suppression, with the indoximod–pembrolizumab from trials, Zakharia said. The ORR in these patients being excluded to standard treatment and often results has been shown to be less responsive patients with ocular melanoma, which been compared head to head.

However, the two regimens have not ORR seen with the indoximod combination. ORR was 33%, much lower than the 52% trial, which tested pembrolizumab alone in this instance, especially in cancer," says Petra Kaufmann, MD, director of the Division of Clinical Innovation Centers: one at Johns Hopkins and Tufts Universities, one at the University of Utah, and one at Duke University and Vanderbilt University Medical Center. As with the NCI CIRB, researchers can opt to use one of the centers’ IRBs. Alternatively, they can meet the new NIH mandate by picking any other IRB of record to review a particular trial, such as one at an institution participating in that clinical trial, or, for cancer trials, the NCI. Many cancer researchers applaud the effort to bring ethics reviews for every trial under one umbrella. “When you have a well-designed, well-constructed, multicenter clinical study with a model consent form that’s been carefully crafted, the likelihood that a local IRB makes any substantive changes to either the protocol or the consent form is extremely small,” says Richard Schilsky, MD, chief medical officer of the American Society of Clinical Oncology.

At the AACR Annual Meeting 2017, Yousef Zakharia called for a phase III trial of anti-PD-1 therapy with the IDO pathway inhibitor indoximod for advanced melanoma.

investigator Yousef Zakharia, MD, assistant professor of internal medicine at the University of Iowa in Iowa City, who presented the findings on April 4. “These robust data reinforce the need for development of a phase III trial of anti-PD-1 therapy with indoximod for advanced melanoma.”

The IDO pathway is involved in suppressing immune responses when appropriate—such as to prevent fetal rejection—by degrading tryptophan and increasing the supply of the metabolite kynurenine, which triggers immunosuppression, Zakharia explained. Tumors can hijack this pathway to evade immune control.

Instead of inhibiting IDO itself, however, indoximod is a tryptophan mimetic that directly influences antigen-presenting cells, such as dendritic cells and macrophages, relieving their immunosuppressive features triggered by IDO-induced low tryptophan levels.

Preliminary data from the trial suggest that blocking both the IDO and PD-1 pathways may be more effective than PD-1 inhibition alone, Zakharia added. For example, in the phase III KEYNOTE-006 trial, which tested pembrolizumab alone in patients with advanced melanoma, the ORR was 33%, much lower than the 52% ORR seen with the indoximod–pembrolizumab combination rises to 59% if only patients with cutaneous and nonocular melanomas are included in the analysis.

“If verified, these data suggest that [combining IDO and PD-1 inhibitors] may be a strategy for enhancing the likelihood of benefit in this disease,” said Louis Weiner, MD, director of Georgetown Lombardi Comprehensive Cancer Center in Washington, DC. “It has the potential to be a very important milestone in the development of combinatorial strategies, akin to the combination of multiple checkpoint inhibitors.”

Medical Centers Sign On to Single IRB Model

The NIH has taken a major step toward ensuring that all multisite trials funded by the agency, including those involving patients with cancer, no longer have duplicative and often superfluous oversight.

The NIH’s National Center for Advancing Translational Sciences (NCATS) announced last month that all 64 medical research institutions funded through the agency’s flagship Clinical and Translational Science Awards (CTSA) program—a $500 million per year effort to move biomedical discoveries into the clinic—had agreed to a legal structure for ceding reviews of human studies conducted at multiple sites to a single Institutional Review Board (IRB). Nearly 100 other medical centers in the United States have also signed on to NCATS’s SMART IRB initiative.

Short for “Streamlined, Multisite, Accelerated Resources for Trials,” the SMART IRB platform is aimed at reducing administrative red tape and ensuring consistency in study plans and consent forms across all sites involved in a study. “Time can be life in this instance, especially in cancer,” says Petra Kauffman, MD, director of both the Division of Clinical Innovation and the Office of Rare Diseases Research at NCATS. “We want to move away from that multiple review process to a single IRB.”

Streamlining IRB oversight isn’t an entirely new idea. For more than 15 years, NCI-funded trials have had the option of going through the agency’s Central Institutional Review Board (CIRB). Initially developed for phase III adult oncology trials, the CIRB has expanded to include pediatric, early-phase, and prevention trials.

The NCI review board has yielded considerable savings, in both time and money, for participating institutions. However, CIRB participation has always been voluntary, and investigators of NCI-sponsored trials can choose to go through their own institution’s oversight board instead. Beginning in September, the NIH is scheduled to enact a policy that all agency-funded multicenter clinical studies will have to abide by one IRB, and smoothing that transition is a task that’s fallen to NCATS (available at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-094.html).

In addition to the SMART IRB platform—which Kaufmann describes as something akin to a treaty or general framework—NCATS is also copying the NCI model and offering centralized IRB services of its own for CTSA-funded investigators. Last year, the center funded three Trial Innovation Centers: one at Johns Hopkins and Tufts Universities, one at the University of Utah, and one at Duke University and Vanderbilt University Medical Center. As with the NCI CIRB, researchers can opt to use one of the centers’ IRBs. Alternatively, they can meet the new NIH mandate by picking any other IRB of record to review a particular trial, such as one at an institution participating in that clinical trial, or, for cancer trials, the NCI.

Many cancer researchers applaud the effort to bring ethics reviews for every trial under one umbrella. “When you have a well-designed, well-constructed, multicenter clinical study with a model consent form that’s been carefully crafted, the likelihood that a local IRB makes any substantive changes to either the protocol or the consent form is extremely small,” says Richard Schilsky, MD, chief medical officer of the American Society of Clinical Oncology.
However, Bruce Gordon, MD, a pediatric hematologist-oncologist and executive chairman of the University of Nebraska Medical Center’s IRB in Omaha, worries that the NIH is rushing to implement its single IRB policy—which had been slated to go into effect in May but has been pushed back to September 25—without giving institutions the time to figure out how best to integrate off-site IRBs with other considerations of their Human Research Protection Program, such as biosafety, conflicts of interest, and patient privacy.

“With that said, I’m in favor of cooperative review and single-IRB models,” adds Gordon, who once chaired the NCI’s pediatric CIRB. “For the most part, it’s going to be better than the system we have now, but it’s not a panacea, and it does require thinking about these other considerations.” —Elie Dolgin

**Exploiting Defective DNA Repair in IDH-Mutant Cancers**

Findings from a preclinical study suggest a better strategy for treating tumors with IDH1 or IDH2 mutations: taking advantage of their vulnerability to PARP inhibition, rather than suppressing the function of altered IDH1/2. The data were presented on April 4 by Ranjit Bindra, MD, PhD, of Yale Cancer Center in New Haven, CT, during the American Association for Cancer Research Annual Meeting 2017 in Washington, DC.

Neomorphic IDH1/2 mutations completely rewire part of the citric acid cycle, resulting in the conversion of α-ketoglutarate (α-KG) to 2-hydroxyglutarate (2-HG), which competitively inhibits α-KG–dependent enzymes downstream. Because 2-HG is thought to be an oncometabolite driving cell proliferation, much effort has been spent on developing drugs that block its production by selectively inhibiting mutant IDH1/2. “The idea is that suppressing 2-HG will cause rapid cell-cycle arrest and halt tumor progression,” Bindra explained. “This ‘oncometabolite hypothesis’ has been the basis for nearly all trials evaluating IDH inhibitors in gliomas, about 70% of which have IDH1/2 mutations.”

Investigational IDH1/2 inhibitors have been described as potentially having a “broad, profound impact on the glioma landscape,” Bindra noted, but as a clinician specializing in this disease, he’s unimpressed by the efficacy data so far. The agents being evaluated have had “nearly zero effect against aggressive, high-grade gliomas,” he said, and have yielded no regression of low-grade tumors, only stable disease.

Exploiting 2-HG–induced defective homologous recombination in IDH1/2-mutant tumors, and their resulting dependence on PARP for DNA repair, may be a better therapeutic strategy, Bindra suggested. His team recently reported this “BRCAness” phenotype in a variety of IDH1/2-mutant preclinical models (Cancer Discov 2017;7:OF4).

“We’ve observed marked PARP inhibitor sensitivity across these models, both in vitro and in vivo,” he said. “We also have unpublished data showing significant synergy with combinations of different DNA-repair blockers [PARP plus ATR inhibition], or when [DNA-damaging] platinum chemotherapy is added to PARP inhibition.”

Overall, there is now “substantial” preclinical evidence—from Bindra’s group and others—that IDH1/2 inhibitors not only are ineffective against tumor cell growth, but rapidly reverse the cells’ “BRCAness” phenotype, he said. As such, these agents are unlikely to be a home run, at least in gliomas. “We may need to rethink the ‘oncometabolite hypothesis’ and, in IDH-mutant tumors, capitalize on targeting defective DNA repair instead, which we know to be a powerful, cytotoxic approach.”

Bindra and his colleagues will soon launch a multicenter phase II study, sponsored by the NCI, to evaluate the PARP inhibitor olaparib (Lynparza; AstraZeneca) in patients with various IDH1/2-mutant tumors, including gliomas, cholangiocarcinomas, and a small subset of breast cancers. Patients in this “all-comers” basket trial will be identified using the NCI-developed Ion AmpliSeq Cancer Hotspot Panel.

The preclinical data from Bindra’s team could have “revolutionary implications” for treating IDH1/2-mutant cancer, noted Louis Weiner, MD, director of the Georgetown Lombardi Comprehensive Cancer Center in Washington, DC. “It’s intriguing that the reflex approach within oncology—focusing on what’s assumed to be a driver mutation—may be exactly the wrong thing to do here. Confirming these findings in the basket trial could provide an interesting twist on how we interpret [tumor] molecular profiles in the future.” —Alissa Poh

**Four Groups Win CRUK “Grand Challenge”**

Cancer Research UK (CRUK) has announced the winners of its first “Grand Challenge” competition, in which investigators from around the world were invited to propose novel approaches to unsolved problems in cancer research. Based on the quality of the entries, the judges awarded between £15–£20 million, or $19–$25 million, over 5 years to each of four winning teams, instead of one as was originally planned.

“We were bowled over by the insight, creativity, and advances these teams had already made in putting their proposals together,” says Edward Harlow, PhD, professor of biological chemistry and molecular pharmacology at Harvard Medical School in Boston, MA, and a member of the Grand Challenge advisory panel that reviewed the proposals. “They offered us new ways of thinking about problems in cancer that were quite exhilarating.”

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