Clarion Healthcare's Highlights from the

ASH 2016 Annual Meeting

Clarion attended this year's ASH and with over 27,000 attendees convening for presentations and discussions of thousands of abstracts, we thought we would highlight some of the themes that emerged:

A CAR-T race nears the finish line while new contests emerge

Chimeric antigen receptor (CAR)-T cell therapies took center stage, as the focus of more than 150 posters and abstracts presented this year.

CD19-directed CAR-T therapies continue to verify their unparalleled efficacy. The so-called second-generation CAR-T therapies—advances over the original experiments in the 1980s and 90s—that target CD19 now have results in late phase trials, and they continue to impress. Kite's KTE-C19 had a complete remission (CR) rate of 47%—*a 6-fold increase over historical responses*—in a pivotal phase 2 study for aggressive refractory DLBCL. Novartis's CTL019 had a CR + CRi (complete remission with incomplete hematologic recovery) rate of 83% in their registration trial for pediatric and young adults with relapsed/refractory B-cell ALL; although lower than last year's report of 93% CR in a smaller study, it remains superior to current standard of care and will support a BLA in 2017.

Hallmark toxicities of CAR-T appear manageable. A key downside of CAR-Ts is their tendency to produce cytokine release syndrome (CRS), neurological events, and other toxicities. On the eve of this ASH meeting, Juno Therapeutics reported that two more patients treated with CAR-T therapy (JCAR015) suffered fatal brain swelling. Fortunately, for most CAR-T therapies, severe cases are now infrequent and reversible with proper management (e.g., with tocilizumab). Furthermore, preliminary evidence suggests that treatment with kinase inhibitors such as ruxolitinib or ibrutinib can reduce the incidence and severity of CRS.

The next wave(s) of CAR-T therapies continue to emerge across multiple fronts. CAR-T therapies in clinical trials now include diverse targets, not just CD19; targets include CD20, CD22, CD38 and BCMA. CAR-Ts with improvements in their co-stimulatory domains (i.e. CD27, CD28, CD134 [OX40], CD137 [4-1BB]) may have an increased expansion rate, prolonged persistence, and improved safety, though clinical testing is still early. Lastly, "off-the-shelf" CAR-T therapies—eliminating reliance on autologous cells, thus reducing the burden of manufacturing—show some progress. One study suggested that a single donor could support up to 50 recipients. As the CD19 second-generation CAR-T race nears the finish, new races are already emerging.

PD1 inhibitors show a dark side

Anti-PD1 agents continue to demonstrate intriguing efficacy in certain hematologic malignancies, but also show significant risks for immunologic toxicity.

Anti-PD1s bolster their activity in classical Hodgkin lymphoma (cHL) and other hematologic malignancies. Nivolumab monotherapy was approved for post-transplant r/r cHL patients earlier this year, and a second PD1 inhibitor, pembrolizumab, has now shown monotherapy responses (ORR > 65%; CR = 22%) in heavily treated r/r cHL patients, regardless of transplant status. Even more impressive, nivolumab combined with brentuximab vedotin (BV) led to an unprecedented complete response in 62% of patients (ORR = 90%). Additional anti-PD1-based combinations are being explored in AML, MDS, Richter's transformation (RT), myeloma, and other malignancies. One highlight was the strong response (ORR = 65%) in r/r multiple myeloma patients treated with pembrolizumab, pomalidomide and dexamethasone. In another study, pembrolizumab combined with ibrutinib produced an ORR of 44% in patients with r/r CLL with Richter's transformation.

However, caution was raised around potential for anti-PD1-related immunomodulatory dysfunction. While anti-PD1s are generally well-tolerated, several studies suggested that treatment with a PD1 inhibitor around allogeneic stem cell transplant can trigger rapid and severe onset of graft-versus-host disease (GVHD). The effect may be most pronounced when treatment is given closer to the time of transplant. Combined with evidence linking PD1 inhibitors to sporadic incidences of autoimmune disorders published earlier this year (i.e. hemolytic anemia, CIDP), it has become clear that some patients are at higher risk for anti-PD1 toxicity, and new biomarker strategies are required to identify these patients and give them optimal care.

CLARION | Healthcare, LLC

One Financial Center, Suite 1610 Boston MA 02111 Ph: 601.757.7850, www.clarionhealthcare.com

Sources: Abstracts #221, #998, #2803, #999, #1851, #1147, #2171, #59, #763, #490, #2219, #2923, ; N Engl J Med 2016; 374:1096-1097; N Engl J Med 2016; 375:296-297

Clarion Healthcare's Highlights from the

ASH 2016 Annual Meeting

Targeted therapies make strong showing

While immunotherapies generated a lot of "buzz", the excitement around strong clinical data for several "targeted therapies" was equally palpable.

Novel agents show promise for AML and other malignancies: **Gilteritinib**, a novel FLT3/AXL inhibitor, was well-tolerated and potentially efficacious in r/r AML showing anti-leukemic activity (ORR >50%) against AML harboring either the ITD or TKD mutations in FLT3. **Selinexor**, a novel, oral selective inhibitor of nuclear export protein XPO1, exhibited clinical efficacy in heavily-pretreated AML (ORR 55%, CR 26%, CRi 26%; in combination with ara-c and idarubicin) as well as multiple myeloma (MM)(ORR 21%; in combination with low-dose dexamethasone). Selinexor is a likely treatment option in the future for MM patients who have become refractory to IMiDs, proteasome inhibitors, and biologics like anti-CD38 antibodies. **Glasdegib** became the first SMO (Hedgehog pathway protein Smoothened) inhibitor to show benefit in AML and MDS by boosting overall survival in a phase 2 trial with patients ineligible for intensive chemotherapy. Analysts predict glasdegib to become a $450M product in AML should it receive FDA approval.

BTK inhibitors continue their impressive run: The first-in-class BTK inhibitor, **ibrutinib** (Imbruvica) reduced the risk of disease progression or death by 88% compared to chlorambucil in a pivotal phase 3 trial and demonstrated substantial efficacy as first-line therapy in CLL (24-mo PFS: 89% vs 34%; ORR: 92% vs 36%). A second-generation BTK inhibitor, **acalabrutinib**, also showed promising activity in relapsed/refractory CLL intolerant to ibrutinib and in patients with Richter's transformation (RT) of CLL (ORR: 79%, 38%, respectively).

BCL-2 inhibitors demonstrate synergies with other agents: Remarkable efficacy was seen with combinations of **venetoclax** (Venclexta), a potent BCL-2 inhibitor, with other targeted agents and chemotherapy. In a single-center study of 12 r/r CLL patients, the combination of venetoclax with **ibrutinib** and **obinutuzumab** resulted in 100% ORR. In another phase 1b study, venetoclax combined with **bortezomib** and **dexamethasone** demonstrated great efficacy and acceptable safety in patients with r/r multiple myeloma. The triplet was particularly effective in bortezomib non-refractory patients with an ORR of 97% and a CR rate of 23%. Remarkably, 31% of bortezomib-refractory patients also responded to the treatment, suggesting that venetoclax might be able to overcome bortezomib resistance.

Weighing cost and outcomes in clinical decision-making

Although progress in developing novel therapies and combinations is no doubt exciting, their cost and the complexity surrounding choice of treatments and their impact on the health-related quality of life of patients (HRQoL) are also critical. Accordingly, over 100 abstracts on these topics were presented at ASH 2016. A few examples:

Inevitable rise in cost of SoC in the future: In several indications, the most promising agents, especially combinations, are likely to significantly increase the cost of treatment in the future as they move toward replacing the current standard-of-care treatments. One study showed that the cost of brentuximab vedotin (BV) treatment in r/r cHL patients is already >$24,000/month; newer combinations with nivolumab may push the amount upwards of $35,000/month, highlighting the magnitude of the financial burden facing patients and our healthcare system.

Curb your enthusiasm? Even though preliminary findings suggest that chemotherapy-free, immunotherapy-based regimens can potentially be effective and a less toxic bridge to stem cell transplantation, questions remain whether this is the most cost-effective approach and if transplantations are necessarily the ultimate goal.

Importance of outcomes research: One study in a large registry of MM patients found no difference in health-related quality of life (HRQoL) for those receiving maintenance therapies compared with those who did not, despite the risks associated with continued active therapy. Another study involving ALL patients reported HRQoL benefit with a bispecific T cell engager (BiTE) antibody over standard chemotherapy as early as 8 days after treatment initiation. Together, they underscore the vital importance of assessing benefit-risk profiles for novel treatments before widespread clinical adoption.

CLARION | Healthcare, LLC

One Financial Center, Suite 1610 Boston MA 02111 Ph: 601.757.7850, www.clarionhealthcare.com

Sources: FDA.gov; Abstracts #222, # 99, #537, #639, #975, #1069, #341, #491, #234, #60, #2377; clinicaltrials.gov; OncLive; ASH clinical news alert