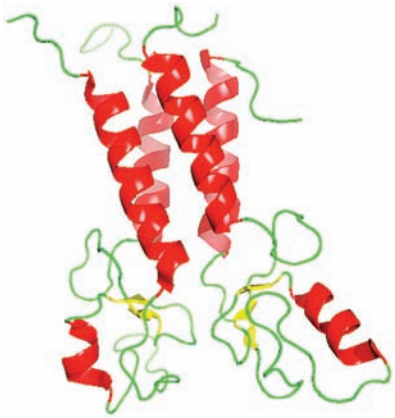

Structure of BRCA1

whom there is no previous targeted therapy approved."

The drug's approval was based on the phase III OlympiAD trial, which enrolled 302 patients with HER2-negative, metastatic breast cancer and germline *BRCA* mutations (N Engl J Med 2017;377:523–33). Patients were randomly assigned to receive olaparib or the physician's chemotherapy of choice in a 2:1 ratio. Median progression-free survival was significantly longer among those treated with olaparib compared with chemotherapy (7 months vs. 4.2 months, respectively). In addition, the response rate for the PARP inhibitor was more than double that for chemotherapy: 59.9% versus 28.8%, respectively.

Patients also tolerated olaparib better than chemotherapy and reported a higher quality of life, says Mark Robson, MD, of Memorial Sloan Kettering Cancer Center in New York, NY, and OlympiAD's lead investigator. Although previous studies found that olaparib could, in rare cases, lead to hematologic malignancies such as myelodysplastic syndrome, Robson says, that didn't occur in the OlympiAD trial.

However, the drug didn't show an overall survival (OS) benefit. Median OS was slightly more than 19 months in both groups.

Assessing OS was difficult in this trial partly "because we don't control what treatment people get after they progress on the study," Robson says. In fact, patients in the chemotherapy group were more likely to be later treated with a PARP inhibitor or platinum-based chemotherapy than those in the olaparib group. That could partially explain the lack of difference in OS, Robson says.

Patients with breast cancer who have germline *BRCA1* or *BRCA2* mutations represent only about 5% of all breast cancer cases, and those with metastatic disease are an even more limited group. Despite the small numbers, Robson is hopeful that olaparib's approval lays the groundwork for further expanding its use. A clinical trial testing olaparib in patients with early-stage *BRCA*-mutated breast cancer is under way, Robson says, adding that olaparib could also prove to be effective even in those without inherited *BRCA* mutations but whose tumors have acquired a BRCA1 or BRCA2 deficiency. *–Rachel Tompa* ■

Celgene Targets Blood Cancers with Major Buys

Celgene inked two multibillion dollar deals in January, buying Seattle, WA–based Juno Therapeutics, a developer of chimeric antigen receptor (CAR) T-cell therapies, and Impact Biomedicines of San Diego, CA, which is testing a JAK2 inhibitor.

One impetus for the acquisitions is the pending arrival of generic competition for Celgene's most profitable drug, lenalidomide (Revlimid). Usually prescribed for the treatment of multiple myeloma, lenalidomide generated global revenue of nearly $7 billion in 2016. To drive new growth, Celgene announced on January 7 that it will buy Impact for $1.1 billion up front and another $5.9 billion in potential milestone payments. Two weeks later, plans to take over Juno for approximately $9 billion were announced.

"They're staring down Revlimid's patent expiry in a couple of years," says David Nierengarten, PhD, head of health-care equity research at Wedbush Securities in San Francisco, CA. The acquisition of Impact in particular "shows that they were really looking for potential near-term revenue opportunities that can fill that hole."

Impact's JAK2 inhibitor fedratinib will likely be the first financial stopgap. Phase III trial data showed that 35% to 40% of patients with previously untreated myelofibrosis taking the drug experienced a reduction in spleen volume, compared with 1% of those taking a placebo (JAMA Oncol 2015;1:643–51). A phase II single-arm trial of patients with the rare bone marrow cancer who did not respond to the JAK1/2 inhibitor ruxolitinib (Jakafi; Incyte) had even better outcomes, with 55% displaying a splenic response (Lancet Haematol 2017;4:e317–24).

A regulatory filing for fedratinib is anticipated later this year. If approved, analysts believe the drug could generate sales of up to $1 to $2 billion annually. The real moneymaker, though, could be Juno's pipeline of CAR T and T-cell receptor therapies now in early-stage trials.

Gilead Sciences, of Foster City, CA, made a similar bet on CAR T-cell therapies last August when it spent nearly $12 billion for Kite Pharma in Santa Monica, CA. Then, on January 23, the company helped bankroll Tmunity Therapeutics, spun off from the University of Pennsylvania in Philadelphia, which counts CAR T-cell pioneer Carl June, MD, among its founders.

The Kite buyout started to pay off in October when the anti-CD19 CAR T-cell therapy axicabtagene ciloleucel (Yescarta) earned FDA approval for patients with refractory or relapsed large B-cell lymphoma.

None of Juno's candidates are as far along, but the company does have a variety of promising agents, at least eight of which are in clinical development for a range of hematologic and solid cancers. These include an anti-BCMA CAR T-cell therapy for multiple myeloma that supplements Celgene's only prior CAR T agent, bb2121, under development with bluebird bio.

However, the lead asset in Juno's collection is JCAR017 (lisocabtagene maraleucel), an anti-CD19 CAR T-cell therapy that the company pushed forward after halting the development of JCAR015 following five deaths in 2016. With that setback, Juno fell behind Kite/Gilead and Novartis, the other company with an approved CAR T-cell therapy. However, Nierengarten says that might not be detrimental.

Nierengarten cites the difficulties Kite/Gilead has faced in securing reimbursement for axicabtagene ciloleucel, and he suggests Celgene could benefit from having a rival address regulatory hurdles first—especially if, as many observers suspect based on phase I data, JCAR017 proves to be best-in-class.

If JCAR017 garners approval next year, as anticipated, Celgene "can come in likely after the reimbursement paradigm has been mostly established and, hopefully, launch a safer and more efficacious product," Nierengarten says. –*Elie Dolgin* ■

Mutation Burden Predicts Anti–PD-1 Response

The most comprehensive report to date, covering 27 cancer types, reveals that the more mutations tumors carry, the more likely they are to respond to anti–PD-1 or anti–PD-L1 treatments (N Engl J Med 2017;377:2500–1). The results strengthen the case for using tumor mutation burden as a biomarker of response and may help researchers choose which cancer types to treat next with the drugs.

Several studies have found that in certain cancers, such as melanoma and non–small cell lung cancer, checkpoint inhibitors tend to work better in patients with a high tumor mutation burden. "To our knowledge, nobody had looked across every single tumor type," says Mark Yarchoan, MD, of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins in Baltimore, MD.

To that end, Yarchoan and his colleagues scoured the literature for studies that recorded objective response rates (ORR) to PD-1 inhibition. After obtaining data for 27 tumor types, including pancreatic, ovarian, breast, and renal cell cancers, they determined the median mutation burden for each type based on genome sequencing of 100,000 tumors performed by Foundation Medicine of Cambridge, MA.

The correlation between mutation burden and ORR held for most of the cancer types, Yarchoan and colleagues found. "We suspected there would be an association, but we were surprised by its strength," he says. Overall, tumor mutation burden explained 55% of the variation in ORRs.

The outliers, in which the results of therapy didn't track with mutation load, also proved informative, Yarchoan says. For example, Merkel cell carcinoma and renal cell carcinoma (RCC) showed disproportionately high response rates, given their moderate number of mutations. These tumor types may stand out because the antigens produced by the virus that triggers Merkel cell carcinoma are immunogenic, as are the genome deletions and insertions that are characteristic of RCC.

In contrast, colorectal cancer with mismatch repair proficiency was much less responsive than its tumor mutation burden would suggest. Why PD-1 inhibition performs so poorly in this tumor type remains unclear, Yarchoan says.

To help determine which tumors to treat with anti–PD-1 inhibitors in future clinical trials, the team also forecast treatment responses for malignancies in which checkpoint inhibitors haven't been tested. Their correlation formula predicted ORRs of 40.1% for basal cell carcinoma and 20.6% for sarcomatoid carcinoma of the lung, suggesting that these cancers might respond well to PD-1 inhibition.

However, the low ORRs for pilocytic astrocytoma and small-intestine carcinoid, both of which were predicted to be less than 5%, suggest that anti–PD-1 or anti–PD-L1 treatments should be studied in combination with other agents.

"We hope that this is an important step toward the possibility of personalized immunotherapy," says Yarchoan.

PD-L1 expression remains the standard criterion for receiving anti–PD-1 therapy. However, the new findings provide more evidence that tumor mutation burden is "a truly valuable biomarker," says Aaron Goodman, MD, of the University of California, San Diego, who wasn't connected to the research. If mutation burden does gain acceptance, it won't replace PD-L1 but will supplement it, he notes. "There is still a place for PD-L1 testing, and it may be most critical in patients with low and intermediate levels of mutations." –*Mitch Leslie* ■

For more news on cancer research, visit *Cancer Discovery* online at http://cancerdiscovery.aacrjournals.org/content/early/by/section.

NOTED

Postmenopausal women with ER-positive breast cancer who have high intratumor heterogeneity of estrogen receptors have twice the risk of death from the disease as patients with low intratumor heterogeneity, researchers found. The study followed 573 women diagnosed between 1976 and 1990 who received either tamoxifen or no systemic therapy after surgery (J Natl Cancer Inst 2018 Jan 19 [Epub ahead of print]).

The American Cancer Society says that **the cancer mortality rate decreased by 26% between 1991 and 2015**—roughly 2.3 million fewer deaths—a change largely attributed to declines in mortality for lung, breast, and prostate cancers (CA Cancer J Clin 2018;68:7–30). The overall mortality rate, however, varied by race: In 2015, it was 14% higher for blacks than for whites.

Alcohol, in the form of ethanol, damages DNA in stem cells in mice, resulting in a rearrangement of chromosomes and irreversible changes to DNA sequences, according to a recent study (Nature 2018;553:171–7). Researchers also found that mice lacking the aldehyde dehydrogenase enzyme ALDH2 that normally breaks down acetaldehyde, a byproduct of ethanol, incurred four times as much DNA damage as control mice.

A gene expression profile test that helps predict the recurrence of breast cancer, **Oncotype DX, may be less cost-effective under real-world conditions than originally thought** (J Clin Oncol 2018 Jan 8 [Epub ahead of print]). The test was previously shown to be cost-effective under ideal conditions. But researchers found that in community practice, the cost-effectiveness ratio for testing versus usual care without testing was $188,125 per quality-adjusted life-year (QALY), almost five times the ratio of $39,496 per QALY under ideal conditions.

Researchers identified a possible biomarker of response to anti–PD-1 therapy in patients with melanoma. They conducted a detailed analysis of the immune cell subsets in the peripheral blood of patients with stage IV melanoma before and after 12 weeks of treatment (Nat Med 2018 Jan 8 [Epub ahead of print]). They found that the frequency of $CD14^{+}CD16^{-}HLA\text{-}DR^{hi}$ monocytes was a strong predictor of treatment success.