PD-L1 blockers take center stage

The following reports are based on presentations at the annual meeting of the American Society of Clinical Oncology held May 31-June 4 in Chicago. Many of the presentations heralded a new era of precision medicine, that is, treatment based on patient and tumor genetics, rather than tumor location alone, according to outgoing ASCO president Sandra Swain, MD. Immunotherapies, specifically the PD-L1 antibodies featured prominently.

PD-L1 blocker shrinks tumors with modest adverse events

Major finding MPDL3280A shrank tumors by at least 50% in 29 of 140 patients, for an overall response rate of 21%. **Data source** A phase 1 study of 171 patients with locally advanced or metastatic solid tumors that progressed despite therapy. **Disclosures** Genentech sponsored the study. Dr. Herbst receives research funding from Genentech.

An investigational drug that targets the PD-L1 pathway was associated with tumor shrinkage in about 20% of patients who had a wide array of incurable or metastatic solid cancers in a phase 1 study. MPDL3280A, a PD-L1 targeted antibody with an Fc-domain designed to optimize efficacy and safety, shrank tumors by at least 50% in 29 of 140 patients, for an overall response rate of 21%. Further, there have been additional delayed responses, and the treatment responses are ongoing, with 26 of 29 patients continuing to respond at follow-ups of 3-15 months.

"We are impressed with the frequency and duration of the responses in these patients with very difficult-to-treat tumors," especially given that this is a phase 1 study, lead investigator Dr. Roy S. Herbst said during a presscast in advance of the ASCO meeting.

The drug also met safety measures, with no maximum tolerated dose, dose-limiting toxicities, or treatment-related deaths in an analysis of 171 patients. One patient discontinued MPDL3280A because of an immune-related adverse event; importantly, no cases of grade 3-5 pneumonitis occurred, reported Dr. Herbst, Ensign Professor of medical oncology at Yale Cancer Center and chief of Medical Oncology at Smilow Cancer Hospital at Yale, both in New Haven, Conn.

PD-L1 is a protein that can essentially hide cancer cells from the immune system. When MPDL3280A attaches to PD-L1, it reveals the cancer cell, eliciting an immune response.

Based on diagnostic testing for PD-L1 expression in archived tumor tissue from 103 patients, tumor shrinkage occurred after MPDL3280A treatment in 13 of 36 (36%) of patients with PD-L1-positive tumors and in 9 of 67 (13%) of patients with PD-L1-negative tumors. The diagnostic test for PD-L1 is still evolving, so a negative result on the PD-L1 test could simply mean that tumors have less PD-L1 than the test detects. The study has expanded to over 275 patients; phase 2/3 studies are planned.

MPDL3280A was administered intravenously 3 times weekly. Responses were observed in multiple tumor types, including non–small-cell lung cancer, renal cell carcinoma melanoma, colorectal cancer, and gastric cancer. The 24-week progression-free survival was 44%. No maximum tolerated dose was identified, and patients received MPDL3280A for a median duration of 127 days (range, 1-330 days). Pharmacokinetics supports thrice-weekly dosing at 15 mg/kg or a fixed-dose equivalent.

— Mary Jo Dales

Expert view. This is an exciting, new chapter in the treatment of cancer. The fact that this drug was active in such a variety of tumors suggests that PD-L1 is part of a universally or generally important immune mechanism. Over the next few years, drugs that target and help activate and direct the immune system will likely take on a growing role in patient care, and it's particularly exciting to see strong effects in patients whose cancer has progressed despite all other standard therapies.

Dr. Clifford A. Hudis, ASCO president-elect, is with Memorial Sloan-Kettering Cancer Center, New York, and is professor of medicine at Cornell University, also in New York. He made his comments during the presscast.

Commun Oncol 2013;10:247-252
DOI: 10.12788/j.cmonc.0052
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Nivolumab results durable in advanced melanoma

Major finding Median overall survival across all doses of nivolumab was 16.8 months. It reached 20.3 months for the 3-mg/kg dose that will be used in phase 3 studies. **Data source** An expanded phase 1 study of 107 pretreated patients with metastatic melanoma. **Disclosures** The research was supported by Bristol-Myers Squibb. Dr. Sznol disclosed that he serves in a consultant or advisory role with Bristol-Myers Squibb.

Nivolumab, an investigational PD-1 inhibitor, shrank tumors by at least 30% in 33 of 107 pretreated patients with metastatic melanoma, based on results from an expanded phase 1 trial reported at ASCO. An additional 11% of patients had prolonged stable disease or nonconventional, immune-related response profiles.

The findings build on favorable results reported last year for nivolumab in melanoma, renal cell carcinoma, and non–small-cell lung cancer. The results in melanoma patients at follow-ups as long as 2 years indicate no new safety signals with nivolumab, which was associated with a 21% rate of grade 3-4 events. The rate of severe immune-related adverse events was 5%. There were no cases of grade 3 or higher pneumonitis.

Median overall survival was nearly 17 months with nivolumab, with a 2-year survival rate of 43%. Median overall survival with vemurafenib is 16 months and with ipilimumab is 10 months, with 2-year survival rates of 24%-33% with ipilimumab, according to Dr. Mario Sznol, who presented the results from the phase 1 trial. "We're very excited that there is potential for even more activity [with nivolumab] in combination with other drugs," said Dr. Sznol, professor of medicine (medical oncology) at the Yale Cancer Center in New Haven, Conn.

Responses were seen at all 5 dose levels tested (0.1, 0.3, 1, 3, and 10 mg/kg), with a 41% objective response rate at the 3-mg/kg dose, which has been selected for evaluation in phase 3 studies. Median overall survival across all doses of nivolumab was 16.8 months. It reached 20.3 months for the 3-mg/kg dose. The 1-year survival rate was 62% and the 2-year survival rate, 43%.

Patients in the nivolumab trial were representative of typical patients with advanced melanoma, Dr. Sznol said. All patients in the study had disease that worsened despite prior standard systemic therapies, 25% of them had 3 or more prior therapies and 63% had 2 or more prior therapies. All had ECOG performance standards of 0 or 1. Patients received up to 12 cycles of treatment, with 4 doses of nivolumab per cycle, until discontinuation criteria were met.

Response has persisted after stopping treatment in 17 of 33 patients, with 12 of the 17 continuing to respond for at least 4 months, Dr. Sznol said. The overall objective response rate included partial and complete responses. Dr. Sznol said that just 1 patient had a verified complete response to nivolumab and 4 others had near complete responses at 2 years. Historical response rates to immunotherapy drugs are 5%-10% in advanced melanoma, he noted, which is lower than the 30% response seen in these pretreated patients. "I have seen a few relapses after 2 years of response, but some patients continue to do well at 4 years. One patient who has been off nivolumab for 2 years continues to do well at over 4 years," Dr. Sznol commented during a question and answer session.

To define the best candidates for nivolumab, molecular markers need to be identified to predict probable response, he added. As nivolumab is a PD-1 inhibitor, one potential marker is the protein PD-L1 on the surface of tumor cells, which is being studied in several other clinical trials.

— Mary Jo Dales

Adding GM-CSF to ipilimumab extended survival in metastatic melanoma

Major finding 1 year after the start of therapy, 69% of patients with metastatic melanoma who received ipilimumab plus GM-CSF and 53% of those who got ipilimumab alone were still alive, for a 35% lower risk of death with the combination therapy. **Data source** A phase 2 randomized trial of 245 patients who received ipilimumab–GM-CSF or ipilimumab alone. **Disclosures** The research was supported in part by the National Cancer Institute (Cancer Therapy Evaluation Program), Sanofi, and Bristol-Myers Squibb. Dr. Hodi disclosed receiving research funding and being a consultant or in an advisory role with Bristol-Myers Squibb.

Combining 2 approved therapies – GM-CSF and ipilimumab – extended overall survival rates by 35% and resulted in fewer grade 3-5 adverse events when compared with ipilimumab alone in a randomized study of 245 patients with metastatic melanoma. At 1 year, the overall survival rate in the combination therapy group was 69%, with a median follow-up of nearly 18 months. At 1 year, survival in the ipilimumab-only group was 53% with a median follow-up of nearly 13 months, Dr. F. Stephen Hodi Jr. reported at the annual meeting of the American Society of Clinical Oncology.

This is the first phase 2 trial to look at ipilimumab (Yervoy, Bristol-Myers Squibb) and the granulocyte macrophage colony-stimulating factor (GM-CSF) sargramostim (Leukine, Sanofi) in combination in any can-

cer, said Dr. Hodi, the principal investigator for the trial, which was conducted by the ECOG-ACRIN Cancer Research Group (formerly the Eastern Cooperative Oncology Group) trial. In this study, ipilimumab was used at a dose of 10 mg/kg, which is higher than the FDA-approved dose of 3 mg/kg. "We are waiting for the data to mature in ongoing studies examining the relative efficacy of 3 mg/kg and 10 mg/kg dosing," said Dr. Hodi, director of the melanoma center at Dana-Farber Cancer Institute in Boston.

The results in the current trial are another indication of the impact that immunotherapy can have for patients with advanced melanoma. Since both GM-CSF and ipilimumab are commercially available, oncologists need to determine the best way to apply these findings in everyday practice. The next step will then be to define the role of GM-CSF in combination with other immune checkpoint – targeting drugs, such as therapies that target the PD-1 and PD-L1 pathway, he said.

"We have been using GM-CSF in melanoma as a stand-alone therapy," Dr. Lynn M. Schuchter, the C. Willard Robinson Professor of Hematology-Oncology at the University of Pennsylvania, Philadelphia, and an expert on melanoma, said at a press conference where the study results were announced. "It will be interesting to see if payers will cover this [combination treatment]."

Ipilimumab targets CTLA-4, a protein that keeps immune T-cells in an inactive state. GM-CSF is a growth factor commonly used to boost white blood cell counts after chemotherapy or stem cell transplantation.

For this study, 245 patients were randomized to receive ipilimumab plus GM-CSF or ipilimumab alone. All study participants were in otherwise good health, with an ECOG performance status of 0-1 and adequate end-organ function, no autoimmune disease, and no prior use of CTLA-4 blockade or CD137 agonists. All had radiographically measurable metastatic melanoma, but with no CNS metastases, and had received up to 1 prior treatment over 4 weeks before starting in the trial. The 123 patients randomized to the combination therapy were given sargramostim at 250 micrograms injected subcutaneously on day 1-14 of a 21-day cycle. For induction therapy, ipilimumab was given at a dose of 10 mg/kg intravenously once every 3 weeks for 4 cycles as induction therapy and once every 12 weeks as maintenance therapy. The 122 patients randomized to ipilimumab alone received the drug on the same schedule.

In both arms, tumor shrinkage rates were comparable at 11% and 14%, and progression-free survival was similar at about 3 months. But the overall survival rate was longer in the combination treatment arm. One year after the start of therapy and with a median follow-up of 13.3 months, 69% of patients given the combination therapy and 53% of those who got ipilimumab alone were still alive, for a 35% lower risk of death with the combination therapy (hazard ratio, 0.64; $P = .014$).

In addition, the combination treatment was associated with fewer serious side effects, compared with ipilimumab alone. The most significant differences were in lung and gastrointestinal toxicities. Grade 3-5 adverse events occurred in 45% of patients given the combination therapy and in 57% given ipilimumab alone. There were 2 possible treatment-related deaths in the combination arm (1 colonic perforation and 1 cardiac arrest) and 7 possible treatment-related deaths in the ipilimumab-only arm (2 cases of multi-organ failure, 2 colonic perforations, 1 case of liver failure, and 2 cases of respiratory failure).

— Mary Jo Dales

aTTom study confirms benefits of 10 years of tamoxifen

Major finding 10 years of tamoxifen significantly reduced risk of recurrence from 32% to 28% in the 10 years or more after diagnosis ($P = .003$). **Data source** Randomized controlled trial in 6,953 women with estrogen receptor-positive or ER untested early breast cancer in England. **Disclosures** The study was funded by Cancer Research UK and the UK Medical Research Council. Dr. Gray had no financial conflicts. Dr. Rugo has received clinical research grants from Genentech, Pfizer, and GlaxoSmithKline.

A second study shows that 10 years of adjuvant tamoxifen is superior to the standard 5 years in women with estrogen receptor-positive early breast cancer. Among nearly 7,000 women randomized in the aTTom (Adjuvant Tamoxifen Treatment Offers More) study, extended tamoxifen significantly reduced the risk of recurrence from 32% to 28% in the 10 years or more after diagnosis ($P = .003$). This translated into a borderline significant difference in breast cancer mortality, reducing it from 24% to 21% ($P = .06$), Richard Gray, MSc, reported in the plenary session at ASCO.

Just 6 months ago, Prof. Gray reported that recurrences were down 25% and breast cancer deaths down 29% in years 10-14 after diagnosis in women on tamoxifen for 10 years in the companion ATLAS (Adjuvant Tamoxifen: Longer Against Shorter) trial. The benefits came at a cost, however. Extended exposure to tamoxifen in aTTom more than doubled the number of endometrial cancers (102 vs. 45 cases; rate ratio, 2.20; P less than .0001) and significantly increased the risk of dying from it (37 vs. 20 deaths; RR, 1.83; $P = .02$). On a population basis, the benefits in reduced breast cancer mortality out-

weigh the risks, according to Prof. Gray, professor of medical statistics at the University of Oxford, England.

Monitoring with ultrasound for endometrial changes could improve early detection and reduce the impact of this known toxicity, Dr. Hope S. Rugo, director of the breast oncology and clinical trials education at the University of California, San Francisco, said in an interview. This risk is also known to vary considerably by age. "The dramatic findings presented in the aTTom study today will clearly have a significant impact on clinical practice on Monday and are arguably some of the most important data for the treatment of women with early-stage, hormone receptor-positive breast cancer," she said, noting that the decision to continue tamoxifen beyond the recommended 5 years should be based on the extent of residual risk of recurrence, and must be balanced against tolerability and alternative options.

Extended-duration tamoxifen is a particularly important option for women at risk for late relapse, who are not candidates for aromatase inhibitors because of menopausal status or tolerability.

ASCO spokesperson Dr. Sylvia Adams, a breast cancer specialist at New York University Langone Medical Center said in a statement that the results are practice changing for premenopausal women with hormone receptor-positive breast cancer, and especially relevant for women at high risk of recurrence.

A retrospective analysis of combined data from aTTom, ATLAS, and 3 smaller trials is planned to determine whether certain subgroups of women are most likely to benefit from longer tamoxifen treatment, according to Mr. Gray.

The aTTom study randomly assigned 6,953 women with estrogen receptor-positive (40%) or ER-untested invasive breast cancer (80% estimated to be ER+) who had been taking tamoxifen for 5 years to continue tamoxifen for another 5 years or stop immediately. Tamoxifen compliance in the continuation arm was about 75%. Breast cancer recurred in 580 women allocated to continue tamoxifen and 672 randomized to stop (RR, 0.85; $P = .003$). There was no benefit in years 5-6 after diagnosis (odds ratio, 1.17), but began to emerge later on, in years 7-9 (OR, 0.99), years 10-14 (OR, 0.79) and 15 years or later (0.75), Prof. Gray said.

Breast cancer deaths were reported in 404 patients on extended tamoxifen and 452 patients in the 5-year group (RR, 0.88; $P = .06$). Tamoxifen had little effect on all-cause mortality in the extended and 5-year groups (885 vs. 939 deaths; $P = .2$).

— Patrice Wendling

Expert view. For women who remain premenopausal on tamoxifen, extended tamoxifen is a great option where there has been no prior standard. These women have a higher risk of disease and therefore potentially have the greatest risk reduction and lowest risk of serious toxicity, including an almost negligible risk of endometrial cancer. The personal cost in terms of fertility may be the greatest in this population. Interestingly, ATLAS also reported a significant increase in pulmonary embolism, but it was coupled with a decrease in ischemic heart disease (Lancet 2012 ;805-16 [doi:10.1016/s0140-6736(12)61963-1]). Cardiovascular events have not been reported for aTTOM. Adherence, which is a challenge in the real world, quality of life, and symptoms such as vasomotor symptoms, alterations in mood, sexual functioning, and musculoskeletal problems also must be considered. We all know that minor side effects can become deeply troubling over time in this setting.

Dr. Ann H. Partridge founded the young women with breast cancer program at Boston's Dana-Farber Cancer Institute and was the invited discussant of the study, presented at the plenary session. Dr. Partridge had no financial conflicts.

Routine CT surveillance questioned in B-cell lymphoma

Major finding Planned CT scans detected DLBCL relapse before clinical symptoms or signs in 8 of 537 patients in posttreatment surveillance. **Data source** Epidemiologic study in 537 patients with diffuse large B-cell lymphoma in the prospective SPORE Molecular Epidemiology Resource. **Disclosures** Dr. Thompson reported having no financial disclosures.

Routine surveillance with computed tomography scans adds little to the surveillance of patients in remission from diffuse large B-cell lymphoma, a large epidemiologic study shows. Planned CT scans detected diffuse large B-cell lymphoma (DLBCL) relapse prior to clinical symptoms or signs in 8 of 537 (1.5%) patients who entered post-treatment surveillance. The majority (62%) of relapses were detected by patients who contacted their provider because of symptoms before their planned visit, according to lead author Dr. Carrie A. Thompson, of the Mayo Clinic, Rochester, Minn.

"The take-home point is that the majority of relapses occur outside of planned follow-up visits and are accompanied by symptoms, exam or lab abnormalities," she said. "In this study, scheduled scans added little for patients who had none of the above." Dr. Thompson noted that DLBCL patients in remission in the United States undergo a median of 2.5 CT or positron emission tomog-

raphy scans per year during surveillance, according to a recent study (Leuk. Lymphoma 2012;53:1113-6). Moreover, 4.2% of patients in the series received no imaging, she said at a press briefing before ASCO.

The National Comprehensive Cancer Network recommends that patients be evaluated every 3-6 months for 5 years, with a CT scan no more often than every 6 months for the first 2 years after treatment completion, and then as clinically indicated.

The investigators enrolled 644 patients with biopsy-proven DLBCL treated with anthracycline-based chemotherapy in the University of Iowa/Mayo Clinic SPORE (Specialized Programs of Research Excellence) Molecular Epidemiology Resource, a prospective cohort of newly diagnosed lymphoma patients. Their median age was 63 years (range, 18-92), 54% were men, and median follow-up was 59 months (range, 8-116). Overall management and follow-up was at the discretion of their oncologist.

Of the 537 patients who entered surveillance, 109 (20%) relapsed. Medical records were available in 100 patients. Of the 38 patients with relapse detected at a planned visit, 26 had an abnormal physical exam and/or labs, Dr. Thompson said. The remaining 12 patients were asymptomatic, and their relapses were detected solely by CT scan. "It is noteworthy that 4 of these relapses turned out to be another form of lymphoma, not diffuse B-cell lymphoma," she added.

Although the data show that scans detected relapses in a minority of patients, it is too early to say definitively how many scans are needed or how often they should be done, she said, adding that a randomized study is needed to determine the best surveillance strategy.

— Patrice Wendling

No survival benefit for routine surveillance scans in classical Hodgkin disease

Major finding The ratio of scans to detected relapses was 18 for the clinical surveillance group and 124 for the routine scan group. The extra charges incurred from scans using the routine surveillance imaging approach were $18,896/patient and $593,698/relapse. **Data source** A retrospective analysis of 241 patients with classical Hodgkin lymphoma in first complete remission. **Disclosures** Dr. Pingali disclosed no relevant conflicts of interest. Dr. Gordon disclosed that he receives honoraria from Genentech and research funding from Millennium and Pharmacyclics. Dr. Salles disclosed serving as an advisor or consultant for Calistoga Pharmaceuticals, Celgene; Genentech, Janssen Pharmaceutica, and Roche. He has served as a speaker or a member of a speakers bureau and has received grants for clinical research from Celgene and Roche.

Routine surveillance imaging does not improve clinical outcomes in patients with classic Hodgkin disease who are in first complete remission and it sharply increases costs, researchers reported at ASCO. The team, led by Dr. Sai Ravi Pingali, retrospectively reviewed the charts of 241 adult patients who achieved a complete remission after first-line therapy. In 68%, the treating physicians' planned approach was routine surveillance imaging, which consisted of radiologic imaging with scans every few months, plus clinical exams and laboratory testing. In the other 32%, the planned approach was clinical surveillance, meaning that radiologic imaging was performed only if concerning signs or symptoms occurred.

The 2 groups had statistically indistinguishable overall survival, and in both groups, all patients experiencing relapse successfully achieved a second complete remission with salvage therapy. In the routinely imaged group, scanning increased costs by nearly $20,000 per patient and by almost $600,000 per each relapse detected. In addition, patients were exposed to the associated radiation. "We were unable to detect an overall survival benefit associated with routine surveillance imaging, although I have to acknowledge that our study was limited in power given the small number of deaths and relapses," commented Dr. Pingali, an oncologist with the Medical College of Wisconsin Affiliated Hospitals in Milwaukee.

"Relapses in both . . . groups were effectively salvaged with autologous stem cell transplantation, arguing against a critical advantage of detection of asymptomatic relapse. Also, we need to keep in mind that the costs associated with routine surveillance imaging are significant, and it is also associated with potential risks, both in terms of radiation exposure and unnecessary work-up. We do not feel that potential risks and costs without overall survival benefit or any other clinical benefit justify the practice of routine surveillance imaging in classical Hodgkin lymphoma patients who have achieved a complete remission after first-line therapy. We recommend that such patients be followed clinically," Dr. Pingali concluded.

Invited discussant Dr. Leo Gordon of Northwestern University in Chicago, agreed that accumulating data argue against routine imaging for surveillance in this context and noted that insurers will likely not continue to cover scans having no proven benefit. The data should prompt a revision of guidelines and reeducation of clinicians and patients, he said. "For translational researchers and investigators and academics, I think we need to convince journal reviewers that a manuscript is acceptable if scans are not so frequent. And for industry trials, I think

we need to discuss with the Food and Drug Administration the endpoint of progression-free survival and that those endpoints may not only be driven by scans but by more mundane parameters," he said – namely, the history and physical examination.

But session comoderator Dr. Gilles A. Salles of Hospices Civils de Lyon, Université Claude Bernard, France, expressed reservations, noting that the study did not provide information on how patients were allocated to groups and the time frame of relapse. "It may be different whether relapses occur early, in the first year, or they occur later, and that may have some implications for the surveillance," he said. "I understand that you and many others jumped over the idea that we should immediately stop. A few people may think that we need more solid data, despite the provocative and quality data that were presented, to really make this jump in clinical practice. That's my personal opinion."

Dr. Pingali and his team retrospectively reviewed the charts of adult patients who received a new diagnosis of classical Hodgkin lymphoma between 2000 and 2010 at 3 institutions, achieved complete remission after first-line therapy and had at least 2 years of follow-up. The routine surveillance imaging and clinical surveillance groups had similar demographic and disease characteristics. The former were significantly more likely to have received ABVD (doxorubicin [Adriamycin], bleomycin, vinblastine, and dacarbazine) and less likely to have received the Stanford V regimen as first-line therapy, and they were significantly less likely to have received radiation therapy.

With a median duration of follow-up of about 4 years, the groups did not differ significantly with respect to overall survival. "When we look at the 5-year time point, when typically the surveillance CT scans are discontinued, the curves are pretty much superimposable," he pointed out.

There were 5 deaths in the routine surveillance imaging group, 1 of which was from relapsed disease; the other deaths were from cancer, heart failure, hip fracture, and myelodysplastic syndrome. There were 4 deaths in the clinical surveillance group: 2 were from non-Hodgkin lymphoma and 2 from unknown causes while the patient was in confirmed remission.

All of the 6 patients in the routinely imaged group and all of the 5 patients in the clinically followed group experiencing a relapse achieved another complete remission with second-line therapy. The mean number of scans received was 1.14 in the clinical surveillance group – usually the scan performed after first-line treatment to confirm remission, according to Dr. Pingali – and 4.25 in the routine surveillance imaging group. The ratio of scans to detected relapses was 18, compared with 124.

The extra charges incurred from scans using the routine surveillance imaging approach were $18,896/patient and $593,698/relapse. "It is important to note that this does not include additional costs from the work-up of the false-positive scans and also the wages lost," he noted.

— Susan London