

ASCO 2015: from data and learning, to daily practice

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The 2015 annual meeting of the American Society for Clinical Oncology, themed “Illumination and innovation: transforming data into learning,” brought together more than 37,000 attendees in Chicago and featured numerous clinical advances that will improve the lives of our cancer patients. That said, to a first-timer, the gathering probably would have felt like an update on using the immune system to fight cancer, despite our more than 30 years of using such strategies. The science behind the development of these promising monoclonal antibodies is outstanding, and the impact will certainly be far reaching.

Many of the disease area discussions focused on the role of immunotherapy, with promising results presented in trials of melanoma, and lung, liver, head and neck, colon, esophageal, ovarian, and renal cell cancers. Much of the excitement came from the recent approvals of the immune checkpoint inhibitors and programmed cell death-1 (PD-1)-targeted monoclonal antibodies nivolumab – approved by the US Food and Drug Administration for metastatic melanoma and relapsed, previously treated squamous cell lung cancer – and pembrolizumab, which has been approved for metastatic melanoma.

The results of CheckMate 067, presented by Jedd Wolchok of the Memorial Sloan Kettering Cancer Center, New York, in the plenary session, compared the combination of nivolumab and ipilimumab with each single agent in 945 patients with treatment-naïve metastatic melanoma (p. 268). In the overall population, the combination was statistically superior in progression-free survival (PFS), with a median of 11.5 months, compared with nivolumab (median PFS, 6.9 months) or ipilimumab (median PFS 2.9 months). Of note, in patients with tumors expressing >5% programmed cell death ligand-1 (PD-L1), the median PFS was much better at 14.0 months for both the single agent nivolumab arm as well as the arm in combination with ipilimumab. That said, there remains substantial debate around the utility of the assay for PD-L1, because only 27% of the study participants tested positive, and the biomarker failed

to identify about two-thirds of the responders to nivolumab monotherapy. Survival data is still maturing.

With the publication ahead of the meeting of positive PFS results for pembrolizumab head to head against ipilimumab in randomized phase 3 study of 834 patients, there are the natural questions surrounding the comparison of these 2 exciting agents as therapy for metastatic melanoma. In the absence of any direct comparisons in a clinical trial, at least in the near term, the physician will be making the treatment decision largely based on personal clinical experience coupled with perceptions around the predictability of biomarkers, and likely, the influences of cost and marketing.

Similar enthusiasm for immunotherapy was found in the lung cancer sessions where the results of 2 phase 3 studies comparing nivolumab with docetaxel in the second-line setting were presented. CheckMate 057 for nonsquamous lung cancer, delivered by Luis Paz-Ares of the University of Madrid, and CheckMate 017 for squamous cell lung cancer, led by David Spigel of the Sarah Cannon Research Institute in Nashville, both demonstrated improvement in median overall survival. The 017 study was the basis for the initial FDA approval earlier this year of nivolumab for the treatment of lung cancer (p. 270). Although all of the subgroups fared well in the 057 trial, those patients with greater PD-L1 expression, >5%, did even better, and debates around the utility of the biomarker persisted among the discussants (p. 269).

In the area of other tumor types that seem to benefit from immunotherapy, Tanguy Seiwert of the University of Chicago described the activity of pembrolizumab against previously treated, squamous-cell head and neck cancer, both HPV-positive and -negative, and reported a 25% response rate in 132 patients (p. 270). Both at ASCO and other recent cancer meetings, these agents are showing promise in difficult areas such as mismatched repair colon cancer and triple-negative breast cancer. However, at a price of more than \$12,000 a month, and with broad applicability across tumor types, there will be mounting pressure to define and describe which patients are likely to benefit.



In the area of targeted monoclonal antibodies for the treatment of breast cancer, the long-awaited results from the MARIANNE study were presented by Paul Ellis of Sarah Cannon Research (UK) and Guy's & St Thomas Hospital in London. The study compared the standard arm of trastuzumab and a taxane, versus ado-trastuzumab (T-DM1) plus pertuzumab, versus single-agent T-DM1. Although the more than 1,100 HER2-positive patients were accrued globally at a rapid pace, the rate of progression events was slow (a positive), thus delaying the reporting of data. Many of us were surprised to learn that there was no difference in outcomes among the 3 arms. The superior results of the CLEOPATRA study with the winning combination of docetaxel, pertuzumab, and trastuzumab had many of us expecting the T-DM1 plus pertuzumab combination would produce an even better result for our HER2-positive patients. There will be many theories put forth as to why there was no difference among the treatments from an efficacy perspective, but most relevantly, the study speaks to the importance of randomized trials. Not unexpectedly, the single agent T-DM1 arm demonstrated an excellent safety profile, and the applicability of its use for metastatic HER2-positive breast cancer will likely continue to expand.

Among the abundance of offerings on novel therapies were some very practical presentations affecting day-to-day practice. One such study was an interesting meta-analysis of 3,481 patients from the breast cancer neoadjuvant Gepartrials. The retrospective evaluation assessed the effect of omitting adjuvant radiation therapy. Those patients who were managed without radiation therapy had significantly worse outcomes for both local regional and overall disease-free survival, regardless of whether they had experienced a pathologic complete response. This report highlights the importance of considering radiation therapy for patients receiving neoadjuvant chemotherapy.

In a similar vein, the ABCSG-18 investigators reported the results of their 3,425-patient adjuvant denosumab trial in postmenopausal women who received aromatase inhibitor for early hormone receptor-positive breast cancer

(p. 271). This double-blind, placebo-controlled, randomized trial demonstrated that adjuvant denosumab reduced fractures in those women and improved overall bone mineral density. Bone health can be a serious morbidity issue and taking time to discuss and consider supportive care in this setting is clearly worthwhile.

Switching to colon cancer, the various media agencies highlighted a study that described the benefits of a daily aspirin after surgery for this disease (p. 272). Simer Bains of the University of Oslo reported that patients who took the aspirin had an overall survival benefit compared with those who did not, and that although aspirin is not without side effects, the benefits of using it certainly outweigh the risks.

Finally, in the area of prostate cancer, the STAMPEDE trial garnered attention around the benefits of docetaxel as an early intervention for advanced prostate cancer (p. 273). The study randomized patients with newly diagnosed, locally advanced or metastatic prostate cancer to receive standard of care hormonal suppression and then docetaxel, or docetaxel plus zoledronic acid, or zoledronic acid alone. Nicholas James of the University of Warwick reported a nearly 1 year and a relative 24% survival improvement for those men who had been randomized to receive docetaxel in 1 of those 2 arms, with about 3,000 patients in the analysis. Prostate cancer experts largely applauded the effort and advised oncologists and urologists to consider not saving docetaxel for later use, when the patient is likely to have more advanced disease or a worse performance status.

Overall, the field of oncology is changing rapidly and the majority of novel agents being developed are focused on primarily the immune system or targeting specific molecular aberrations. Education and awareness on the appropriate use of these treatments, managing the side effects, and incorporating molecular profiling into the decision making will be a priority for our oncology community. The need to emphasize participation in clinical research has never been more important, as we have more questions than answers to date on how best to prescribe these new therapies.