metastatic castration-resistant prostate cancer (CRPC). These men all had genetic aberrations in various DNA damage repair genes, notably BRCA2 and ATM.

The trial data were reported by Joaquin Mateo, MD, a medical oncologist at The Institute of Cancer Research in the United Kingdom, at the American Association for Cancer Research Annual Meeting 2015 in Philadelphia, PA, April 18–22.

Olaparib operates on the concept of synthetic lethality: Cancer cells lacking BRCA1 or BRCA2 depend instead on PARP-regulated DNA repair, and are hypersensitive to PARP suppression.

“Preclinical models of prostate cancer have shown that mutations in other DNA damage repair genes also induce sensitivity to PARP inhibition,” Mateo said. “This study was about proving that if you have aberrations in any of these genes, not just BRCA, the effect is the same—a good response to olaparib. It’s provided the first data supporting molecular stratification for prostate cancer patients.”

TOPARP-A enrolled 50 patients with advanced CRPC, none having received PARP inhibitor therapy, but all having previously been given drugs such as the CYP-17 inhibitor abiraterone (Zytiga; Janssen Biotech), the androgen receptor antagonist enzalutamide (Xtandi; Medivation), and taxane chemotherpay. Sixteen of 49 evaluable patients responded to olaparib—four for over a year, which Mateo considered “quite a big achievement for a late-stage cancer population.” Five study patients are still being treated with olaparib.

Next-generation sequencing of tumor samples from the 16 responders revealed defects across a panel of DNA damage repair genes, including FANCA, CHEK2, PALB2, and HDR2. Mutations in BRCA2 and ATM were the most common. Interestingly, three of five patients with ATM defects had germline mutations, “something not well described in prostate cancer before,” Mateo said. He also noted that the two patients with PALB2 and HDR2 aberrations, respectively, represented the first proof of preclinical observations that both of these loss-of-function mutations sensitize tumor cells to olaparib.

The main side effects seen with olaparib were anemia and fatigue; overall, the drug was much better tolerated by these patients, with none of the gastrointestinal effects observed in ovarian cancer studies.

Mateo and his group are currently enrolling patients who have the relevant DNA damage repair gene mutations in TOPARP-B, the second stage of this trial, hoping to validate their initial findings.

“We’ve gotten good mileage out of androgen receptor–targeting drugs, and my prediction is that we’ll see more drug development around new targets in coming years,” said William Nelson, MD, PhD, director of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins in Baltimore, MD, who moderated the press conference at which the results were presented.

“I think we’ll also see more studies trying to identify other molecularly distinct subsets of prostate cancer patients, and attempts to develop drugs for these groups,” Mateo added. □

NCI Posts New “Provocative Questions”

The NCI has earmarked another $40 million over the next 2 years for its Provocative Questions (PQ) Initiative, aimed at funding neglected or understudied areas of cancer research that relate to gaps in current knowledge or address unresolved questions.

The agency has extended the application window from 1 to 2 years and winnowed the list of questions down to 12 from the more than 20 in the previous Requests for Applications (RFA) issuances published since 2011, says Emily Greenspan, PhD, PQ program director in the NCI’s Center for Strategic Scientific Initiatives. The latest RFA specifies four possible deadlines: June 29 and October 29 of this year, and June 29 and October 28 in 2016. Details are available at http://provocativequestions.nci.nih.gov.

“We’ve learned that the longer period of time is important to give applicants time to carefully consider their applications rather than trying to fit what they’re already doing into one of the questions,” says Greenspan. “Our hope is that they will now have time to put together an entirely new application.” The NCI intends to commit $15 million per year to fund 30 to 40 R01 awards for well-developed projects, and another $5 million per year to fund 15 to 20 R21 awards for exploratory or developmental projects in fiscal years 2016 and 2017. Project periods cannot exceed 5 years for R01 awards and 2 years for R21 awards.

The PQs are not intended to represent the full range of priorities in cancer research but to highlight important areas that may not have received sufficient attention, says Greenspan. To create the new list of questions, the NCI held a series of workshops last fall to get input from the extramural scientific community. Seven questions grew out of those sessions, while the other five were carried over from previous years.

“The questions span the whole gamut of cancer research, from prevention, prognosis, and treatment to health disparities and clinical effectiveness,” says Greenspan. “They are specific but lend themselves to a variety of approaches.”

Successful applicants from previous years have already published some results related to individual PQs. For example, a team funded in 2011 and led by Maja Oktay, MD, PhD, at the Albert Einstein College of Medicine in New York, NY, addressed the PQ, “Given the difficulty of studying metastasis, can we develop new approaches, such as engineered tissue grafts, to investigate the biology of tumor spread?”

Oktay developed an approach to study the invasion of cancer cells into blood vessels, or intravasation, which includes an intravasation assay, optimized isolation of cancer cells from patient samples, and multiphoton imaging to explore cellular interactions that lead to intravasation. Her studies show that intravasation can be prevented in human breast cancer.
by blocking signaling between cancer cells and macrophages. The findings lay a foundation for developing therapeutic targets to prevent metastasis of multiple breast cancer subtypes (Sci Signal. 2014;7:ra112).

Another study funded in 2011 relating to the PQ “How does obesity contribute to cancer risk?” investigated whether dietary fat can be directly taken up by cancer cells to be remodeled into complex lipids which can, in turn, stimulate cancer malignancy and fuel tumorigenicity. Research led by Daniel Nomura, PhD, at the University of California, Berkeley, led to findings suggesting a novel mode of glycolytic control in cancer cells that may promote key oncogenic lipid signaling pathways that drive cancer (ACS Chem Biol 2014;9:1340–50).

“Some of the researchers are producing data that is directly in line with what the PQs are getting at,” says Greenspan. “That’s important because these questions are areas where we know there are gaps in our research portfolio.”

**Immunotherapy Slows TNBC Progression**

An investigational immunotherapy that blocks the interaction between two proteins that inactivate the immune system is showing promise for treating triple-negative breast cancer (TNBC), according to preliminary results from a phase I trial announced at the American Association for Cancer Research Annual Meeting 2015, held in Philadelphia, PA, April 18–22.

The trial is evaluating the experimental monoclonal antibody MPDL3280A (Genentech) in a variety of advanced solid tumors. MPDL3280A blocks the binding of PD-L1, expressed on many cancer and immune cells, to the PD-1 receptor. Interaction between the two proteins interferes with the ability of T cells to mount an immune response.

The trial enrolled 54 patients with previously treated metastatic TNBC, 21 of whom had PD-L1–positive disease, defined as having PD-L1 on 5% or more of immune cells that infiltrate the tumor. Among those 21 patients, there was a 24-week progression-free survival rate of 27% and an objective response rate of 19% after treatment with MPDL3280A, said Leisha Emens, MD, PhD, a member of the Cancer Immunology and Breast and Ovarian Cancer Programs at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins in Baltimore, MD, at a news conference. After 56 weeks, the median duration of response had not yet been reached.

“Importantly, these responses [in the PD-L1–positive group] included two complete responses and two partial responses, and three of the four responses were ongoing at the time of data cutoff,” said Emens. “Moreover, there were three patients who appeared to experience a phenomenon known as pseudoprogression, which is an atypical response pattern seen in some patients treated with this class of agents.”

The patients who experienced pseudoprogression showed durable shrinkage of their target lesions while developing new lesions at other sites, explained Emens. However, the patients remained clinically well and eventually showed regression of the secondary lesions, suggesting that the emergence of other lesions does not necessarily call for an immediate change in therapy, she said.

TNBC, for which chemotherapy is the only approved treatment option, may be particularly susceptible to immunotherapy, said Emens. It has a higher mutation rate and a higher number of tumor-infiltrating lymphocytes relative to other breast cancer subtypes, both of which help boost the immune response. Emens noted that greater numbers of tumor-infiltrating lymphocytes have been associated with better clinical outcomes in patients with TNBC.

Based on the promising results, Genentech’s parent company, Roche Holding AG, announced last week that it plans to proceed directly to a phase III trial for MPDL3280A later this year. The FDA has already designated the drug as a Breakthrough Therapy for PD-L1–positive advanced non–small cell lung cancer and metastatic bladder cancer.

“Further evaluation of MPDL3280A is ongoing in this study in both PD-L1–expressing and PD-L1–nonexpressing patients,” said Emens. “We are now preparing to launch a global randomized trial testing MPDL3280A in combination with Abraxane (nab-paclitaxel; Celgene) as first-line therapy for patients with metastatic triple-negative breast cancer.”

**CTCs Could Shorten Drug Trials**

As cancer progresses, tumor cells dissociate and enter the bloodstream. Considered a “liquid biopsy,” these circulating tumor cells (CTC) can show how a patient’s cancer evolves and responds to treatments. A recent study highlights a new prognostic utility: Combined with another blood marker, CTC counts could serve as a surrogate predictor of survival, according to a phase III trial in metastatic castration-resistant prostate cancer (J Clin Oncol 2015;33:1348–55).

Surrogate measures are sorely needed. So many therapies have proven effective for advanced prostate cancer that it’s hard for trials of new drugs to show a survival benefit, running the risk that effective therapies may not get approved. “You’d like to get drugs approved faster,” says the study’s lead author Howard Scher, MD, chief of the genitourinary oncology service at Memorial Sloan Kettering Cancer Center in New York, NY.

Disease progression can be tracked by PSA tests, and bone scans can reveal if cancer has spread. However, PSA changes can be misleading, and bone
NCI Posts New "Provocative Questions"

Cancer Discovery 2015;5:569-570. Published OnlineFirst April 30, 2015.

Updated version
Access the most recent version of this article at:
doi:10.1158/2159-8290.CD-NB2015-062

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.