUMP) tumors or frank stromal sarcoma, are the predominant mesenchymal tumors of the prostate. Though five histologic patterns have been described for STUMP tumors, it is important to note that all minimal mitotic activity, minimal necrosis and otherwise benign microscopic features, even though they do not behave aggressively, are recognized as neoplasms, as some may occasionally demonstrate local recurrence after resection, be associated with local morbidity or have unrecognized malignant potential. Hence, the management of these lesions requires a thorough evaluation for evidence of malignant potential, especially undetected sarcoma, and subsequent management based on shared decision making with the patient.

Comprehensive assessment includes, but is not limited to, prostate biopsy (or biopsies, in cases of insufficient tissue), appropriate staging with cross-sectional imaging, and additional evaluations to ensure appropriate management for the patient. As the authors noted in this case, a prostate biopsy that identifies STUMP without any degree of sarcoma does not guarantee a stable disease course nor is it always consistent with final surgical pathology. If sarcoma is suspected, but unable to be confirmed on tissue diagnosis, management should be tailored accordingly. Appropriate staging with cross-sectional imaging is critical, as findings of aggressive local disease or metastatic disease not appreciated on initial evaluation, can significantly impact treatment decision making.

STUMP tumors, even though they do not behave aggressively, are recognized as neoplasms, as some may occasionally demonstrate local recurrence after resection. Along those lines, cross-sectional imaging, and additional evaluations, such as cystoscopy, cystogram, etc., may be important in cases of STUMP tumors with locally aggressive disease. For example, in a case at our center, the STUMP tumor presented as a 19 cm multilocular solid and cystic mass replacing the prostate gland with resultant left-sided bladder displacement. Subsequent evaluation with CT scan, MRI and cystoscopy enabled us to better plan for eventual surgical resection, including consideration of radical cystoprostatectomy.

Finally, shared decision making is of the utmost important. As this is a rare condition, management options range from observation to more extensive surgical resection. A multi-disciplinary approach, in conjunction with colleagues from medical oncology and radiation oncology, is highly suggested. As sarcoma is often radiosensitive, radiation therapy should be considered as either neoadjuvant therapy or alternative to surgical excision. As the presence of sarcoma is the driving feature of oncologic outcomes, surgical management should revolve about optimizing local control, minimizing risk of positive surgical margins, and, in our opinion, preclude focal therapy.

While the authors of this case report advocate for active surveillance, due to the lack of correlation between prostate biopsy and final surgical pathology, risk of sarcomatous differentiation, and lack of long-term surveillance data, it is our opinion that patients with STUMP tumors warrant active treatment, either with surgical excision or radiation therapy. However, if STUMP tumor without evidence of sarcoma is confirmed on final surgical pathology, close follow-up without adjuvant therapy appears to be safe.

FINANCIAL DISCLOSURE: The authors have no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

For references visit cancernetwork.com/PcaSTUMPx

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Dr. Chandrasekar is a physician with the Department of Urology and the Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, Pennsylvania.
enocarcinoma of the prostate, but could not be readily differentiated from other prostatic tumors, including sarcomas – of note, the authors state sarcomas would not have a true cystic component, but if large would have areas of necrosis with a cystic appearance. In their case report, the mass was quite large (110 mL), and the extent of the lesion could not be accurately discerned given proximity to the seminal vesicles and anterior rectal wall. The patient ultimately underwent RP. There was no evidence of tumor extending beyond the prostate, and surgical pathology was consistent with STUMP.[14]

For our patient, we recommended a protocolled MRI and a repeat chest CT. A large lesion size or suspicion of extent into surrounding tissues on MRI would favor aggressive treatment, including RP and possible adjuvant chemoradiation. Enlarged pulmonary nodules on CT would raise concern for metastasis and might prompt biopsy. Conversely, a smaller, contained lesion on MRI and stable pulmonary nodules on CT would favor close monitoring of the lesion. A repeat prostate biopsy is a reasonable option, but the yield would be much higher if it were MRI-guided; likewise, focal cryoablation could be used in the future in the setting of a localized and better-defined lesion.

Our patient had no malignant features consistent with co-existing stromal sarcoma, and we thus did not immediately recommend RP. However, risk remained that the patient harbored malignant tissue not sampled by the needle biopsy, or that the STUMP could undergo malignant transformation over time. We had limited information on the size of the lesion – the patient had not undergone MRI at his outside hospital due to body habitus. Because of the concern for coexisting malignancy and lack of knowledge of tumor size, we did not recommend delayed follow-up.

Published case series are few and far between, and within those series, the histology and clinical course of the lesions are so varied that no protocol or guidelines can easily be applied to all STUMP tumors. We presented this information to the patient and his family. They were averse to undergoing a large operation as initial intervention and elected to gather further diagnostic information prior to initiating any treatment.

**Outcome**

An MRI was obtained which found a 0.8 x 0.8 cm lesion in the left medial posterior peripheral zone of the prostate, consistent with the location of the positive core biopsy. (Figure 1) There was focal bulging of the capsule overlying the lesion without evidence of definite extension. It had a circumscribed, homogenous appearance on T2 weighted image. The CT chest showed stable pulmonary nodules.

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For references visit cancernetwork.com/PcaSTUMP

Micrograph of a prostatic stromal tumor of uncertain malignant potential, (STUMP), a lesion of the prostatic stroma that cannot be determined as either benign or malignant.
With US Food and Drug Administration (FDA)-approved indications for both chronic lymphocytic leukemia (CLL) and acute myeloid leukemia (AML), and continued investigation within multiple disease states, venetoclax has become an exciting oral targeted therapy among oncologists. Venetoclax is a small molecule inhibitor of the antiapoptotic protein BCL-2 and was first approved in the spring of 2016 as monotherapy in relapsed or refractory CLL with deletion 17p.[1] Initial attention to venetoclax focused not only on the clinical benefit of this agent but also on reported fatalities related to tumor lysis syndrome (TLS) seen in early studies. Much of the provider and patient education for venetoclax focuses on the risk for TLS and the importance of the ramp-up dosing packaged in a user-friendly manner in the starter pack. Various reminders for adequate hydration are prominent within the starter pack, and the manufacturer even has a 28-oz water bottle that can be obtained for patients. Detailed risk assessment and instructions for adjunctive supportive agents for prevention of TLS (eg, allopurinol, rasburicase, fluids) are outlined clearly in the prescribing information. Aside from being cognizant of TLS risk, there are a few additional practical considerations to review in prescribing this specialty medication.

A factor that can complicate patient counseling and medication prescribing is the recommended timing and duration of venetoclax in combination regimens. For example, when using the combination of venetoclax and obinutuzumab in the frontline setting for CLL, therapy begins with the CD20-directed monoclonal antibody (Table 1).[2] Patients should receive obinutuzumab on days 1, 2, 8, and 15 before starting their venetoclax ramp-up on day 21 of the first 28-day cycle.[1] Furthermore, this combination has allowed for a time-limited upfront treatment approach in which, as well as a finite period of 6 months for obinutuzumab, venetoclax is stopped after completing 12 months of therapy. This is different than the current recommendation for ibrutinib, the other breakthrough targeted agent, in the frontline setting. Conversely, when following the protocol used in the MURANO study, in which venetoclax is combined with rituximab in the relapsed or refractory setting, patients should complete the venetoclax ramp-up before the first infusion of rituximab and continue for 2 years, or until progression or unacceptable toxicity occurs (Table 1).[3]

In contrast, when used in combination therapies for AML, venetoclax should begin at the same time as the selected partner medication: decitabine, azacitidine, or low-dose subcutaneous cytarabine.[1] Another key difference when prescribing venetoclax in this setting is much faster ramp-up schemas over days instead of weeks without worrisome rates of TLS.[4,5] It should be noted that a target dose of venetoclax 400 mg daily is used when venetoclax is combined with the hypomethylating agents decitabine or azacitidine, but a higher target dose (600 mg) is recommended when patients receive a combination

**TABLE 1** Timing of Venetoclax Ramp-Up in CLL Combination Regimens

<table>
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<td>Begin after 3 weekly doses of obinutuzumab*</td>
<td>Fischer et al[2]</td>
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<tr>
<td>CLL, relapsed/refractory</td>
<td>Venetoclax + rituximab</td>
<td>Complete ramp-up before first dose of rituximab</td>
<td>Seymour et al[3]</td>
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</table>

*The first weekly dose of obinutuzumab should be split over 2 days with 100 mg on day 1 and the remaining 900 mg on day 2. CLL = chronic lymphocytic leukemia
Venetoclax is not an easy drug to start. In CLL there is a 5 week dose ramp-up scheme which requires outpatient or in hospital monitoring for tumor lysis based on disease burden. This necessitates a multidisciplinary approach and can be difficult to implement in practice. Adding to the complexity, the approved anti-CD20 monoclonal antibody for combination and timing of starting this relative to venetoclax is different in the treatment-naive or relapsed/refractory settings.[1,2] Similarly, AML has different dosing schemes depending on the combination agent and the choice of azole antifungal prophylaxis.[3,4] Safely starting venetoclax places a burden on the healthcare team to ensure correct dosing and adequate monitoring for tumor lysis. It also places a burden on patients due to frequent clinic visits and in some cases hospital stays. When considering this effort, it is important to also consider the benefit for our patients.

In CLL venetoclax is superior to standard chemoimmunotherapy in terms of progression-free survival and has replaced it as a standard of care. This was demonstrated in the randomized phase 3 MURANO trial where it was compared to bendamustine and rituximab in relapsed/refractory CLL patients.[1] Similarly, in the recently reported CLL14 study which randomized previously untreated CLL patients with coexisting medical illnesses to either venetoclax and obinutuzumab or chlorambucil and obinutuzumab, venetoclax and obinutuzumab provided improved progression free survival.[2] Additionally, venetoclax has demonstrated efficacy in patients progressing after ibrutinib.[5] This is a population where other approved therapies are of limited benefit and venetoclax dramatically increases survival expectations.

The impact of venetoclax on the treatment of AML is also substantial. Both approved combinations offer effective therapy for patients who are not suitable for standard induction chemotherapy. Both also have a more rapid time to recovery of peripheral blood counts than a hypomethylating agent or low dose cytarabine treatment, which decreases transfusion needs and risk of infection.[3,4] Importantly, responses were seen in AML patients with adverse risk disease, a population with limited alternative treatment options and inferior responses to traditional cytotoxic chemotherapy.

In addition to the approved indications for venetoclax which have positively impacted both diseases, the potential for highly-effective venetoclax combinations will only expand the uses for this drug. It is important to realize that the work required to safely use venetoclax is absolutely worth it based on the value venetoclax has for our patients in terms of disease outcomes.

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For references visit cancernetwork.com/OP-Venetoclax

Dr. Rogers is a Hematologist Oncologist and Assistant Professor in the Division of Hematology, Ohio State University, College of Medicine, Columbus, Ohio.
The Food and Drug Administration (FDA) recently approved cabozantinib for the treatment of hepatocellular carcinoma in patients who previously received sorafenib.

Cabozantinib (Cometriq [capsule] or Cabometyx [tablet]) is an oral tyrosine kinases inhibitor of MET, VEGFR, and AXL. Receptor tyrosine kinases play important roles in both normal cellular function and pathologic processes, including oncogenesis, metastasis, tumor angiogenesis, and tumor microenvironment maintenance.

The FDA first approved cabozantinib for treatment of medullary thyroid cancer. Later, the FDA approved its use in renal cell carcinoma.

Medullary Thyroid Cancer
The FDA approved cabozantinib (Cometriq) to treat metastatic medullary thyroid cancer (MTC) in November 2012. It was based on results from an international, multicenter, randomized, double-blind, controlled trial including 330 subjects. Participants needed to exhibit progressive disease within 14 months before study entry, which was confirmed via an independent radiology review committee or the treating physician.

Patients were randomized to receive either cabozantinib 140 mg or placebo orally once daily until progressive disease or intolerable toxicity. Randomization was stratified according to age < 65 years vs > 65 years and previous utilization of a tyrosine kinase inhibitor.

Primary endpoints were progression-free survival (PFS), objective response (OR), and response duration employing modified RECIST criteria. Patients in the cabozantinib group had prolonged PFS compared to those receiving placebo (P < .0001). Specifically, median PFS in the cabozantinib arm was 11.2 months and median PFS in the placebo arm was 4.0 months.

Only patients taking cabozantinib experienced a partial response (27% vs 0; P < .0001). Furthermore, the median duration of OR was 14.7 months for those treated with the drug. No significant differences in overall survival were observed between arms.

In a 2019 meta- and economic analysis evaluating the utility of cabozantinib and vandetanib in patients of England’s National Health Service, Tappenden et al. concluded:

“The identified trials suggest that cabozantinib and vandetanib improve PFS more than the placebo; however, significant OS benefits were not demonstrated. The economic analyses indicate that within the EU-label population, the ICERs [incremental cost-effectiveness ratios] for cabozantinib and vandetanib are > £138,000 per QALY (quality-adjusted life year) gained. Within the restricted EU (European Union)-label population, the ICER for vandetanib is expected to be > £66,000 per QALY gained.”

Advanced Renal Cell Carcinoma With History of Anti-Angiogenic Therapy
In April 2016, the FDA approved cabozantinib tablets for the treatment of patients with advanced renal cell carcinoma (RCC) who had received previous anti-angiogenic therapy. This approval came on the heels of the drug receiving Fast Track and Breakthrough Therapy designations by the FDA. 

Cabozantinib, which targets multiple tyrosine kinases involved in the development of RCC, including MET, AXL, and three VEGF receptors, was approved in December 2017, and it is distinct from other approved treatment options, as it targets multiple tyrosine kinases involved in the development of RCC, including MET, AXL, and three VEGF receptors. At the same time, physicians are very familiar with this class of drug and how to use dose adjustments to balance safety and efficacy. The approval of Cabometyx is wonderful news for physicians who are looking for a new option for their previously treated patients with advanced kidney cancer.”[4]

METEOR[1] was an open-label, randomized phase 3 trial, in which patients ≥ 18 years were randomly assigned (1:1) to receive 60 mg cabozantinib daily (n=330) or 10 mg everolimus (Afinitor) daily (n=328). Participants had advanced or metastatic clear-cell RCC, harbored measurable disease, and were previously treated with one or more VEGF tyrosine-kinase inhibitors.

The primary outcome was PFS assessed by an independent radiology review committee, and secondary outcomes included OS and objective response. Safety measures were analyzed in all patients who received at least one dose of study drug. Median duration of follow-up for OS and safety in participants taking cabozantinib was 18.7 months (IQR 16.1–21.1) vs 18.8 months (16.0–21.2) in those taking everolimus. Median OS in patients taking cabozantinib was 21.4 months (95% confidence interval [CI], 18.7–not estimable) vs 16.5 months (14.7–18.8) in those taking everolimus (hazard ratio [HR] 0.66 [95% CI 0.53–0.83]; P = .00026). Cabozantinib treatment was associated with improved PFS (HR 0.51 [95% CI 0.41–0.62]; P < .0001) and objective response (17% [13–22] with cabozantinib vs 3% [2–6] with everolimus; P < .0001) per independent review.

The most frequent grade 3 or 4 adverse events in the study were hypertension, diarrhea, fatigue, palmar-plantar erythrodysesthesia, anemia, hyperglycemia, and hypomagnesemia. Severe adverse events (grade 3 or more) were observed in 130 patients (39%) taking cabozantinib vs 129 patients (40%) taking everolimus. One treatment-related death was observed in the cabozantinib group and two were observed in the everolimus group.

“The improvements in progression-free survival, overall survival, and objective response suggest that cabozantinib should be considered as a new treatment for previously treated patients with advanced renal cell carcinoma,” the authors concluded. “Recently, the immune checkpoint inhibitor nivolumab also improved overall survival compared with everolimus in this population, but without improving progression-free survival.”[1]

Advanced RCC

In December 2017, the FDA approved cabozantinib tablets for first-line treatment of advanced RCC based on results of the CABOSUN trial. In CABOSUN, cabozantinib use was associated with extended PFS and improved objective response rate (ORR) compared with sunitinib in patients judged intermediate or poor risk per International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria.

In total, 157 patients aged ≥ 18 years without prior systemic treatment were randomized 1:1 to cabozantinib (n=79) 60 mg orally daily or sunitinib (n=78) 50 mg orally daily for 4 weeks followed by 2 weeks off; treatment continued until disease progression or intolerable toxicity. Patients were stratified per IMDC risk group and bone metastases. PFS and objective response rate (ORR) were assessed using subgroups of baseline characteristics and determined by an independent radiology committee.

In general, cabozantinib treatment was related to better PFS and ORR compared with sunitinib across subgroups (eg, defined by IMDC risk, bone metastases, age, and tumor burden). Estimated median PFS for patients taking cabozantinib was 8.6 months (95% CI, 6.8–14.0) vs 5.3 months (95% CI, 3.0, 8.2) for patients administered sunitinib (HR 0.48; 95% CI, 0.31, 0.74; P = .0008).

The most common grade 3-4 adverse reactions (≥ 5%) in those taking cabozantinib were hypertension, diarrhea, hyponatremia, hypophosphatemia, palmar-plantar erythrodysesthesia, fatigue, increased ALT, decreased appetite, stomatitis, pain, hypotension, and syncope.[5,6]

“The treatment landscape for first-line RCC is rapidly evolving, with approval of the combination of nivolumab and ipilimumab for patients with advanced RCC of intermediate or poor IMDC risk and ongoing trials of VEGF pathway and checkpoint inhibitor combinations,” wrote George et al., authors of the CABOSUN trial.

Although results of the trial were intended to be hypothesis-generating, the authors noted that “the positive MET status may be associated with a greater treatment benefit with cabozantinib versus sunitinib, although patients benefited with cabozantinib irrespective of MET status.”[6]

Hepatocellular Carcinoma

In January 2019, the FDA approved cabozantinib tablets for patients with hepatocellular carcinoma (HCC) previously treated with sorafenib. The approval was based on results from the CELESTIAL trial.

continued on page 382
Introduction
Biliary cancers are a heterogeneous group of tumors that originate from the epithelial lining cells of the small ducts within the liver and the main ducts of the biliary system extending into the gallbladder. Included under this designation are the cancers of gallbladder, intrahepatic and extrahepatic bile ducts, and variably, ampullary carcinoma. Extrahepatic ductal tumors are further divided into lesions that arise at the liver hilum, or at the extrahepatic ductal system. Inconsistent use of designations based on anatomical characteristics such as intrahepatic/extrahepatic or hilar has confounded the analysis of epidemiological trends of this cancer. The true incidence of biliary cancers is unknown due to the difficulty in establishing an accurate diagnosis. The incidence of cholangiocarcinoma in the western world is between 0.35 to 2 per 100,000 per year.[1] However, in China and Thailand, the incidence can be up to 40 times the rate observed in the western world in part due to liver fluke (ie, *Opisthorchis viverrini*) infestation. [2] Over the past 30 years the incidence of intrahepatic cholangiocarcinoma in the western world seems to be rising with an increase from 0.1 per 100,000 to 0.6 per 100,000 while the incidence of gallbladder cancer is on the decline. [3-7] This year, it is estimated that there will be 12,360 new cases of biliary cancer in the United States with 3,960 deaths.[8] About 50-60% of cholangiocarcinomas emerge in the bile ducts of the perihilar region; 20-30% emerge in the distal extrahepatic region; and 5-10% emerge in the intrahepatic region. [9-11] (Figure 1).

Appropriate evaluation and choice of management for cholangiocarcinoma requires a multidisciplinary approach. Surgery, the backbone of curative treatments for biliary cancer, is effective in early, completely-resectable stages or in combination with neoadjuvant or adjuvant chemotherapy and/or radiation therapy for locally advanced stages. Systemic therapies in unresectable and recurrent cases are associated with poor outcomes. The introduction of next-generation sequencing technologies has opened new horizons for a better understanding of the molecular basis of this cancer with potential identification and evaluation of new treatment options.
likely to benefit from surgical intervention. It is helpful to select the patients who are most likely to benefit from surgical intervention, such as patients with jaundice, in patients with locally advanced gallbladder cancer, or in patients who have lymph node involvement. In a prospective study of locally advanced gallbladder cancer, 25 patients were given neoadjuvant chemoradiation and 15 patients were given neoadjuvant chemotherapy only. Six (two chemoradiotherapy and four neoadjuvant chemotherapy) patients were able to undergo curative intent resection. Four of them (66.7%) were alive at 18-month follow up. In a retrospective study involving 74 patients with locally advanced or node positive gallbladder cancer who underwent neoadjuvant therapy, one-third of the patients were able to undergo resection, 45% of whom had definitive surgery. A median 51-month overall survival (OS) was associated with definitive resection compared with 11 months for the group who could not undergo resection.[12] Neoadjuvant chemotherapy should be considered in patients with evidence of locoregionally advanced disease. Chemotherapy regimens such as gemcitabine/cisplatin, gemcitabine/oxaliplatin (GEMOX), gemcitabine/capecitabine, capecitabine/cisplatin can be utilized. In a prospective study of 28 patients with locally advanced gallbladder cancer, R0 resection was possible in 14 patients. Following neoadjuvant treatment with gemcitabine and concurrent radiation therapy, 5-year survival in this group was 47%.[13] Although data on neoadjuvant chemoradiation remain limited to use in gallbladder cancer, this approach may also have a role in selected patients with cholangiocarcinoma. There is an unmet need for good quality, randomized trials in this setting.[14]

**Surgical Therapy**

The underlying surgical principle for the management of biliary cancers is to offer resection in the appropriate surgical candidate when R0 can be safely achieved. Surgical management of biliary tract cancers is tailored to the patient based on preoperative evaluation of both the patient and the tumor. Techniques for resection include hepatic and biliary resection with lymphadenectomy, paired with very careful peri-operative management. An individual approach is employed to balance the risk of surgical resection. This requires evaluating patient comorbidity, underlying liver disease, and tumor anatomy and biology. Since surgery for biliary cancers can cause morbidity, patients who have poor performance status or who have post-operative complications may not remain candidates for adjuvant therapy.

Surgical management of cholangiocarcinoma requires careful pre-operative evaluation of the location and extent of tumor. Pre-operative axial imaging with CT and MRI, as well as evaluation of biliary anatomy with endoscopic retrograde cholangiopancreatography (ERCP) can provide valuable information for operative planning. Anatomically, cholangiocarcinoma can arise from the extra-hepatic bile duct (either distal or hilar bile duct) or be more proximal and therefore completely intra-hepatic. Surgical resection is typically offered for patients without retro-pancreatic and para-celiac nodal metastasis, vascular involvement (of the portal vein and hepatic artery), or metastatic disease. Multifocal intra-hepatic tumor may be representative of metastatic disease rather than separate primary tumors and therefore is often considered a contraindication to surgical resection. Diagnostic laparoscopy or laparotomy for staging can be performed prior to resection. Complete resection of hilar cholangiocarcinoma most often requires major hepatectomy and bile duct resection with reconstruction along with hilar lymphadenectomy. Distal cholangiocarcinoma and ampullary cancers may be treated using similar surgical approach to pancreatic head tumors involving pancreaticoduodenectomy. Intra-hepatic cholangiocarcinoma often requires major hepatic resection; however, non-anatomical resection or segmental resections may be offered if negative margins can be achieved along with regional lymphadenectomy.[15]

Gallbladder adenocarcinoma is often diagnosed pathologically after cholecystectomy performed for presumed benign disease. Further resection to achieve negative margins and lymphadenectomy is often based on the depth of invasive carcinoma. For T1a tumors, cholecystectomy alone may be considered definitive resection, however T1b or greater tumors may require partial liver resec-
tion of the gallbladder bed, en bloc bile duct resection, or lymphadenectomy to clear local disease.[16]

Evaluation of the surgical patient with biliary cancer includes identification of comorbidities that would preclude major abdominal surgery, including evaluation of hepatic function and reserve. This can include axial imaging in the form of CT or MRI and assessment of hepatic volume including future liver remnant. Optimization of patients should include management of reversible obstructive jaundice with ERCP stent or percutaneous transhepatic biliary catheters prior to resection.[17]

Specific complications of surgery for biliary malignancies include bile leak, biliary stricture, positive resection margins or in situ disease at the margin, and post-hepatectomy liver failure. Due to the variability in location and extent of biliary cancers at the time of diagnosis, the rates of patients who undergo resection ranges from 56% to 91%.[18] Of those patients who do not undergo surgical resection, palliative interventions may be required. Typically, biliary decompression can be achieved by ERCP or percutaneous transhepatic biliary drains. In the recent era, the rates of palliative surgeries necessary for biliary cancers is lower due to improvements in pre-operative imaging and intervention procedures.[19]

Liver transplantation has been employed as a treatment option for select patients in the setting of biliary malignancy. Given the technical difficulty of achieving R0 resection of hilar cholangiocarcinoma, -short of complete hepatectomy-, liver transplantation has been explored. Some multicenter retrospective analyses demonstrate a survival benefit for select patients with hilar cholangiocarcinoma who received liver transplantation following neoadjuvant treatment.[20] Candidacy criteria for transplantation can include individuals with surgically unresectable tumors <3 cm, absence of nodal or metastatic disease, and those that have not undergone prior percutaneous biopsy. Transplantation is performed under specified protocols for hilar cholangiocarcinoma that typically include neoadjuvant external beam radiation and radiosensitizing chemotherapy, and variably brachytherapy or maintenance chemotherapy. Evaluation of outcome is limited by retrospective design of analyses, however one multicenter study found a dropout rate of 25% prior to transplantation, and a post-transplant recurrence free survival rate of 65% at 5-years.

Adjuvant Therapy

Complete resection remains the gold standard of treatment and offers the best chance of cure for patients with biliary tract cancers. However, 5-year OS rates even after complete resection range from 30% to 40% for perihilar lesions, 21% to 63% for intrahepatic cholangiocarcinoma, and 20% to 54% for distal cholangiocarcinomas managed by pancreaticoduodenectomy.[21-24] Due to low incidence of biliary cancer there is a lack of prospective randomized trials to evaluate efficacy and safety of adjuvant therapy. Most of the retrospective trials with limited sample size and inclusion of heterogeneous patient population (combining gallbladder and cholangiocarcinoma patients) suggested a marginal benefit of chemoradiotherapy in reducing locoregional recurrence but an uncertain impact on survival.[25] Recurrence patterns differ by primary site: cholangiocarcinomas show a tendency to recur locally and provide a rationale for additional local therapy after definitive surgery while majority of gallbladder cancers have distant spread.[26]

A meta-analysis of 10 retrospective studies evaluating adjuvant radiotherapy after curative resection for extrahepatic cholangiocarcinomas demonstrated a significant benefit in OS in patients who received adjuvant radiotherapy. [27] On the contrary, a Surveillance, Epidemiology, and End Results (SEER) analysis of adjuvant radiotherapy failed to show a survival benefit; however, key data in this study, including margin status and the use of combined chemotherapy were not available through the SEER database.[28] In 2012, a systematic review and meta-analysis was undertaken to evaluate published data from 1960 to 2010. Twenty studies that compared surgery alone to surgery plus adjuvant therapy included 6712 patients, 1797 of whom received adjuvant therapy. In the overall analysis, adjuvant therapy was associated with a trend toward improvement in survival (odds ratio [OR], 0.74; P = .06). Chemotherapy and chemoradiation produced greater survival benefit than radiation alone. In patients with node-positive or margin positive disease, any adjuvant therapy had a significant benefit. Patients with R1 resection benefited from adjuvant radiotherapy and those with margin negative (R0) resection did not.[29]

The Southwest Oncology Group (SWOG) evaluated the use of adjuvant chemotherapy (gemcitabine and capcitabine) followed by chemoradiation (concurrent radiotherapy and capcitabine) for resected extrahepatic cholangiocarcinoma or gallbladder tumors. Out of 79 evaluable patients, 49 (62%) had extrahepatic cholangiocarcinoma. Twenty-five patients (32%) underwent an R1 resection. Two-year OS was 65% for all patients (67% and 60% for R0 and R1 resections, respectively). Median OS was 35 months, and only 14 patients developed a local recurrence. Grade 3 adverse events were observed in 52% and grade 4 in 11% of patients.[30]

The first randomized study evaluating the impact of adjuvant chemotherapy in biliary tract cancer was conducted by Takada et al [31] in 2002. Patients with pancreatic cancer (n = 158), extrahepatic biliary tract cancer (n = 118), gallbladder cancer (n = 112), and ampulla of Vater cancer (n = 48) were randomly assigned to adjuvant mitomycin plus 5-fluoroura-
(5-FU) chemotherapy or to surgery alone. While patients with resected gallbladder cancer who had received mitomycin/FU had significantly better 5-year disease-free survival compared with control (20.3% versus 11.6%) no difference was observed for all biliary tract cancers. [28] A decade later, the European Study Group for Pancreatic Cancer reported the results of ESPAC-3 trial which found a survival benefit for patients with ampullary cancers who received adjuvant 5-FU plus folic acid or gemcitabine compared with observation after adjusting for prognostic variables.[32]

More recently, the PRODIGE 12-ACCORD 18-UNICANCER GI trial randomly assigned 196 patients to adjuvant GEMOX or to observation alone in resected biliary tract cancer (including all types). R1 resection rates were 13.8% in the GEMOX arm and 12.1% in the observation arm; lymph node involvement was 37.2% and 36.4%, respectively. No difference in the primary end point of relapse-free survival between the experimental and observation groups was observed (39% v 33% at 4 years; P = .31).[33] In contrast, in the BILCAP study which randomized 447 patients with resected biliary tract cancer to receive adjuvant capecitabine versus observation, median recurrence-free survival was 24.4 versus 15.5 months, respectively and median OS was 51.1 months versus 36.4 months, respectively, favoring the capecitabine arm.[34] Finally, the phase III Japanese Bile Duct Cancer Adjuvant Trial (BCAT) which only included patients with extrahepatic cholangiocarcinoma and excluded patients with gallbladder cancer showed no difference in OS (median OS, 62.3 vs 63.8 months) or relapse-free survival (median relapse-free survival, 36.0 vs 39.9 months) between gemcitabine versus observation groups.[35]

Given the heterogeneity of tumor sites, variation in nodal and margin statuses, and nonuniform chemotherapy regimens, interpretation of all these data becomes very challenging. One may conclude that, with the ESPAC-3 data, there seems to be some benefit for adjuvant chemotherapy in ampullary cancers, and with the data from Takada et al. study some benefit for use of adjuvant chemotherapy for gallbladder cancers. Despite the paucity of level-I evidence to support adjuvant therapy for biliary tract cancer, available guidelines at present support consideration of adjuvant chemotherapy, radiation therapy, and chemoradiation therapy, alone or in combination in most stages and subtypes of biliary cancer, particularly in node-positive and margin-positive disease. The optimal sequencing of these modalities and optimal chemotherapy regimens await larger randomized trials to address these questions.

**Systemic Therapy for Advanced Metastatic Disease**

Unfortunately, biliary cancer is often diagnosed at an advanced stage when resection is no longer possible. Even in patients with initial resectable disease, early postoperative recurrence makes systemic therapy necessary. The prognosis of patients with advanced biliary tract cancers is poor and median survival for those undergoing supportive care alone is short. Treatment options at this stage include gemcitabine plus cisplatin chemotherapy, fluoropyrimidine-based chemotherapy, pembrolizumab for patients with microsatellite instability high/deficient mismatch repair (MSI-H/dMMR) tumors, fluoropyrimidine-based chemoradiation, or palliative radiotherapy without chemotherapy and most certainly clinical trials. The randomized phase III clinical trial (ABC-02 Trial) which enrolled 410 patients with locally advanced or metastatic cholangiocarcinoma, gallbladder cancer, or ampullary cancer demonstrated the superiority of the combination of gemcitabine and cisplatin over gemcitabine monotherapy in terms of OS and PFS by 30%.[36] Other gemcitabine-based or fluoropyrimidine-based regimens with activity in this setting include GEMOX, oxaliplatin/5-FU/leucovorin, capecitabine/oxaliplatin, gemcitabine/albumin-bound paclitaxel, gemcitabine/cetuximab, and gemcitabine/oxaliplatin/5-FU.[37-42] In a Phase II study combination of panitumumab/gemcitabine/irinotecan showed encouraging results.[43]

A standard regimen in the second-line setting has not yet been established. Agents with different mechanisms of action are needed. Fluoropyrimidines such as 5-FU, capecitabine, and S-1 are frequently used in clinical practice outside the USA. Several clinical trials are being conducted to evaluate the efficacy of molecularly targeted agents in the second-line or later settings. In a systematic review including 25 studies in advanced biliary cancer with data on 761 patients, the efficacy of second-line chemotherapy regimens was evaluated, and insufficient evidence was found to recommend a specific second-line regimen.[44]

**Molecular Targets in Biliary Cancer**

More than 90% of biliary tract cancers are well-differentiated, mucin-producing adenocarcinomas, whereas a very small proportion is squamous or small cell in origin. Novel therapeutic targets are desperately needed due to dismal overall progress in therapy and limited beneficial effects of standard treatments.
prognosis for most cases of biliary tract cancer.\[45,46\] The information coming from molecular studies of biliary cancer has clearly shown that various human biliary cancer subsets characterized by heterogeneous molecular alterations exist. These alterations result in the activation of distinct signaling pathways which can be targeted. However, despite the identification of multiple targetable mutations (Figure 2.), due to the molecular complexity of biliary cancer the pioneering targeted approaches so far have produced less than satisfactory results.\[47\]

Biliary cancers share frequent genomic aberrations in the cell cycle regulators (specifically CDKN2B) and chromatin remodeling (ARID1A). Intrahepatic cholangiocarcinomas feature FGFR fusions, IDH1/2 substitutions, BRAF substitutions, and MET amplifications with a low KRAS mutational frequency.\[48, 49\] In a study of 153 biliary cancers (70 intrahepatic, 57 extrahepatic cholangiocarcinoma and 26 gallbladder carcinoma) the most frequently involved genes were KRAS (28%), TP53 (18%), ARID1A (12%), IDH1/2 (9%), PBRM1 (9%), BAP1(7%) and PIK3CA (7%). While IDH1/2 and BAP1 mutations were likely to be seen in intrahepatic cholangiocarcinom, KRAS and TP53 were more common in extrahepatic cholangiocarcinoma and gallbladder carcinoma.\[49\]

Somatic mutations in IDH1 and IDH2 cause a single amino acid change at a conserved arginine residue within the isocitrate binding site of IDH1 (R132) or IDH2 (R172, R140), causing reduced oxidative decarboxylation of isocitrate to \(\alpha\)-ketoglutarate.\[50\] Rates of IDH1 mutations are higher than IDH2 (15%-23% vs 3%-4%, respectively) across reports of intrahepatic cholangiocarcinoma sequencing; studies evaluating IDH1 inhibitors in cholangiocarcinoma are ongoing.\[51\]

The EGFR pathway involvement has been shown in all of intrahepatic cholangiocarcinomas, half of extrahepatic cholangiocarcinomas, and more than a third of gallbladder cancers.\[52\] Erlotinib, a selective and reversible inhibitor of EGFR, has been studied in the management of advanced biliary tract cancer in several phase II studies with no definitive conclusions.\[53\] Monoclonal antibodies targeting EGFR in combination with chemotherapy have shown some success. Cetuximab in combination with GEMOX produced an impressive response rate of 63% with 8.3 months of progression-free survival (PFS) and 12.7 months of OS.\[53\] Because the expression of HER2 has been observed in about 26% of extrahepatic cholangiocarcinomas and 10% of gallbladder cancers\[49\], a phase II study of lapatinib, a dual HER2/EGFR inhibitor did not result in any response for patients with advanced biliary tract cancer.\[54\]

The MEK/ERK signaling pathway can be a therapeutic target for biliary tract cancers. A phase II study of the MEK1/2 inhibitor selumetinib in advanced biliary tract cancer resulted in a median PFS of 3.7 months and OS of 9.8 months, with a response rate of 12%.\[55\] Clinical studies using other MEK inhibitors are underway. A list of currently active National Cancer Institute-supported trials in biliary cancer are listed in Table 1.

**Conclusion**

Biliary cancer is a heterogeneous disease with a very poor prognosis. Many patients are diagnosed at an advanced stage when cure is not possible. It is crucial to implement a multidisciplinary team approach prior to initiation of any treatment. Complete resection, including liver transplantation in highly selected cases, is the only possibility for a curative therapy. Unfortunately, this is applicable only in a minority of cases. One of the main challenges is to find ways in increasing the number of resectable cases by expanding early diagnosis. A personalized diagnostic work-up and therapeutic approach must be applied by dedicated teams with multidisciplinary expertise. Participation in prospective clinical trials is the preferred option for all stages of disease (Table 1). Better understanding of the gene expression profile and mutational burden in biliary tract cancer will hopefully allow identification of new therapeutic targets and treatment options.

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<td>Not Provided</td>
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Dr. Merani is Assistant Professor, Transplantation Surgery, University of Nebraska, Omaha, Nebraska.

Dr. Vargas is Assistant Professor, Transplantation Surgery, University of Nebraska, Omaha, Nebraska.
ONCOLOGY recently discussed therapy options for patients with hepatocellular carcinoma (HCC), including a newly approved therapy for a subpopulation of these patients, with Dr. Crystal S. Denlinger, an Associate Professor of Hematology and Oncology and the Chief of the Division of Gastrointestinal Medical Oncology at the Fox Chase Cancer Center in Philadelphia. Dr. Denlinger specializes in the care and treatment of patients with liver cancers, gastroesophageal cancers, and gall bladder and bile duct cancers.

**Q:** First, what is HCC, how frequent is it, and are there other types of liver cancer besides HCC?

**Dr. Denlinger:** HCC is a cancer that arises from the hepatocytes, the primary cells of the liver. It typically arises in the setting of other chronic liver diseases. It is a cancer that is on the rise. Actually, both incidence and mortality are rising, and it is now the fifth leading cause of cancer deaths in men and the seventh leading cause of cancer deaths in women. [1] There are a number of risk factors associated with liver cancer including hepatitis B virus, hepatitis C virus, alcoholic cirrhosis, and fatty liver disease and nonalcoholic fatty liver disease. As we get better at treating the viral hepatitis causes like hepatitis B and hepatitis C with antiviral therapy, we anticipate that fatty liver disease is going to become a leading cause of HCC in the future.[2]

There are other cancers that are considered to be liver cancers, including primary bile duct cancers, that are treated with other cytotoxic therapies. There are also some varieties of HCC, like fibrolamellar HCC, that have a different biology and treatment paradigm. We are focusing on the most common form of HCC.

**Q:** What are the therapy options for earlier-stage HCC? Is this cancer potentially curable at these earlier stages?

**Dr. Denlinger:** It is a potentially curable cancer at the earlier stage. We know that for patients who are at risk for HCC, screening is important because it can identify patients with potentially curable disease.

Cirrhosis is a known risk factor and increases the incidence by 2% to 4% annually. So, screening with an abdominal ultrasound in high-risk patients can identify patients with early-stage disease for whom curative therapy is possible. For patients who have a small HCC with preserved liver function, we can ablate these tumors or we can surgically resect them with high rates of a cure. We know that for patients who do have surgical resection, survival is greater than 60% at 5 years. However, surgical resection or ablation in someone who has cirrhosis does carry with it a risk of tumor recurrence in up to 70% of patients at 5 years. For patients who have known cirrhosis and a small HCC, we can consider liver transplantation because that cures not only the liver cancer but also potentially the underlying hepatic cirrhotic disease.

There are criteria for who can get a liver transplant. We follow the Milan criteria, defining patients who have one tumor that is 5 cm or less in size or three tumors each no more than 3 cm in size as transplant candidates. If
In the past two years, we have seen quite a few new drugs approved for hepatocellular carcinoma (HCC), particularly in the second line setting. We now have phase 3 data demonstrating a role for sorafenib and lenvatinib in the front-line setting and for regorafenib, cabozantinib, and ramucirumab in the second-line setting, as well as pembrolizumab in this setting as well. Both pembrolizumab and nivolumab received accelerated approval for second-line HCC. Ramucirumab is a monoclonal antibody against human monoclonal antibody against vascular endothelial growth factor receptor 2 (VEGFR2). The drug is unique in being the first drug approved for HCC based on a biomarker for patient selection, that is those with an elevated alpha fetoprotein (AFP). The data initially showing that ramucirumab could work in this select patient population was from a second line clinical trial that did not meet its overall survival primary endpoint in the entire study population but the retrospective analysis showed that those patients with a high AFP in the control arm did poorly and that those patients with a high AFP received a significant improvement in survival in the ramucirumab arm. Subsequently, the REACH-2 phase 3 study evaluated this hypothesis and was the basis for the approval of ramucirumab by the Food and Drug Administration. This study enrolled only those patients with an elevated AFP demonstrated a survival benefit for that population. There are patients who have high AFP since their diagnosis and there are patients who have a rising AFP as their disease advances. Both patients appear to benefit from ramucirumab. The other approved agents work in this subpopulation of patients as well but what is advantageous about ramucirumab is that its side effect profile is different from that of the tyrosine kinase inhibitors (TKIs) and is tied to its activity against the VEGF receptor, including hypertension and proteinuria. Recently, a phase 3 study with the PD-1 monoclonal antibody pembrolizumab showed a relatively high response rate and those that responded had a long disease control rate and increased overall survival but the results did not reach the pre-specified statistical criteria for being considered a positive clinical trial. However, pembrolizumab is an important drug for managing patients with HCC. In this context, my strategy is to expose patients to as many active drugs, sequentially, in the course of their disease. A patient that is progressing quickly through their first line advanced HCC therapy with a TKI may be a better candidate for a second-line immunotherapy such as pembrolizumab to have a chance at the durable and deep responses that have been seen. Ramucirumab is a good option for patients with high AFP who experienced toxicities while on a TKI and are in need of a break from those side effects. Given the newer therapy options, we are still figuring out how to best sequence these therapies, including ramucirumab, for our patients with HCC. With all of these new options, it is imperative that we start patients on systemic treatments when there disease advances, before their liver function starts to decompensate.

FINANCIAL DISCLOSURES: Dr. Finn has been a consultant for AstraZeneca, Bristol Myers Squibb, Eli Lilly, Merck, Novartis, Pfizer, Roche, and Genentech.
Q: What about metastatic disease, what are the standard therapy options and how have these options evolved over the last few years?

Dr. Denlinger: For metastatic disease, there are a number of options and two groups of patients in whom palliative therapy can be very helpful. Patients with intermediate-stage disease, who may have multiple tumors within the liver but no disease outside of it, can be treated with chemoembolization or radioembolization. This is where we deliver either chemotherapy or radiation therapy directly into the liver and can also embolize off the blood supply to that tumor to control multifocal disease within the liver. For patients with advanced disease, who have disease outside of the liver or for whom liver-directed therapy is not an option for a variety of reasons, there are a number of systemic therapies for the treatment of liver cancer.[3] Until recently, we only had one drug, sorafenib, which was approved in 2007. Sorafenib was approved for patients with preserved liver function and advanced disease for whom liver-directed therapy is not an option. It was shown to improve survival by about 2.7 months compared to best supportive care and to control disease in about 50% to 60% of patients. More recently, we have developed additional drugs in the frontline setting.

There is a new drug called lenvatinib that has been shown to be noninferior to sorafenib in terms of survival with a slightly better disease control rate. We also now have second-line therapeutic options in the form of regorafenib, cabozantinib, nivolumab, pembrolizumab, and ramucirumab. Regorafenib, cabozantinib, and ramucirumab have all demonstrated survival benefit compared to best supportive care. Nivolumab and pembrolizumab have demonstrated survival benefit compared to historical controls. So, we have a number of drugs now in first- and second-line therapy for advanced cancer patients with good liver function.

Q: In May 2019, the US Food and Drug Administration (FDA) approved ramucirumab for patients previously treated for HCC, including with sorafenib, and who have alpha-fetoprotein (AFP)

KEY QUESTION

Where do you see ramucirumab fitting into the treatment scheme besides those who have AFP levels of at least 400 ng/mL? Are there certain patient characteristics that make them more suitable for this therapy in terms of tolerating treatment and in terms of efficacy?

Dr. Denlinger: For most of my patients who received sorafenib or lenvatinib up front and progress on it or who have intolerance to it, ramucirumab remains an option for those who have preserved liver function and a high AFP. I do talk about this drug with my patients as one option for the second line. The decision about whether to use this medication versus one of the other oral medications is based on the patient’s preference regarding intravenous versus oral therapies, as well as their tolerance to the previous and antiangiogenic tyrosine kinase inhibitors that they received. Ramucirumab has a very different side-effect profile from cabozantinib and regorafenib, in that it doesn’t have the hand–foot toxicities and some of the anorexia, weight loss, and appetite toxicities associated with these other medications.

Ramucirumab is certainly a reasonable treatment option in the second line. One of the most important things that we have to think about in liver cancer is the underlying liver function. So, we will not only assess how much disease the patient has but also their underlying hepatic function based on the Child-Pugh Score. Child-Pugh Score A patients have typically been the patients for whom all of the drugs we talked about earlier have been tested. The ramucirumab studies initially enrolled patients with Child-Pugh Score A and Child-Pugh Score B. During the first ramucirumab trial called the REACH trial, it was found that for Child-Pugh Score B patients, there were higher rates of adverse liver function-associated events compared to the placebo arm and enrollment of Child-Pugh Score B patients was stopped.[4] Therefore, it’s important with ramucirumab, but actually with all antiangiogenic agents, to ascertain the liver function of the patient. For ramucirumab specifically, it’s important to restrict use of this drug to patients with Child-Pugh Score A, because we don’t want to exacerbate hepatic dysfunction in patients with more advanced cirrhosis.

For most of my patients who received sorafenib or lenvatinib up front and progress on it or who have intolerance to it, ramucirumab remains an option for those who have preserved liver function and a high AFP. I do talk about this drug with my patients as one option for the second line. The decision about whether to use this medication versus one of the other oral medications is based on the patient’s preference regarding intravenous versus oral therapies, as well as their tolerance to the previous and antiangiogenic tyrosine kinase inhibitors that they received. Ramucirumab has a very different side-effect profile from cabozantinib and regorafenib, in that it doesn’t have the hand–foot toxicities and some of the anorexia, weight loss, and appetite toxicities associated with these other medications. So, if a patient has a really difficult time on sorafenib or lenvatinib with respect to hand–foot syndrome or other side effects, ramucirumab might be a good alternative in some because it typically does not have those same side effects.
levels of 400 ng/mL or greater. This is the first therapy targeted for a specific subpopulation of patients with HCC that has been approved. Can you talk about this AFP biomarker and what it means in terms of the biology of HCC?

Dr. Denlinger: AFP is a protein that is made by the HCC. It has been used as a marker of diagnosis and also prognostication, and it is used to be part of the diagnostic screening criteria for patients with liver cancer. Liver cancer is the only cancer that can actually be diagnosed without a biopsy based on radiographic criteria alone. Older diagnostic criteria also required an elevated AFP. That has since been removed from the diagnostic criteria because it is not a validated biomarker for hepatocellular cancers.

That being said, it is a poor prognostic marker, meaning that patients who have high AFP levels do have lower long-term survival and worse survival outcomes compared to patients who have lower AFP levels. We think that it may be associated with a marker of more advanced disease or disease that has higher angiogenic activity. This may be why AFP was a marker that was associated with better outcomes in the ramucirumab studies, because ramucirumab is a drug that targets angiogenesis and AFP is associated with highly angiogenic tumors. Then targeting angiogenesis in this subpopulation makes sense and could actually be associated with better outcomes.

Q: Finally, are there drugs or combination therapies for HCC now in development, either early or late stage, that have particularly interesting targets or a combination that is showing signs of efficacy that you could highlight?

Dr. Denlinger: This is a great time to be a doctor who treats HCC because there is a lot of research right now looking at not only new therapies but also combination therapies, which is wonderful because HCC didn’t have any positive trials for 10 years. We had tons of negative studies. So, in addition to the recent FDA approvals and the large phase III trials that demonstrated survival benefit, there are now earlier-phase studies showing promise for combination therapies where you’re combining an antiangiogenic therapy with an immunotherapy. There are studies looking at lenvatinib combined with immune checkpoint inhibitors, bevacizumab combined with immune checkpoint inhibitors, and cabozantinib combined with immune checkpoint inhibitors. Combining these antiangiogenic therapies with immune checkpoint inhibitors is one potential avenue of research that looks very promising where response rates are higher than what we see with antiangiogenic therapy alone or immunotherapy alone. Also, combining multiple immune therapies together and targeting different components of the immune pathways seems very promising. There are studies looking at combining PD-1 or P-L1 inhibitors with other targeted immunotherapies in the hope that targeting the immune pathways through two different mechanisms may increase the chances of response and/or prolong survival. [3]

There are a lot of different options now, and we have a lot of clinical trials that are enrolling patients with Child-Pugh Score A liver function in the hope we’ll be able to define a better treatment paradigm compared to what we currently have with single agents. We do have many needs for HCC patients. One of those unmet needs is therapeutic options for the non-Child-Pugh A patients. Many of our patients come to us with Child-Pugh Score B or Child-Pugh Score C disease, meaning that their liver function is not well compensated or is decompensated. In Child-Pugh Score C patients, therapy is not typically given because we know that the liver function is not going to be able to support it. But for the Child-Pugh Score B patients in whom liver function may be compromised because of disease burden and not necessarily because of underlying cirrhosis, we need more studies and data on how to use these drugs, how effective these drugs might be, and in what sequence to use them. So, there’s an active research interest in looking at these agents in the non-Child-Pugh Score A population. Some data suggest that the therapies for HCC may have similar relative benefit in non-Child-Pugh Score A patients, but we need further data, especially with these newer agents, to really see how they perform.

FINANCIAL DISCLOSURES: Dr. Denlinger has received grants or research support from Astex Pharmaceuticals, Bayer HealthCare, ImClone Systems Incorporated, MedImmune Inc., Merimack Pharmaceuticals, OncoMed Pharmaceuticals, and Pfizer Inc., and has served as a scientific advisor for Eli Lilly and Company.

For references visit cancernetwork.com/HCC-Denlinger
Several promising drugs for the treatment of lung cancer have been garnering attention over recent years. These new treatments have been highlighted at conferences and are sure to impact the standard of care. Some of these new treatments are detailed below.

**LOXO-292**

Various multikinase inhibitors (MKI) with some activity against RET have been studied, usually demonstrating low response rates and substantial toxicities. Consequently, efforts are being made to create safer, more potent agents, such as the selective RET inhibitor LOXO-292.[1] In preclinical studies, LOXO-2 demonstrated activity against activating RET fusions/mutations, potential resistance mutations, and brain metastases.[2]

Results of a global phase 1 study of LOXO-292 involving patients with RET-altered cancers were presented at the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting.[2] Patients studied had advanced solid tumors, including RET fusion+ non-small cell lung cancer (NSCLC), papillary thyroid cancer (PTC), RET-mutant medullary thyroid cancer (MTC), and other cancers. Patients received oral doses in 28-day cycles, and dose escalation adhered to a 3+3 design. Determination of maximum tolerated dose (MTD) was the primary endpoint; secondary endpoints included safety, overall response rate (ORR, RECIST 1.1) and duration of response (DoR).

In the study population (n=57), there were 35 RET fusion+ tumors (27 NSCLC, 7 PTC, 1 pancreatic) and 20 RET-mutant MTCs. Additionally, 67% of patients were pre-treated with MKIs. Patients received LOXO-292 at 7 doses (20 mg daily escalated to 160 mg twice daily).

The ORR in RET fusion+ patients who could be evaluated was 69% (95% confidence interval [CI], 50%-84%, n = 22/32, 11 pending confirmation, 9/13 MKI-naïve, 13/19 MKI pretreated). ORR in NSCLC was 65% (n = 17/26) and 83% (n = 5/6) in PTC. Radiographic tumor reduction occurred in 84% (27/32) (range -19% to -67%). Of note, NSCLC responses occurred independently of the upstream partner when known and included three patients with brain metastases at baseline.

No dose-limiting toxicities were noted, and neither the MTD nor DoR were reached. Over 90% of patients continued with treatment. Adverse events included fatigue (16%), diarrhea (16%) and dyspnea (12%). Most adverse events were grade 1-2, and no higher-grade adverse events were ascribed to the drug.[2]

At the International Association for the Study of Lung Cancer (IASLC)
Capmatinib
The receptor tyrosine kinase (RTK) MET (c-Met, cMET, or c-MET) has been established as an enviable therapeutic target in cancer treatment. MET alterations hypothesized to be oncogenic include activating mutations, overexpression, gene amplification, and translocations. However, clinical development of MET inhibitors has been difficult, potentially due to the use of nonselective agents and failure to utilize a firm biomarker-based patient selection strategy during drug development.[4]

Capmatinib is a potent, highly selective MET inhibitor with activity limited to a small number of genomic parameters. It has been studied as monotherapy and in combination trials for lung and other types of cancer.[4]

Presented at the 2019 ASCO Annual Meeting, a primary analysis of capmatinib in the GEOMETRY mono-1 study indicated promising efficacy associated with capmatinib in patients with locally advanced or metastatic NSCLC with the MET exon-14 skipping (METex14) mutation. GEOMETRY mono-1 is a non-randomized, open-label phase II study evaluating capmatinib monotherapy in patients with EGFR wildtype, ALK-negative, advanced NSCLC harboring MET amplification and/or mutations. The ORR in patients receiving capmatinib was 68% for treatment-naive vs 41% for previously treated patients; median DoR was also clinically important regardless of the prior line of therapy.[5,6]

Capmatinib was given Breakthrough Therapy Designation by the FDA for the treatment of patients with metastatic NSCLC harboring METex14 mutation with disease progression before or after platinum-based chemotherapy.[6]

Tepotinib
Between 3-4% of NSCLCs harbor METex14 mutations, which appear to be sensitive to c-Met inhibition. A single-arm phase II trial presented at the 2018 ASCO Annual Meeting assessed the efficacy and safety of the potent, selective c-Met inhibitor tepotinib in patients with stage IIIIB/IV EGFR/ALK negative NSCLC with METex14 mutations. Study participants, who had previously received 0-2 lines of therapy, received tepotinib 500 mg daily until disease progression, intolerable toxicity, or for other reason.

In total, 9 of 15 evaluable patients (60%) had a confirmed partial response (PR) and 3 (20%) had stable disease (SD). All responders remained in response during the investigation. According to independent review, 6 patients had confirmed PR (46.2%) and 1 patient exhibited SD (7.7%). Thirteen of 22 patients with evaluable data had grades 1-2 treatment-related adverse events (TRAEs), 3 patients had grade 3 TRAEs, and 1 patient had a serious TRAE.

TAK-788
TAK-788 is an investigational potent, selective tyrosine kinase inhibitor with activity against EGFR and HER2 mutations being evaluated in NSCLC with EGFR exon 20 insertions.

At the 2019 ASCO Annual Meeting, updated results from a phase 1/2 first-in-human, open-label, multicenter study demonstrated that TAK-788 exhibits antitumor activity with adverse effects comparable to other EGFR TKIs.[8]

TAK-788 was associated with a median progression-free survival of 7.3 months and a confirmed ORR of 43% in patients diagnosed with either locally advanced or metastatic NSCLC with EGFR exon 20 insertions.[9]

In an interview with Cancer Network in June 2018, Robert C. Doebele, MD, PhD, University of Colorado, Denver said the following about TAK-788[10]:

“...it was specifically designed to meet an unmet need in non–small-cell lung cancer, which is that patients currently with certain types of EGFR and HER2 mutations do not have effective FDA-approved therapies. Specifically, these are patients who have EGFR exon 20 insertion mutations or patients with HER2 mutations. So, although we’ve had a plethora of EGFR inhibitors for non–

small-cell lung cancer, drugs like erlotinib, gefitinib, alectinib, and osimertinib have not been shown to be efficacious in patients with EGFR exon 20 insertions or HER2 insertion mutations.”

On a final note, in the same interview, Dr. Doebele mentioned a challenge experienced during the trial:

“The difficulty that has occurred in this setting is that EGFR exon 20 binding molecules are very similar in appearance and drug binding to wild-type EGFR binding molecules, and that has made getting appropriate doses into patients difficult.”

FINANCIAL DISCLOSURE: The author and reviewer have no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.
Breast cancer is one of the three most common cancers diagnosed in women, and accounts for 30% of new cancer cases in women in the United States. [1] About one in eight women will develop malignant breast cancer over her lifetime. [2] Deaths from breast cancer in women have declined by 40% from 1989 to 2016 [1] possibly due to treatment advances, earlier detection, and increased awareness. [2] Yet it is estimated that in 2019, 41,760 women will die of breast cancer, accounting for about 6.9% of all cancer deaths. [3]

Endometrial cancer is the most common cancer of the female reproductive organs among United States residents. The American Cancer Society estimates that about 61,880 cases of cancer of the uterine body will be diagnosed in 2019 [4] accounting for about 3.5% of all new cancer cases. [5] Some 12,160 women will die from endometrial cancer in 2019. These estimates include both endometrial cancers and uterine sarcomas; sarcomas make up about 10% of uterine body cancers. [4]

Breast cancer is most frequently diagnosed in women between the ages of 55 and 64. [3] Black women are at higher risk of dying from this disease compared to women of other ethnicities. Risk is nearly double for women with a first-degree relative who have a history of breast cancer. In addition, about 5-10% of breast cancers can be linked to a germline gene mutation such as BRCA1 or BRCA2. [2] Breast cancers are generally categorized as hormone receptor positive (estrogen receptor and/or progesterone receptor positive), HER2-positive, or triple negative (absence of hormone receptor or HER2 mutations).

Endometrial cancer is uncommon in women under the age of 45 and mainly affects post-menopausal women; the average age of women diagnosed with endometrial cancer is 60 years. Based on 2014-2016 data from the National Cancer Institute, about 3.1% women will be diagnosed with uterine cancer during their lifetime. An estimated 772,245 women were living with uterine cancer in the United States in 2016. [5]

Many clinical trials are underway in all of these patient populations and recruiting patients to test novel therapies, approaches, and alleviate side effects of cancer therapies.

Estadiol. “Data from laboratory and epidemiologic studies support a relationship between endogenous hormones and the increased risk of several female cancers.” - Brown, DB, and Hankinson, SE. Steroids. 2015;99(Pt A):8-10.
A Study of Atezolizumab and Paclitaxel Versus Placebo and Paclitaxel in Participants With Previously Untreated Locally Advanced or Metastatic Triple Negative Breast Cancer (TNBC) (IMpassion131). ClinicalTrials.gov Identifier: NCT03312502. Hoffmann-La Roche, 201 international locations.

DS-8201a Versus T-DM1 for Human Epidermal Growth Factor Receptor 2 (HER2)-Positive, Unresectable and/or Metastatic Breast Cancer Previously Treated With Trastuzumab and Tanezum (DESTINY-Breast03). ClinicalTrials.gov Identifier: NCT03592110. Daiichi Sankyo, Inc./ Daiichi Sankyo Co., Ltd. & AstraZeneca, 120 international locations.


Melatonin Supplementation for Cancer-related Fatigue in Patients Receiving Radiotherapy. ClinicalTrials.gov Identifier: NCT02339276. Virginia Commonwealth University / National Cancer Institute, Virginia Commonwealth University/Massey Cancer Center, Richmond, Virginia.


Doxorubicin Hydrochloride and Cyclophosphamide Followed by Paclitaxel With or Without Carboplatin in Treating Patients With Triple-Negative Breast Cancer. ClinicalTrials.gov Identifier: NCT02488967. NRG Oncology/ National Cancer Institute, 1296 locations in the United States and Canada.

A Study Comparing Atezolizumab (Anti PD-L1 Antibody) In Combination With Adjuvant Anthracycline/Taxane-Based Chemotherapy Versus Chemotherapy Alone In Patients With Operable Triple-Negative Breast Cancer (IMpassion030). ClinicalTrials.gov Identifier: NCT04886716. Hoffmann-La Roche/ Breast International Group, Alliance Foundation Trials (AFT), Institut Jules Bordet/Clinical Trials Support Unit (UB/CTSU), & Frontier Science and Technology Research Foundation Inc (FS), 423 international locations.

Pembrolizumab is being studied in clinical trials for the treatment of both breast and endometrial cancers.


Standard of Care Therapy With or Without Stereotactic Radiosurgery and/or Surgery in Treating Patients With Limited Metastatic Breast Cancer. ClinicalTrials.gov Identifier: NCT02364557. NRG Oncology/ National Cancer Institute, 180 U.S. locations.

Hypofractionated Radiation Therapy After Mastectomy in Preventing Recurrence in Patients With Stage I-IIa Breast Cancer. ClinicalTrials.gov Identifier: NCT03414970. Alliance for Clinical Trials in Oncology/ National Cancer Institute & Canadian Cancer Trials Group, 748 locations in the United States and Canada.

DS-8201a in Pre-treated HER2 Breast Cancer That Cannot be Surgically Removed or Has Spreading Disease (DESTINY-Breast02). ClinicalTrials.gov Identifier: NCT03523585. Daiichi Sankyo, Inc./ Daiichi Sankyo Co., Ltd. AstraZeneca, 144 international locations.

A Study To Evaluate the Efficacy and Safety Of Atezolizumab or Placebo in Combination With Neoadjuvant Doxorubicin + Cyclophosphamide Followed By Paclitaxel + Trastuzumab + Pertuzumab In Early Her2-Positive Breast Cancer (IMpassion050). ClinicalTrials.gov Identifier: NCT03728679. Hoffman-La Roche/ Chugai Pharmaceutical, 84 international locations.

A Phase II Study Comparing The Efficacy Of Venetoclax + Fulvestrant Vs. Fulvestrant In Women With Estrogen Receptor-Positive, Her2-Negative Locally Advanced Or Metastatic Breast Cancer Who Experienced Disease Recurrence Or Progression During Or After CDK4/6 Inhibitor Therapy. ClinicalTrials.gov Identifier: NCT03584009. Hoffmann-La Roche, 43 international locations.

A Trial to Evaluate Efficacy and Safety of Ribociclib With Endocrine Therapy as Adjuvant Treatment in Patients With HR+/HER2- Early Breast Cancer (NAPA/LEC). ClinicalTrials.gov Identifier: NCT03701334. Novartis Pharmaceuticals/ Translational Research in Oncology, 149 international locations.


Study of Adagloxad Simolimunin (OBI-822) and OBI-821 Versus Placebo Treatment for High Risk Early Stage Triple Negative Breast Cancer Patients (TNBC) Following Neoadjuvant or Adjuvant Chemotherapy. ClinicalTrials.gov Identifier: NCT03562637. OBI Pharma, Inc., 92 international locations.


ENDOMETRIAL CANCER TRIALS

Lenvatinib in Combination With Pembrolizumab Versus Treatment of Physician’s Choice in Participants With Advanced Endometrial Cancer (MK-3475-775/E7080-0000-369 Per Merck Standard Convention [KEYNOTE-775]). ClinicalTrials.gov Identifier: NCT03317449. Eisai Inc. / Merck Sharp & Dohme Corp, 177 international locations.


Testing the Addition of the Immunotherapy Drug Pembrolizumab to the Usual Chemotherapy Treatment (Paclitaxel and Carboplatin) in Stage III-IV or Recurrent Endometrial Cancer ClinicalTrials.gov Identifier: NCT03914162. National Cancer Institute / NRG Oncology, Greater Baltimore Medical Center, Baltimore, Maryland.

Adjuvant Sequential & Concurrent CarboTaxol + Radiotherapy for High Risk Endometrial Cancer ClinicalTrials.gov Identifier: NCT03935256. Loyola University, Loyola University Medical Center Maywood, Illinois.

Health and Recovery Program in Increasing Physical Activity Level in Stage IA-IIIA Endometrial Cancer Survivors ClinicalTrials.gov Identifier: NCT03336793. Stanford University, 2 U.S. locations.

Mepotestone Acetate With or Without Pterostilbene in Treating Patients With Endometrial Cancer Undergoing Hysterectomy ClinicalTrials.gov Identifier: NCT03671811. City of Hope Medical Center / National Cancer Institute, City of Hope Medical Center, Duarte, California.

A Study of Durvalumab With or Without Tremelimumab in Endometrial Cancer ClinicalTrials.gov Identifier: NCT03015129. Memorial Sloan Kettering Cancer Center, 8 New Jersey and New York locations.

Enzalutamide, Carboplatin, and Paclitaxel in Treating Patients With Stage III-IV or Recurrent Endometrioid Endometrial Cancer ClinicalTrials.gov Identifier: NCT02684227. M.D. Anderson Cancer Center, 6 locations in Texas.

Cabozaftinib S-malate and Nivolumab in Treating Patients With Advanced, Recurrent or Metastatic Endometrial Cancer ClinicalTrials.gov Identifier: NCT03367741. National Cancer Institute, 34 locations in the United States and Canada.

Levonorgestrel-Releasing Intrauterine System With or Without Everolimus in Treating Patients With Atypical Hyperplasia or Stage IA Grade 1 Endometrial Cancer ClinicalTrials.gov Identifier: NCT02397083. National Cancer Institute / National Cancer Institute Center, 10 U.S. locations.

Radiation Therapy With or Without Cisplatin in Treating Patients With Recurrent Endometrial Cancer ClinicalTrials.gov Identifier: NCT04092778. Gynecologic Oncology Group / National Cancer Institute, 409 locations in the United States and Canada.

Phase II Study of Atezolizumab + Bevacizumab in Endometrial Cancer ClinicalTrials.gov Identifier: NCT03526432. University of Oklahoma / Genentech, Inc., Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma.

Single Agent ONC201 in Recurrent or Metastatic Endometrial Cancer ClinicalTrials.gov Identifier: NCT03899499. Fox Chase Cancer Center / Oncocutects, Inc., Fox Chase Cancer Center, Philadelphia, Pennsylvania.


Pembrolizumab in Ultramutated and Hypermutated Endometrial Cancer ClinicalTrials.gov Identifier: NCT02899793. Yale University / Merck Sharp & Dohme Corp, Yale New Haven Hospital, New Haven, Connecticut.

A Phase 2 Study of Mirtexitsumab Soravtansine (IMGN853) and Pembrolizumab in Endometrial Cancer (EC) ClinicalTrials.gov Identifier: NCT03835819. Dana-Farber Cancer Institute / ImmunoGen, Inc. & Merck Sharp & Dohme Corp., 2 U.S. locations.

A Study of Avelumab in Patients With MSS, MS-H and POLE-mutated Recurrent or Persistent Endometrial Cancer ClinicalTrials.gov Identifier: NCT03835819. Dana-Farber Cancer Institute / Eli Lilly and Company, 3 U.S. locations.

Rucaparib vs Placebo Maintenance Therapy in Metastatic and Recurrent Endometrial Cancer ClinicalTrials.gov Identifier: NCT03675893. Dana-Farber Cancer Institute / Eli Lilly and Company, 3 U.S. locations.

For references visit cancernetwork.com/BreastEndTrials

Visit our site for more news and expert insight on breast and endometrial cancers.
In the randomized (2:1), double-blind, placebo-controlled, multicenter trial, patients were randomized to cabozantinib 60 mg orally once daily (n=470) or placebo (n=237) until the time of disease progression or unacceptable toxicity. Investigators also measured the primary endpoint OS. PFS and ORR, assessed using RECIST 1.1. Cabozantinib use was associated with a median OS of 10.2 months (95% CI: 9.1-12.0) vs 8 months (95% CI: 6.8-9.4) for those receiving placebo (HR 0.76; 95% CI: 0.63, 0.92; P = .0049).

Median PFS was 5.2 months (4.0-5.5) in the cabozantinib arm compared with 1.9 months (1.9-1.9) in the placebo arm (HR 0.44; 95% CI: 0.36, 0.52; P < .001). The ORR was 4% (95% CI: 2.3, 6.0) in those taking cabozantinib vs 0.4% (95% CI: 0.1, 0.7) in those taking placebo.[7]

Grade 3 or 4 adverse events were higher in patients taking cabozantinib (68%) than in those taking placebo (36%).

Authors of the CELESTIAL trial concluded that “Among patients with previously treated advanced hepatocellular carcinoma, treatment with cabozantinib resulted in longer overall survival and progression-free survival than placebo. The rate of high-grade adverse events in the cabozantinib group was approximately twice that observed in the placebo group.”[8]

**Fusion and complicate prescribing. With the possibility of new FDA indications, current off-label utilization based on emerging data, and investigational combinations comes the potential for more nuances to arise with the use of venetoclax in practice. Although much of the information outlined in this brief review is covered within the prescribing information, multidisciplinary collaboration for venetoclax dosing has, at least in my practice, ensured safe, effective, and patient-friendly application of this therapeutic option.**

**TABLE 2: Dose Ramp-Up Schemas for Venetoclax in AML[1]**

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2</th>
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<td>100 mg</td>
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¹ Including fluconazole, isavuconazole.
² Includes posaconazole, voriconazole.
³ 70-mg dose would require either 7x10 mg tablets or 1x50 mg tablet + 2x10 mg tablets.

AML = acute myeloid leukemia.

**FDA Approved Uses of Cabozantinib**

Continued from page 364

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

For references visit cancernetwork.com/OP-Venetoclax

For references visit cancernetwork.com/ND-Cabozatinib