Highlights From the ASCO Annual Meeting—New Approaches to Cancers of the Blood, Brain, Lung, and More

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At this year’s American Society of Clinical Oncology (ASCO) annual meeting, which took place in early June, new research ranged from novel treatments for various cancers to fecal transplants for patients resistant to immunotherapy. For an inside look, JAMA Deputy Editor and JAMA Oncology Editor Mary (Nora) L. Disis, MD, who is also a professor of medicine at the University of Washington and a member of the Fred Hutchinson Cancer Center, spoke with Kimmie Ng, MD, MPH. Ng chaired the meeting’s Scientific Program Committee and is the associate chief of the Division of Gastrointestinal Oncology at Dana-Farber Cancer Institute. The following conversation has been edited for clarity and length.

DR DISIS: You were able to choose the 4 plenary session abstracts, and this year’s theme of the meeting was “Partnering With Patients: The Cornerstone of Cancer Care and Research.” How did these abstracts fit together for that theme?

DR NG: Many of them showcased advances in targeted therapies and immunotherapies that can often delay the need for treatments that may have more adverse events, such as radiation or chemotherapy. Some were de-escalation trials where certain modalities of treatment could be completely eliminated for better tolerability. And they showed how cooperation and publicly funded research can really come together to significantly change the standard of care for our patients.

DR DISIS: Let’s start with the first abstract, which was the INDIGO trial for brain cancer. Tell us a little bit about that study.

DR NG: This was a randomized trial that looked at patients who had IDH [isocitrate dehydrogenase] 1- or IDH2-mutated low-grade gliomas. These tumors, although low grade, are not currently curable and inevitably lead to infiltration of the brain and significant neurologic deficits as well as symptoms including seizures. So this trial tested a novel targeted therapy called vorasidenib, which is an IDH1 and IDH2 [enzyme] inhibitor in patients with low-grade gliomas who had surgery only as their prior therapy and who their investigators didn’t think necessarily needed to go on to receive radiation or chemotherapy right away.

These patients were randomized 1 to 1 to receive either the vorasidenib at 40 mg once a day or a placebo. The primary end point was progression-free survival, and the investigators also looked at an important end point called time-to-next-treatment intervention. What they found was that the vorasidenib arm resulted in significantly prolonged and improved progression-free survival and a significantly longer time to the next required treatment intervention. This is hugely significant because if we can delay the need for treatments like radiation or chemotherapy for this group of patients with an incurable tumor, that is a significant advance for their quality of life.

DR DISIS: I agree. I think it’s important to note that these grade 2 gliomas are mostly astrocytomas and oligodendrogliomas, not glioblastomas. These are the tumors found in patients who are younger than 50 years old. And all these patients had surgery only prior to starting the treatment, so they were able to avoid radiation therapy. That’s highly morbid in this patient population, isn’t it, Dr Ng?

DR NG: It is very morbid. It can affect cognitive ability and lead to other adverse events, and the chemotherapy is not tolerated easily. In contrast, vorasidenib was tolerated quite well among patients. The most common toxicities were elevations in liver function tests. Again, this represents a huge advance for these patients, both in terms of prolonging their progression-free survival and their quality of life.

DR DISIS: I understand that to get an overall survival end point in this population will take quite a long time. Is that correct?
DR NG: Yes, the overall survival is, in general, quite long for this group of patients, although this disease is not curable. So in order to look for an overall survival benefit, you would have to conduct a study for quite a long time, which is why the investigators instead chose to focus on clinically relevant end points of progression-free survival and the time-to-next-treatment intervention.

DR DISIS: I guess as we wait for the overall survival data, we'll get a sense of whether the patients end up developing mechanisms of resistance. That will be something I'm sure the investigators are going to be looking at as they follow the patients longer.

DR NG: Definitely. I do think that's a concern with many of these targeted agents. Resistance can develop through a variety of different mechanisms, so better understanding what those mechanisms are and whether we can choose therapies that target the resistance mechanism subsequently, or even explore novel combination therapies, will be important.

DR DISIS: In summary, since this grade 2 glioma population after surgery really only has 2 choices—to watch and wait or get chemoradiation if they're higher risk—do you think this targeted approach represents a new standard of care for these patients?

DR NG: I do think the results of this trial will be practice changing, and this will become a new, standard option for patients.

DR DISIS: The next abstract was the PROSPECT trial, which actually started in 2012. It addressed a big question in locally advanced rectal cancer. Can you tell us a bit about PROSPECT?

DR NG: The rationale is that for certain tumors higher up in the rectum and perhaps not as locally advanced, with the improvement in surgical techniques and our ability to stage these tumors more accurately, would it be possible to selectively eliminate concurrent chemoradiation from the standard treatment algorithm for these patients? Keep in mind, the standard of care back then was to start with neoadjuvant concurrent chemoradiation followed by surgery, followed by adjuvant chemotherapy.

But the incidence of young-onset rectal cancer has been increasing significantly in the past few decades. For many of these young people, fertility and sexual dysfunction is of utmost concern, so trying to avoid detriments in these adverse events is important. The rationale was, are there a certain subset of patients with rectal cancer where we can just start with chemotherapy, re-stage to see if there's been an adequate response, and then selectively eliminate chemoradiation and go straight to surgery? That's what the PROSPECT trial was trying to test.

DR DISIS: It was amazing that in the group randomized to go directly to surgery, patients who didn't get greater than a 20% response rate could get the chemoradiation. But it was only 9% of patients out of a trial that enrolled more than 1000 that didn't get a great response with just FOLFOX [combination fluorouracil, leucovorin, and oxaliplatin] chemotherapy alone.

DR NG: That's absolutely right. FOLFOX is extremely effective in this type of cancer, and I think that element of the study design is important because in de-escalation trials where the intent is to cure patients, you really need to be careful that the de-escalation strategy being tested does not compromise the efficacy of the treatment. So building in that restaging to make sure patients are benefiting from chemotherapy alone is critical to make sure that we are not compromising the potential curative ability of this treatment.

DR DISIS: This trial was a noninferiority study, and the investigators really went to the wall in terms of showing no difference in disease-free survival, overall survival, and time to recurrence in pathological CR [complete response] or RO [no residual tumor] resection. It showed that the elimination of chemoradiation therapy did not significantly impact any outcome. Tell us a little bit about the unique patient population.

DR NG: The way that the PROSPECT trial was designed and thought out is a great reflection of the meeting's theme—an interdisciplinary approach that incorporates oncologists, medical oncologists, and surgeons, but also, very importantly, with patients about what they would accept and what would be meaningful to them in terms of designing the end points of this study. So this was indeed a true partnership with patients—not just patients enrolling in the trial but also having input early on about the design of the study.

DR DISIS: When we talk about the standard of care, I started by saying that this trial had gone on for a long time. It enrolled more than 1000 patients, and they were highly selected. During that time, treatment for locally advanced rectal cancer has changed. We've gotten different chemotherapies and shorter courses, as well as shorter courses of radiation. Now, we have immune therapy. Where do the results of this trial fit into the treatment paradigm?

DR NG: There are new approaches to treating patients with localized rectal cancer, including what we call total neoadjuvant therapy, which is putting all of the chemoradiation and chemotherapy upfront prior to surgery. And we think one of the major benefits of doing a total neoadjuvant therapy approach is that patients may have a better chance at an organ preservation strategy and be able to avoid going to surgery, which is also associated with a lot of morbidity and complications. So that is something that has developed in the interim since the PROSPECT trial started.

Another development is short-course radiation, and where that fits into the treatment paradigm of patients with locally advanced disease. Then, finally, for the very small subset of patients with microsatellite instability-high rectal cancer, a recent study showed that immunotherapy alone may obviate the need for chemoradiation radiation and surgery. So all of these different approaches need to be considered to decide the best approach for a specific patient.

DR DISIS: Let's go on to the 5-year follow-up of the ADAURA trial looking at EGFR [epidermal growth factor receptor]-mutated non–small cell lung cancer.

DR NG: The ADAURA phase 3 trial enrolled patients with stage IB to IIA non–small cell lung cancer that harbored a mutation in EGFR. This trial randomized patients after surgery to receive either a placebo or osimertinib, which is a tyrosine kinase inhibitor against EGFR, for a duration of 3 years.
The primary end point was disease-free survival in the stage II/IIIA patient population with secondary end points of disease-free survival in the overall population, as well as overall survival, safety, and quality of life.

The disease-free survival end point had been reported previously and was statistically significant in favor of the osimertinib arm prolonging disease-free survival. Also, CNS [central nervous system] disease-free survival was prolonged significantly in patients who received osimertinib. The importance of this updated result on the overall survival benefit is that this is now the first study to show that adjuvant therapy with an EGFR tyrosine kinase inhibitor can lead to a statistically significant overall survival benefit in this group of patients. That is very important for making sure there is access to this drug for patients around the world.

**DR DISIS:** It's really remarkable. There was a 51% reduction in the risk of death, and it was for all subgroups, whether you had IB or IIIA, so we have a clear indication of how we should be treating non-small cell lung cancer after the tumor has been resected by surgery.

**DR NG:** Definitely. And there was a survival benefit regardless of whether patients had received adjuvant chemotherapy or not. So regardless of whether that was given, there was a survival benefit in favor of osimertinib.

**DR DISIS:** Our final practice-changing abstract is SWOG S1826, looking at a new way to approach advanced Hodgkin lymphoma. Can you tell us about that study?

**DR NG:** This study was for patients diagnosed with advanced stage Hodgkin lymphoma, so stage 3 or 4. Traditionally, the standard of care has been different in different parts of the world and according to the age of the patient population, so different chemotherapy backbones were used for pediatric patients and for adult patients. Whether you were in the US or Europe, the standard of care differed. This trial was remarkable in that it was able to study both the pediatric population and the adult population in the US and consolidate and standardize the treatment to AVD [doxorubicin, vinblastine, and dacarbazine], and then randomize patients to receive either nivolumab or brentuximab. Patients randomized to nivolumab had significantly improved progression-free survival, which was the primary end point, compared with patients randomized to brentuximab in combination with the AVD backbone.

**DR DISIS:** I understand they also looked at patients who might need consolidative radiation therapy, and only 6 patients out of almost 1000 patients in the entire trial needed that extra radiation boost after treatment.

**DR NG:** That’s a really important point. Many patients with Hodgkin lymphoma are quite young when they’re diagnosed, and many children are diagnosed. If they go ahead and receive radiation therapy, it can potentially lead to long-term consequences and health conditions that significantly impact quality of life as well as overall health. So a treatment that leads to most patients not needing radiation will have huge implications for their long-term life, not just their survival.

**DR DISIS:** Although it’s a little too early to get overall survival data, the benefit of nivolumab was seen across all subgroups, every place that they stratified, old vs young. It looks like this may be heading toward a potential new standard of care treatment.

**DR NG:** I do agree that it is poised to potentially become a new standard of care for patients with advanced Hodgkin lymphoma. Certainly, many questions remain, and it will be very important to wait for that overall survival data to make sure there is an overall survival benefit. But again, the potential ability to avoid radiation and to have a nivolumab immunotherapy option for patients is a significant advance.

**DR DISIS:** I’d like to end with a new approach looking at a fecal transplant in patients who were resistant to immunotherapy. Tell us a little bit about that small study.

**DR NG:** This is a fascinating trial, but I do want to caution that it is still preliminary with a small number of patients. But it certainly provides initial proof of concept that the microbiota may have a significant role in responses to this class of checkpoint inhibitors.

The concept of fecal transplant to induce a response to PD-1 [programmed cell death protein 1] inhibition in patients who previously did not have a response to PD-1 inhibition had already been shown in diseases such as metastatic melanoma. The unique thing about this trial is that it enrolled patients with gastrointestinal cancers, which historically have not been as responsive to immunotherapy. The 13 patients who were enrolled had cancers like gastric adenocarcinoma, esophageal squamous cell carcinoma, as well as hepatocellular carcinoma.

What this group was able to show is that in patients who progressed or had their tumors progress on anti-PD-1 therapy, if they received a fecal transplant from somebody who had a durable response to anti-PD-1 therapy, you can see a partial response or stabilization of disease after that fecal transplant. The authors conducted several correlative studies as well to understand the organisms responsible for inducing this response. For example, did the subsequent microbial community resemble that of the donor, and how was the immune infiltrate affected by this fecal transplant? It’s fascinating as proof of concept.