TRENDS-in-MEDICINE

BULLETIN:

AMERICAN SOCIETY OF HEMATOLOGY (ASH) – PREVIEW

November 21, 2017
by Lynne Peterson

In a webinar with reporters, ASH officials highlighted a number of abstracts to be presented at the meeting (December 9-12, 2017) in Atlanta. ASH officials pointed to four areas of focus: CAR T cell therapies, gene therapies, targeted therapies, and hemostasis/thrombosis as well as six late-breaking studies and five abstracts that Joseph Mikhael, MD, MEd, a hematologist from the Mayo Clinic Arizona and chair of the ASH Committee on Communications, said were "likely to have real clinical impact."

The presentations were all based on the abstracts; there wasn't any information above and beyond what is in the abstracts, but the studies chosen provide a glimpse at what ASH officials consider the key studies out of the 1,000 oral talks and 3,500 posters to be presented at ASH. Some of the therapies highlighted this year were also in the spotlight last year.

Normally, meeting review webcasts with reporters highlight 3-7 studies. ASH highlighted 23! And it was spread across 16 companies: AbbVie, Ablynx, BioMarin Pharmaceutical, bluebird bio, Blueprint Medicines, Celgene, Daiichi Sankyo, Gilead Sciences/Kite Pharma, GlaxoSmithKline, Global Blood Therapeutics, Johnson & Johnson, Kyowa Hakko Kirin, Novartis, Poseida Therapeutics, Roche/Genentech, and Seattle Genetics.

At some meetings this year, the majority of trials have been positive. At ASH, all the highlighted trials are positive.

CAR T CELL THERAPY

ASH president Kenneth Anderson, MD, PhD, an oncologist/hematologist from Dana-Farber Cancer Institute, reviewed three abstracts. He said that in addition to promising data for CAR T therapies, they will all offer "futuristic thoughts" on how to improve efficacy, selectivity, and safety by reducing toxicity.

GILEAD SCIENCES/KITE PHARMA's Yescarta (axicabtagene ciloleucel, axi-cel, KTE-C19) – non-Hodgkin's lymphoma (NHL)
Abstract #578 – Monday 12/11, 7:15 am

The results of the pivotal ZUMA-1 trial were presented at the American Society of Clinical Oncology (ASCO) meeting in June 2017 and recapped at the Society for Immunotherapy of Cancer (SITC) meeting earlier this month. At ASH, there will be longer-term follow-up data from this trial in refractory advanced NHL. This therapy was approved by the FDA on October 18, 2017, so the data are likely to mostly be reassuring to doctors starting the therapy or considering starting it rather than educating them about an exciting new development in CAR T therapy.

Dr. Anderson said the trial showed "very promising data" for Yescarta: 82% overall response rate (ORR), 54% complete responses (CRs), and 44% ongoing responses at 8 months of follow-up – and 1-year follow-up will be presented at the meeting. He also noted

that there is toxicity, cytokine release syndrome (CRS) and neurological events, adding, "But there was this remarkable response… What will be presented is not only toxicity and response, but mechanisms of resistance, whether cells become CD19-negative…It is very promising present data, but there will be thoughts on improving efficacy and lessening toxicity in the future."

NOVARTIS' Kymriah (tisagenlecleucel-T, CTL-019) – acute lymphoblastic leukemia (ALL)
Abstract #577 – Monday 12/11, 7 am

This intravenous CAR T therapy is FDA approved for treating pediatric and young adult patients (age 3-25) with relapsed/refractory B-cell ALL, but at ASH there will be data from the pivotal Phase II JULIET trial in diffuse large B-cell lymphoma (DLBCL). Dr. Anderson said, "What I think is important here is that this is a multicenter trial…It sort of demonstrates for all that this technology can be done in an international scope."

He said the 81-patient trial showed that, with >3 months of follow-up, the response rate was 53%, including 39% CR; and at 6 months, the CR was 30% and PR was 7%…It would appear that if a patient is in CR at Month 3, 95% kept that response at 6 months…There was CRS again, and it can be severe. Nonetheless, this is very promising data – very much like the ZUMA trial. And it highlights that this technology can be done in the real-world in a multicenter trial."

BLUEBIRD BIO and CELGENE's bb2121 – multiple myeloma
Abstract #740 – Monday 12/11, 3 pm

This anti-BCMA CAR T therapy was recently granted breakthrough therapy designation by the FDA as a treatment for relapsed/refractory multiple myeloma, and updated trial data will be presented at ASH. Dr. Anderson said, "In 21 patients, the response rate was 84%, and there was dose-dependence. It was 100% if one got to $15x10^7$ cells infused. There was remarkably good tolerability in terms of CRS…This demonstrates, again, in patients with multiple myeloma and no other options, you can achieve very impressive responses."

GENE THERAPIES

GLAXOSMITHKLINE's GLOBE lentiviral vector gene therapy – beta thalassemia
Abstract #355 – Sunday 12/10, 9:15 am

This gene therapy was developed by Fondazione Telethon and Ospedale San Raffaele in Italy and licensed to GSK. At ASH, the results of the Phase I/II TIGET-BTHAL trial in beta thalassemia will be presented. ASH secretary Robert Brodsky, MD, a hematologist from Johns Hopkins University School of Medicine, noted, "Gene therapy grabbed headlines in the '80s and '90s, but the technology was not quite there…They've made a lot of progress…And this is an example of that…The only cure for severe thalassemia is bone marrow transplant…For this group of patients, the concept of gene therapy…is very appealing."

The data show that, with a median follow-up of more than a year, 3 of the 7 patients became transfusion independent. Four are still requiring transfusions but much fewer than before the trial. This is an early Phase I/II trial, but it demonstrates the potential to treat/cure beta thalassemia."

Customized induced pluripotent stem cell-derived red cell reagents – sickle cell disease
Abstract #3 – Sunday 12/10, 2-4 pm

This is an investigator-initiated and sponsored study with no apparent commercial involvement of transfusions in sickle cell disease. Dr. Brodsky said pluripotent stem cells "really haven't found a clinical application yet. This probably is the first clinical application of induced pluripotent stem cells in hematology…These investigators tried to overcome the problem of cross-matching…particularly for patients with sickle cell anemia – or any other severe anemia where patients require a lot of transfusions…The problem is patients develop antibodies to the donors…and it can be very hard to…detect these antibodies…This group used CRISPR to knock out the problem genes…This technology needs to go a little further, but it is proof of principle to show pluripotent stem cells can be used."

GLOBAL BLOOD THERAPEUTICS' voxelotor (GBT-440) – sickle cell disease
Abstract #689 – Monday 12/11, 3:45 pm

This is an oral drug designed to improve hemoglobin levels, fatigue, pain, and quality of life in patients with severe, transfusion-refractory sickle cell disease. Dr. Brodsky said, "This once-daily oral drug inhibits polymerization of hemoglobin. This is a new target for sickle cell disease. We don't have many effective drugs here – just hydroxyurea. Of 13 patients, only 4 reached 12 weeks at the time of the abstract…But they saw a rise in hemoglobin and decreased hemolysis. Based on these promising results, a Phase III trial is planned. It is clear this drug has activity."

Gene therapy for X-linked SCID – severe combined immunodeficiency (SCID)
Abstract #523 – Sunday 12/10, 4:30 pm

There will be interim results from an investigator-initiated Phase I/II study with no apparent commercial involvement in what is sometimes called "bubble boy" disease. Dr. Brodsky said, "It used a newer, safer lentivirsus…and reduced-intensity chemotherapy. Six patients were treated, and all have complete T-cell reconstitution. And the early suggestion of the data is that they have improved B-cell function as well…This is an advance in that it is a safer vector, with less chemotherapy, and hopefully is safer and will make gene therapy more available for this disorder."

TARGETED THERAPIES

KYOWA HAKKO KIRIN's Poteligeo (mogamulizumab) – mycosis fungoides (MF) and Sézary syndrome (SS)
Abstract #817 – Monday 12/11, 4:30 pm

The FDA granted breakthrough therapy as a treatment for MF and Sézary syndrome to this anti-CCR4 in August 2017 based on the results of the Phase III MAVORIC trial. Dr. Anderson said there will be follow-up data from this trial at ASH, adding that T-cell lymphomas are ~10% of all lymphomas. He said this study was highlighted "because there were a large number of patients (372) on ≥3 prior therapies. The novel therapy basically doubled progression-free survival [PFS] – 8 months vs. 3 months, improved ORR and quality of life. This is…very promising."

BLUEPRINT MEDICINES' Blu-285 – advanced systemic mastocytosis (AdvSM)
Abstract #2 – Sunday 12/10, 2-4 pm

The results of a Phase I first-in-man trial of this KIT-D816V inhibitor in AdvSM will be presented at ASH. Dr. Anderson said, "The reason we think this is so exciting is it is reminiscent of Gleevec [Novartis, imatinib] in chronic myeloid leukemia [CML] which occurred ~20 years ago…Gleevec targets a Bcr-Abl abnormality that causes CML…And now we have long-term survival and cures…due to Gleevec. In this study, Blu-285 targets the mutation that causes proliferation of mast cells that [cause this disease]…Excitingly, in this dose-escalation trial, the vast majority of patients responded, with 28 of 30 still on treatment."

He said the 300 mg dose is going forward, adding, "It is very promising because not only did patients feel better, but the clinical signs, like edema and peripheral swelling, were markedly decreased…It is the same kind of medicine as Gleevec in another disease, albeit a rare disease."

JOHNSON & JOHNSON's Imbruvica (ibrutinib) + ABBVIE and ROCHE/GENENTECH's Venclexta (venetoclax) – chronic lymphocytic leukemia
Abstract #428 – Sunday 12/10, 12:15 pm

The initial results of the CLARITY TAP trial combining these two agents – a BTK inhibitor and a BCL2 inhibitor – in relapsed/refractory chronic lymphocytic leukemia (CLL) will be presented. Dr. Anderson said, "All of the patients – 25 of 25 – had a response, and 15 had a CR. At 6 months 84% have no CLL in their bone marrow. Minimal residual disease was achieved in 28% of patients. That means less than 1 in 10,000 or 1 in 100,000 or 1 in a million cancer cells in bone marrow. This demonstrated that combining targeted therapies, each with a different mechanism of action, is synergistic."

SEATTLE GENETICS and TAKEDA's Adcetris (brentuximab vedotin), an anti-CD30 drug conjugate – Hodgkin's lymphoma
Abstract #6 – Sunday 12/10, 2-4 pm

Dr. Anderson said the ECHELON-1 trial in front-line Hodgkin's lymphoma showed that a regimen with Adcetris is superior to one with bleomycin. That is, A+AVD (brentuximab-doxorubicin-vinblastine-dacarbazine) is superior to standard ABVD (doxorubicin-bleomycin-vinblastine-dacarbazine), "This is of note because the 2-year event-free survival was 82% vs. 77%…There was more lung toxicity with A+AVD but more infection and neuropathy with ABVD."

HEMOSTASIS/THROMBOSIS

Dr. Brodsky said, "This is arguably one of the most interesting areas in all of hematology, where some really ground-breaking, paradigm-shifting, home-run trials are being done."

ROCHE's Hemlibra (emicizumab-kxwh) – hemophilia A
Abstract #85 – Saturday 12/9, 9:45 am

The FDA recently approved this agent to prevent or reduce bleeding in adult and pediatric patients with hemophilia A with Factor VIII (FVIII) inhibitors. The drug was given a boxed warning that severe blood clots (thrombotic microangiopathy and thromboembolism) have been observed in patients who were also given a rescue treatment (activated prothrombin complex concentrate) to treat bleeds for 24 hours or more while taking Hemlibra.

Dr. Brodsky said, "This is an incredibly exciting drug." He explained that this is the most common form of hemophilia and is treated with Factor VIII concentrate, given IV, "The problem with Factor VIII concentrate is it is not only inconvenient and has to be given IV twice a week, but a large number of patients get antibodies, and it stops working. There are some bypass agents that are very expensive and have some activity but are not very satisfying. Emicizumab is given subcutaneously weekly…These are young, pediatric patients, and 90% of these children had no treated bleeds on the study…The conclusion was that emicizumab, given subcutaneously weekly, prevented or substantially reduced bleeding…It is really a game-changer for hemophilia A with inhibitors."

BIOMARIN PHARMACEUTICAL's BMN-270 – hemophilia A
Abstract #603 – Monday 12/11, 7:30 am

This AAV5-F8 gene therapy was also described by Dr. Brodsky as a "game-changer." He said that at ASH 2016 there were data on using this viral vector in long-term control of hemophilia B (Factor IX deficiency), "but Factor VIII deficiency [hemophilia A] was thought to be a much more difficult target because the gene is very big and doesn't fit well into the vector…They made a truncated Factor VIII and put it into the vector…and the long and short of it is: it is very effective."

He explained that a single IV infusion "showed that activity plateaued at 8 weeks ***in the normal range***, which is really amazing. They could stop the infusions and had sustained Factor VIII activity…Optimal dosing will be evaluated in Phase III. This is a potential ***cure*** for hemophilia A…and it may just require a single IV infusion…Clearly, long-term safety needs to be studied, but it is a ground-breaking trial."

JOHNSON & JOHNSON/JANSSEN's Xarelto (rivaroxaban) – venous thromboembolism
Abstract #625 – Monday 12/11, 10:30 am

Venous thromboembolism (VTE) – pulmonary embolism (PE) or deep vein thrombosis (DVT) – is very common in cancer patients. Low molecular weight heparin (LMWH) has been the treatment of choice. This trial was aimed at seeing if a novel oral anticoagulant, a Factor Xa inhibitor, would be as safe and effective as the LMWH dalteparin, given subcutaneously. Dr. Brodsky said the results showed a VTE rate of 11% with dalteparin vs. 4% with rivaroxaban, with major bleeds comparable. There were more clinically-relevant non-major bleeds with rivaroxaban, but he said, "So, there is a little more bleeding with the oral agent, but these were not major bleeds. Major bleeds were comparable. There was no survival difference."

He called this "another study that shows that oral anticoagulants are safe in cancer patients. And that is big news because it [LMWH] has been a difficult way to administer anticoagulation in patients with cancer."

LATE BREAKERS

Four of the late-breaker trials were highlighted on the webcast:

Tuesday 12/12, 7:30-9 am – Late-Breaker session

ABBVIE and ROCHE/GENENTECH's Venclexta (venetoclax) + ROCHE's Rituxan (rituximab) – CLL – Abstract LBA-2

An interim analysis of the Phase III MURANO trial showed that adding venetoclax to Rituxan is superior to the combination of bendamustine + Rituxan. Dr. Anderson said, "The reason this is exciting is it is using a novel agent (venetoclax) with a standard agent [Rituxan] and comparing it to standard of care in 389 patients. It showed PFS, overall survival, ORR, CR, and MRD [minimal residual disease] were all superior with venetoclax."

JOHNSON & JOHNSON's Darzalex (daratumumab) – multiple myeloma – Abstract LBA-4

Dr. Anderson said the international Phase III ALCYONE trial of >700 patients looked at adding this anti-CD38 to standard of care (bortezomib-melphalan-prednisone) in newly diagnosed multiple myeloma. The hazard ratio was impressive: 0.5 across all subgroups. Dr. Anderson said, "That means there was a doubling of PFS if you added daratumumab to standard of care. And ORR, very good PR, and MRD were all in favor of daratumumab…And it was very well tolerated…This is a major advance in non-transplant patients."

ABLYNX's caplacizumab – acquired thrombotic thrombocytopenic purpura (TTP) – Abstract LBA-1

The results of the HERCULES trial of this anti-von Willebrand factor (anti-VWF) nanobody will be presented. Dr. Brodsky said, "The time to platelet response greatly favored the caplacizumab arm, even death…favored caplacizumab…It was a very positive trial. It is a potential game-changing drug for the management of TTP."

DAIICHI SANKYO's Savaysa (edoxaban) – acquired thrombotic thrombocytopenic purpura (TTP) – Abstract LBA-6

The results of the 1,050-patient Hokusai-VTE-Cancer trial showed this oral Factor Xa inhibitor is safe to use to prevent VTE in cancer patients. Dr. Brodsky said, "This is a larger study than the previous study [the rivaroxaban trial]. The big question was whether it is safe to use a novel oral anticoagulant [NOAC]. This was a non-inferiority trial, and the primary endpoint was VTE or major bleeding, and the long and short is, again, that it confirmed that novel oral anticoagulants are at least as good as LMWH. This is of very broad interest to cancer doctors and hematologists."

ADDITIONAL ABSTRACTS TO WATCH

Five other abstracts were highlighted, but without detail. They are:

- **POSEIDA THERAPEUTICS' P-BCMA-ALLO1 – multiple myeloma**
  Abstract #503 – Sunday 12/10, 5:30 pm
  This is another CAR T therapy. Dr. Mikhael said, "This is a little early for prime time, but the idea is a more universal CAR T."
- **ABBVIE and ROCHE/GENENTECH's Venclexta (venetoclax) + ROCHE's Gazyva (obinutuzumab) – CLL**
  Abstract #430 – Sunday 12/10, 12:45 pm
  Gazyva was recently granted expanded approval by the FDA to treat previously untreated advanced follicular lymphoma. This is a Phase Ib study in previously untreated CLL.
- **Abstract #277** – Transfusion dependence and use of hospice among Medicare beneficiaries.
- **Abstract #861** – An FDA report on the enrollment of older adults in hematologic malignancy trials.
- **Abstract #128** – Pain trends in sickle cell disease in Wisconsin emergency rooms.