

# An ASCO 2017 recap: significant advances continue

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As we head into vacation season and the dog days of summer, let's reflect for a few minutes on some of the very important advances we heard about at this year's annual meeting of the American Society of Clinical Oncology in Chicago. Nearly 40,000 individuals registered for the conference, an indication of both the interest and the excitement around the new agents and the emerging clinical trial data. Scientific sessions dedicated to the use of combination immunotherapy, the role of antibody drug conjugates, and targeting molecular aberrations with small molecules were among the most popular.

In the setting of metastatic breast cancer, several trials produced highly significant results that will positively affect the duration and quality of life for our patients. The use of PARP inhibitors in *BRCA*-mutated cancers has been shown to be effective in a few areas, particularly advanced ovarian cancer. The OlympiAD study evaluated olaparib monotherapy and a physician's choice arm (capecitabine, eribulin, or vinorelbine) in *BRCA*-mutated, HER2-negative metastatic breast cancer. The 2:1 design enrolled 302 patients and demonstrated a 3-month improvement in progression-free survival (PFS) for olaparib compared with the control arm (7.0 vs 4.2 months, respectively;  $P = .0009$ ). The patient population for this *BRCA*-mutated trial was relatively young, with a median age of 45 years, and 50% of the women were hormone positive and 30%, platinum resistant.

The CDK4/6 inhibitors continue to be impressive, with the recently reported results from the MONARCH 2 trial showing encouraging PFS and overall response rate results with the addition of the CDK4/6 inhibitor abemaciclib to fulvestrant, a selective estrogen-receptor degrader. In this study, hormone-positive, HER2-negative women who had progressed on previous endocrine therapy were randomized 2:1 to abemaciclib plus fulvestrant or placebo plus fulvestrant. A total of 669 patients were accrued, and after a median follow-up of 19 months, a highly significant PFS difference of 7 months between the abemaciclib-fulvestrant and fulvestrant-only groups was observed (16.4 vs 9.3 months, respectively;  $P < .0000001$ ) along with an overall

response rate of 48.1 months, compared with 21.3 months. Previous findings have demonstrated monotherapy activity for abemaciclib, and the comparisons with palbociclib and ribociclib will be forthcoming, although no comparative trials are underway. These agents will be extensively assessed in a variety of settings, including adjuvantly.

The results of the much anticipated APHINITY study, which evaluated the addition of pertuzumab to trastuzumab in the adjuvant HER2-positive setting, were met with mixed reviews. Patients were included if they had node-positive invasive breast cancer or node-negative tumors of >1.0 cm. A total of 4,804 patients (37% node negative) were enrolled in the study. The intent-to-treat primary endpoint of invasive disease-free survival (DFS) was statistically positive ( $P = .045$ ), although the 3-year absolute percentages for the pertuzumab-trastuzumab and trastuzumab-only groups were 94.1% and 93.2%, respectively. It should be noted that the planned statistical assumption was for a delta of 2.6% – 91.8% and 89.2%, respectively. Thus, both arms actually did better than had been planned, which was based on historical comparisons, and the node-positive and hormone-negative subgroups trended toward a greater benefit with the addition of pertuzumab. There was, and will continue to be, much debate around the cost-benefit ratio and which patients should be offered the combination. The outstanding results with the addition of pertuzumab in the neoadjuvant setting will continue to be the setting in which the greatest absolute clinical benefit will be seen. It is unusual in this era to see trials this large planned to identify a small difference, and it is likely that resource constraints will make such studies a thing of the past.

The very active hormonal therapies, abiraterone and enzalutamide, for castrate-resistant prostate cancer remain of high interest in the area of clinical trials. The LATITUDE study evaluated a straightforward design that compared abiraterone with placebo in patients who were newly diagnosed with high-risk, metastatic hormone-naïve prostate cancer. Patients in both arms received androgen-deprivation therapy and high risk was defined by having 2 of 3



criteria: a Gleason score of  $\geq 8$ ; 3 or more bone lesions; or visceral disease. Of note is that 1,199 patients were enrolled before publication of the CHAARTED or STAMPEDE results, which established docetaxel as a standard for these patients. The median age in the LATITUDE trial was 68 years, with 17% of patients having visceral disease and 48% having nodal disease, making it a similar patient population to those in the docetaxel studies. The results favoring abiraterone were strikingly positive, with a 38% reduction in the risk of death ( $P < .0001$ ) and a 53% reduction in the risk of radiographic progression or death ( $P < .0001$ ). The regimen was well tolerated overall, and it is clear that this option will be widely considered by physicians and their patients.

Two studies addressing the importance of managing symptoms and improving outcomes were also part of the plenary session. The IDEA Collaboration conducted a prospective pooled analysis of 6 phase 3 studies that assessed 3 and 6 months of oxaliplatin-based regimens for stage 3 colon cancer. FOLFOX and CAPOX given to 12,834 patients in 6 studies from the United States, European Union, Canada, Australia, New Zealand, and Japan were evaluated for DFS, treatment compliance, and adverse events. As would be anticipated, fewer side effects, particularly neurotoxicity, and greater compliance were observed in the 3-month group. Although DFS noninferiority for 3 months of therapy was not established statistically, the overall data led the investigators to issue a consensus statement advocating for a risk-based approach in deciding the duration of therapy and recommending 3 months of therapy for patients with stage 3, T1-3N1 disease, and consideration of 6 months therapy for T4 and/ or N2 disease. The investigators also acknowledged the leader and creator of IDEA, the late Daniel Sargent, PhD, of the Mayo Clinic, who passed away far too young after a brief illness last fall (1970-2016).

The second symptom-based study was performed at Memorial Sloan Kettering Cancer Center (MSKCC) in New York and designed by a group of investigators from the Dana-Farber Cancer Institute in Boston; the Mayo Clinic in Rochester, Minnesota; the University of North Carolina in Chapel Hill; and MSKCC. The hypothesis was simply that proactive symptom monitoring during chemotherapy would improve symptom management and lead to better outcomes. For the study, 766 patients with advanced solid tumors who were receiving outpatient chemotherapy were randomized to a control arm with standard follow-up or to the intervention arm, on which patients self-reported on 12 common symptoms before and between visits using

a web-based tool and received weekly e-mail reminders and nursing alerts. At 6 months, and compared with baseline, the self-reporting patients in the intervention arm experienced an improved quality of life ( $P < .001$ ). In addition, 7% fewer of the self-reporting patients visited the emergency department ( $P = .02$ ), and they experienced longer survival by 5 months compared with the standard follow-up group (31.2 vs 26.0 months, respectively;  $P = .03$ ). Although there are limitations to such a study, the growth in technological advances should create the opportunity to expand on this strategy in further trials and in practice. With such an emphasis in the Medicare Oncology Home Model on decreasing hospital admissions and visits to the emergency department, there should be great motivation for all involved to consider incorporating self-reporting into their patterns of care.

A continued emphasis on molecular profiling, personalized and/or precision medicine, and identifying or matching the patient to the best possible therapy or the most appropriate clinical trial remains vital to improving outcomes. Just before the ASCO meeting, the US Food and Drug Administration approved pembrolizumab for the treatment of patients with high-level microsatellite instability (MSI-H) and mismatch-repair deficient (dMMR) cancers, regardless of the site of origin. The approval was based on data from 149 patients with MSI-H or dMMR cancers, which showed a 40% response rate in this group of patients, two-thirds of whom had previously treated colon cancer. This landmark approval of a cancer therapy for a specific molecular profile and not the site of the disease, will certainly shape the future of oncology drug development. One of the highlighted stories at ASCO was the success of the larotrectinib (LOXO 101) tropomyosin receptor kinase inhibitor in patients with the TRK fusion mutations. The data, including waterfall charts, swimmer plots, and computed-tomography scans, were impressive in this targeted population with a 76% response rate and a 91% duration of response at 6 months with a mild side effect profile.

In summary, across a variety of cancers, with treatment strategies of an equally diverse nature, we saw practice-changing data from the ASCO meeting that will benefit our patients. Continuing to seek out clinical trial options for patients will be critical in answering the many questions that have emerged and the substantial number of studies that are ongoing with combination immunotherapies, targeted small molecules, and a growing armamentarium of monoclonal antibodies.