

American Society of Hematology (ASH) annual meeting 2017

A Clarion team was among over 25,000 attendees at the premier scientific and clinical congress for hematology. We highlight here key advances in malignant hematology from the meeting.

CAR-T breaks through



On the heels of the historic first approvals for CAR-T (chimeric antigen receptor T cell) therapy—Novartis’s Kymriah (**tisagenlecleucel**) and Gilead/Kite’s Yescarta (**axicabtagene ciloleucel**, “axi-cel”)¹—this year’s ASH included over 140 abstracts on CAR-T, more than any previous ASH meeting. The wealth of data, from an array of competitors, shows that the era of CAR-T is only just beginning. Some of the latest advances:

- **Encouraging signs of durability:** The initial CAR-T approvals were based on outstanding response rates, but longer follow-up (>15 mo. median) of **axi-cel** for R/R NHL finds that CR rates hold steady at ~40% from 6 to 12 mo.² This raises optimism for other CD19 CAR-Ts for R/R NHL, including **tisagenlecleucel**, which has comparable CR rates³, and **JCAR017** (Juno), whose 6-month CR rate seems even higher⁴. Durability is not restricted to CD19 CAR-T, either; follow-up (40 weeks median) of the BCMA CAR-T **bb2121** (bluebird/Celgene) for R/R multiple myeloma finds the CR rate has *doubled* since May to 56%⁵.
- **Insight into long-term toxicities:** Safety is a key concern for CAR-T; much research has focused on acute events such as cytokine release syndrome and neurotoxicities⁶. However, maturing data reveal serious late-onset or chronic toxicities: B-cell and bone marrow aplasia, infection risk, and persistent cytopenias have emerged in multiple studies^{7,8}. Long-term monitoring may be needed to mitigate these risks.
- **Progress on allogeneic “off-the-shelf” CAR-T:** After the FDA placed a clinical hold on **UCART123** (CD123 CAR-T) earlier this year⁹, Cellectis rebounded with favorable efficacy and safety data for **UCART19** (CD19 CAR-T) in R/R ALL (CR in 5 of 7 adults)^{10,11}, and promising preclinical data for **UCARTCS1** (SLAMF7 CAR-T) in multiple myeloma models¹². Mustang’s **MB-102** (CD123 CAR-T) demonstrated that CD123 can be an effective and safe target in R/R AML¹³. Poseida’s **P-BCMA-ALLO1** (BCMA CAR-T) showed compelling preclinical data for a non-viral vector, which may improve safety and reduce manufacturing costs¹⁴.

Sources: 1) FDA; 2) #578; 3) #577; 4) #581; 5) #740; 6) Brudno, 2016 Blood 127:3321; 7) Maude, “Monitoring for long-term complications of CAR-T Therapies”, 8) Buechner EHA 2017; 9) FierceBiotech Sep 5, ‘17; 10) #887, 11) #1271, 12) #502, 13) #811; 14) #167

New combinations and mechanisms raise the bar



Impressive clinical efficacy results likely to be practice-changing include the following:

- **Venetoclax-based combinations for CLL:** **Venetoclax** (Venclexta, a BCL-2 inhibitor; AbbVie/Genentech) + **ibrutinib** (Imbruvica, a BTK inhibitor; AbbVie/ Janssen) achieved 100% CR/CRi with 100% bone marrow MRD-negativity in frontline CLL, and 80% CR/CRi, with 100% of patients (n=33) still alive at 15 months, in R/R CLL¹⁵. These results far exceed current standards of care (SoC). **Venetoclax + rituximab** (Rituxan; Genentech/Biogen) in R/R CLL was also excellent: 2-yr PFS = 85% vs 36% for bendamustine + rituximab.¹⁶
- **Brentuximab vedotin (BV)-based combinations for R/R Hodgkin lymphoma (HL):** Two combinations with BV (Adcetris; Seattle Genetics) may become the new SoC for R/R HL. **BV + ibrutinib** demonstrated an 85% ORR and 46% CR, albeit in a small trial (n=13)¹⁷. **BV + nivolumab** (Opdivo, an anti-PD1 immunotherapy; BMS) demonstrated an 83% ORR and 62% CR (n=62)¹⁸. BV alone produces a 73% ORR, 32% CR¹⁹.
- **Inotuzumab ozogamicin (INO) for CD22+ R/R ALL:** **INO** (Besponsa; Pfizer) is approved for R/R ALL, but despite an 81% CR/CRi rate, INO improves mOS by only +1.5 mo vs standard chemo²⁰. New biomarker analyses revealed that patients who are MLL- with CD22 expression $\geq 90\%$ are the only subgroup to benefit from INO²¹. Future use of INO may focus on CD22+ subgroups, including the combination of **INO + mini-hyper-CVD**^{22,23}; in patients who responded to the regimen, the mPFS was as high as 30 months.²⁴
- **Targeted therapy for mutation-defined subgroups of AML:** IDH2-mutant AML has an approved IDH2 inhibitor, **enasidenib** (Idhifa; Agios/Celgene) which achieves 67% ORR and 33% CRc (vs. 20% CRc for SoC in 1L “unfit” AML)^{25,26}. IDH1-mutant AML may soon have **ivosidenib** (Agios), which achieves 73% ORR and 45% CRc²⁶. For FLT3-mutant AML, new competitors to **midostaurin** (Rydapt; Novartis)²⁷ may include **quizartinib** (Daiichi) and **gilteritinib** (Astellas), both of which have strong efficacy data^{28,29}.

Sources: 15) #429; 16) LBA-2; 17) #738; 18) #649; 19) Adcetris PI; 20) Besponsa PI; 21) #2574; 22) #1272; 23) #2557; 24) #2597; 25) Idhifa PI; 26) #639; 27) #2580; 28) #723; 29) #2705

Stem cell transplantation: continued refinement



Stem cell transplantation (SCT) is a cornerstone of hem-onc; important near-term improvements may include:

- **Non-genotoxic conditioning:** Conditioning for allogeneic SCT relies on toxic chemo and/or radiation therapy. **AMG191** (Amgen), a humanized mAb targeting c-Kit, may offer a safer approach, as shown in an early phase 1 trial for infants with severe combined immunodeficiency (SCID). Preclinical work suggests that combining **AMG191 + α CD47** may be better than monotherapy in non-immunodeficient subjects.³⁰
- **Improved prevention/treatment of GVHD:** Graft-versus-host disease (GVHD) is a frequent, life-threatening complication of allogeneic SCT³¹, and diverse approaches are being studied to address it. The **ProTmune** platform (Fate Therapeutics) may reduce GVHD severity through ex-vivo treatment of donor cells: in a phase 1 study, 3 of 7 recipients developed GVHD, but all were cleared by steroids within 1 week.^{31,32} **Abatacept** (Orencia, a CTLA4-Ig fusion; BMS) may provide effective prophylaxis: in patients undergoing SCT for various hem. malignancies, abatacept (vs the SoC arm) cut the rate of Gr 3/4 GVHD from 32% to only 3%, and boosted 12-month OS from 57% to 85%^{33,34}. **Ruxolitinib** (Jakafi/ Jakavi, a JAK inhibitor; Incyte/Novartis) continues to show effectiveness in treating both acute and chronic GVHD³⁵.
- **Optimizing autologous SCT for multiple myeloma:** AutoSCT is already a mainstay of MM treatment, but the decision algorithm has now become clearer: a study of 496 patients followed for >4 yr revealed that patients who achieve at least stable disease on induction do better moving directly to SCT, rather than delaying SCT in an attempt to first deepen induction response.³⁵ Furthermore, a phase 2 study suggests that autoSCT may be efficacious for smoldering MM, although long-term assessments are pending.³⁶

Sources: 30) SCI-21; 31) #4498; 32) Press release Dec 11, '17; 33) #212; 34) #1983; 35) #4538; 36) #402

The cost of a cure: striking the right balance



While oncology therapies continue to rise in efficacy, their rising cost is straining health care budgets and is ultimately unsustainable. Hem-onc is no exception and indeed illustrates the extremes of this issue:

- **Stem cell transplantation sets a high price for a cure:** Many hem. malignancies have a curative option with SCT, but recent analyses shows how expensive those cures can be. Among 692 ALL patients, 123 of whom relapsed, the mean SCT-related cost by the end of the first year post-index was **~\$400,000**, including ~50 days in the hospital; >\$275,000 of the cost was associated with the index hospitalization³⁷. In AML, a similar study found a mean cost of **~\$330,000** in a sample of 1,000 SCT procedures³⁸.
- **BV in newly diagnosed HL—multiplying cost for incremental benefit:** In the phase 3 ECHELON-1 trial in 1L HL, the commonly used, highly curative chemo regimen ABVD achieved 83% ORR, 70% CR, and 77.2% 2-yr PFS, while a regimen swapping bleomycin with BV (BV + AVD) achieved 86% ORR, 73% CR, and 82.1% 2-yr PFS³⁹. This marginal increase in efficacy may come with a whopping increase in price: a 6-cycle course of BV + ABV costs **~\$300,000** whereas 6 cycles of ABVD costs **~\$4,000**⁴⁰. Although still less expensive than SCT, BV + ABV is likely to find its use severely limited by the low cost of its alternatives.
- **CAR-T therapy may exceed \$1 million per patient:** Axi-cel is priced at **\$373,000** and tisagenlecleucel at **\$475,000** (for responders). These are already high numbers, but some estimate that hospitals will mark up CAR-T by as much as 400% due to how CMS processes charges on claims⁴¹. Even without that markup, toxicity management and prior and subsequent lines of therapy will certainly drive up the overall cost per patient. The future of this new technology likely depends on significant improvement of its economics.

Sources: 37) #3376; 38) #4694; 39) #6, 40) Hodgkin Lymphoma: New Insights and New Approaches, 41) Special Session on CAR T

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