TRENDS-in-MEDICINE

BULLETIN:

AMERICAN SOCIETY OF HEMATOLOGY (ASH) – PREVIEW

November 21, 2018
by Lynne Peterson

In a web briefing for reporters in advance of the annual ASH meeting in San Diego CA December 1-4, 2018, ASH officials noted that there will be ~1,000 oral presentations and ~3,900 poster presentations at the meeting. They highlighted three themes this year – sickle cell disease, CAR T therapies, and big trials with big results – as well as the late-breaking studies they predicted would be most important – and practice-changing. The big focus this year is chronic lymphocytic leukemia (CLL).

Sickle cell disease – 4 trials

- BLUEBIRD BIO's LentiGlobin – **Abstract #1023** – A first-in-man presentation of this gene therapy looks promising. *Oral, Monday, December 3, 6:15p-7:45p, Room 6B*
- **Abstract #3** – A study in the Democratic Republic of the Congo found that use of hydroxyurea had findings similar to results in the U.S.
- **Abstract #162** – Less than 15% of sickle cells patients have an appropriately-matched sibling donor, the gold standard treatment, but many do have a haploidentical family member, and this study found that at 2 years a haploidentical transplant improved long-term health-related quality of life, though there is an increased risk of mortality.
- **Abstract #315** – This study found that the high-dose opioids often prescribed in the hospital for sickle cell patients do not appear to increase their mortality vs. non-sickle cell patients.

CAR T Therapies – 5 studies

- GILEAD SCIENCES/KITE PHARMA's Yescarta (axicabtagene ciloleucel) – **Abstract #299** – A 36-patient study of this CD19 CAR T therapy alone or in combination with a BTK inhibitor [+ AbbVie and Johnson & Johnson's Imbruvica (ibrutinib)] in relapsed/refractory CLL showed that the combination was well tolerated, may decrease the cytokine release syndrome often seen with CAR T therapy, and may increase the response rate. *Oral, Sunday, December 2, 7:30a-9a, Marriott Marquis, Pacific Ballroom*
- NOVARTIS' Kymriah (tisagenlecleucel)
  - **Abstract #895** – Updated results from the ELIANA trial of this CAR T therapy in 97 acute lymphoblastic leukemia (ALL) patients had an overall response rate (ORR) of 81%. ASH secretary Robert Brodsky, MD, director of the Division of Hematology at Johns Hopkins University School of Medicine, said, "The impact is that two-thirds of responders are still in remission at 18 months, and they are fast-growing tumors and refractory patients, so as you get further and further out, it is encouraging to see responses." *Oral, Monday, December 3, 4:30p-6p, Room 6A*
  - **Abstract #1685** – An updated analysis of the JULIET trial in 19 refractory diffuse large B-cell lymphoma (DLBCL) patients showed that at 19 months, 40% of patients were still in remission. Dr. Brodsky said, "Again, that's very encouraging." *Oral, Saturday, December 1, 6:15p-8:15pm, Hall GH*

Trends-in-Medicine ■ 2731 N.E. Pinecrest Lakes Blvd ■ Jensen Beach FL 34957
772-285-0801 ■ Fax 772-334-0856 ■ www.trends-in-medicine.com

- JUNO THERAPEUTICS' SCRI-CAR19v1 – **Abstract #967** – This single-center, retrospective study looked at CAR T therapy and bone marrow transplantation (BMT), finding that:
  - Of 17 patients who did not get a BMT before CAR T and who went into remission
    - ✓ 3 did not get a transplant after remission, and 2 of those relapsed.
    - ✓ 14 patients had BMT after remission, and 12 are still in remission (2 relapsed).
  - Of 33 patients who had BMT before CAR T therapy and were offered a second transplant
    - ✓ 5 of 10 who were transplanted a second time stayed in remission.
    - ✓ Half of the 23 who did not get a second transplant relapsed.

  Dr. Brodsky said, "This…suggests BMT is a good way to consolidate remission after CAR T therapy.
  Oral, Monday, December 3, 4:30p, Manchester Grand Hyatt, Seaport Ballroom A
- MERCK MSD's Keytruda (pembrolizumab) – **Abstract #556** – A 14-patient, single-center study in children with ALL found that adding this PD-1 inhibitor to CAR T therapy (Kite's Yescarta) was safe and may be effective in getting the immune response back. Dr. Brodsky said, "The idea is to take the brakes off, and we saw that in roughly half the patients…It's a small study with preliminary data, but it is exciting." *Oral, Monday, December 3, 7a-8:30a, Room 20A*

Big Trials/Big Results – 7 studies

- ROCHE's Rituxan (rituximab) – **Abstract #781** – A 592-patient FLYER trial in DLBCL patients with early-stage, non-bulky disease found that 4 cycles of R-CHOP (followed by 2 cycles of Rituxan alone) was sufficient for younger patients. The modified regimen was as effective as the standard 6 cycles of R-CHOP, meaning patients can avoid 2 cycles of CHOP. Dr. Brodsky said, "Both arms did extremely well, and there were no differences. The reason this is important is chemotherapy can have late effects, including cardiac toxicity from adriamycin, so there is a big advantage of de-escalating care. This will almost certainly be practice-changing." *Oral, Monday, December 3, 2:45p-4:15p, Ballroom 20*
- ABBVIE and JOHNSON & JOHNSON's Imbruvica (ibrutinib) – **Abstract 6** – This study found ibrutinib in combination with Rituxan produces superior overall survival in untreated, older CLL patients. Dr. Brodsky said, "This will be practice-changing, too…The reason it is important is that ibrutinib has been approved for CLL since 2016, but before it was compared to chlorambucil, which is not very effective. It was never compared to 'modern' standard of care, which is chemo-immunotherapy with bendamustine [Teva's Bendeka] + rituximab. The trial showed that, at 32 months, progression-free survival [PFS] was improved in both ibrutinib arms vs. bendamustine – 41 months with the current standard but PFS not reached in the other [ibrutinib] arms. This shows that ibrutinib has superior PFS in older patients (age ≥65). This is likely to be practice-changing." *Oral, Sunday, December 2, 2p-4p, Hall AB*
- CELGENE and ACCELERON PHARMA's luspatercept
  - **Abstract #163** – The results of the Phase III BELIEVE trial of this erythroid maturation agent (EMA) in adult beta-thalassemia patients. *Oral, Saturday, December 1, 2p-3:30p, Room 30D*
  - **Abstract #1** – The results of the Phase III MEDALIST trial in transfusion-dependent patients with very low-to-intermediate myelodysplastic syndromes (MDS) showed this drug reduced the need for transfusions by reducing anemia. ASH president Alexis Thompson, MD, MPH, a pediatric hematologist from the Robert Lurie Comprehensive Cancer Center of Northwestern University, said, "This drug is moving through the pipeline in the U.S. and Europe. It is fast tracked and one to look forward to that is potentially practice-changing." *Oral, Sunday, December 2, 2p-4p, Hall AB*
- **Abstract #793** – A method for stratification of MDS patients.
- **Abstract #811** – A study of the role of the gut microbiome.
- **Abstract #559** – An initial report from the BEAT AML UMBRELLA trial which showed that it is feasible to use next-generation sequencing (NGS) early in the treatment of acute myeloid leukemia (AML) patients age >60 to figure out which mutation is driving the leukemia, so therapy can be tailored. Dr. Thompson said this "will change how we do clinical trials in the future." *Oral, Monday, December 3, 7a-8:30a, Manchester Grand Hyatt, Seaport Ballroom F*

Late-breaking trials – 7 studies

Dr. Brodsky said all of these will change practice. They are all being presented as orals on *Tuesday, December 4, 7:30a-9:15a, Hall AB*

- ABBVIE and ROCHE/GENENTECH's Venclexta (venetoclax) – **LBA7** – This study found that the Gly101Val mutation is responsible for patients becoming resistant to this Bcl-2 inhibitor. Dr. Brodsky said, "We can screen patients for the outgrowth of this mutation, and when it is found, there is the potential to switch therapies…or, I think what will happen is this will be a new drug target, and we will see new drugs to overcome this resistance."

- JOHNSON & JOHNSON
  - and ABBVIE's Imbruvika (ibrutinib) – **LBA4** – This Phase III E1912 trial compared ibrutinib to chemo-immunotherapy with fludarabine + cyclophosphamide + Rituxan (FCR) in untreated patients (not restricted to older patients) with CLL. Dr. Brodsky said, "This showed that not only did ibrutinib improve PFS, but it also improved overall survival, so it is practice-changing…Ibrutinib will be front-line for CLL."
  - and GENMAB's Darzalex (daratumumab) – **LBA2** – The Phase III MAIA trial of Celgene's Revlimid (lenalidomide) + dexamethasone ± this anti-CD38 in 737 newly diagnosed multiple myeloma patients ineligible for a bone marrow transplant found deep responses with the addition of daratumumab. PFS had not been reached with daratumumab vs. 32 months without it. The CR rate was 47.6% with daratumumab vs. 24.7% without it. Dr. Thompson said this is a "large, randomized trial that will change practice."
  - Xarelto (rivaroxaban) – **LBA1** – The results of the >800-patient CASSINI trial showed that this Factor Xa inhibitor markedly reduced the incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients with high-risk malignancies, with good tolerability and little bleeding.

- NOACs – **LBA5** – The PAUSE trial found that when a patient is on a novel oral anticoagulant (e.g, a Factor Xa inhibitor), the NOAC should be stopped two days before and restarted two days after an operation/procedure in high-risk patients and one day before and after for low-risk patients.

- SILVER LAKE RESEARCH's HemoTypeSC – **LBA3** – This is a positive report on a study in Uganda of this simple screening test for sickle cell disease. Dr. Brodsky said, "It uses just 1.5 ml of blood…and had *incredible* accuracy…This will have a huge impact on newborn screening and counseling and treating patients. It will certainly be practice-changing in low resource areas."

- SWEDISH ORPHAN BIOVITRUM (Sobi) and NOVIMMUNE's Gamifant (emapalumab) – **LBA6** – This interferon gamma antibody, was approved on November 20, 2018, to treat refractory/recurrent primary hemophagocytic lymphohistiocytosis (HLH). At ASH a pediatric study will be presented in which the primary endpoints were met, with a response rate >70%, whether patients got chemotherapy for emapalumab first. Dr. Thompson said, "There [were] no approved drugs for HLH, so this will have a major impact."