MYELOMA HIGHLIGHTS FROM ASH CONFERENCE "VIRTUALLY" 12/10-13/2021

According to Jack Aiello (definitely not medically trained)

PREFACE

This is my 16th year attending ASH (American Society of Hematology), where typically over 30,000 attendees from all over the world (hematologists/oncologists, lab researchers, oncology nurses, scientists & 300 pharma companies) attend. However, due to COVID-19, ASH was set up as a hybrid meeting where some attended in person and many, including myself, virtually. That said, I watched most of the presentations as they were happening, asked a few questions that were answered in real time, and watched replays of other talks. Both oral and poster abstracts were presented on all blood diseases, especially cancers. This year there were more than 879 myeloma-related abstracts, with about 100 selected for oral presentation. (I also included a few poster abstracts as well.) I'm grateful to the IMF (www.myeloma.org) and their pharma donors for registering me for ASH so that I could learn and subsequently share my patient perspective with you.

Rather than attending talks on Biology, I typically focus on the Clinical Trials, which I'm able to understand and are more relevant near-term to patients. One advantage of the virtual experience is that I could replay presentations that I either missed or wanted to be clear on details after having viewed the printed abstracts in November. You might want to view the published abstracts as well at www.hematology.org and various press releases. Wherever possible, I've listed Day-Abstract#-Lead Investigator after the trial results, e.g. {Sat-79-J Laubach} and clicking on the abstract number will take you to the actual abstract for a limited amount of time. Note though that the data results presented is often updated from the printed abstract.

There are other ways to learn more about results from this conference. There's already a wonderful replay available recorded the day after ASH ended which you can find as part of the IMWG Conference Series at https://www.myeloma.org/videos/imwg-conference-series-ash-2021. There are scheduled webinars (IMF-12/16/21 https://www.myeloma.org/videos/best-ash-2021-webinar, MMRF-12/21/21 https://themmrf.org/event/multiple-myeloma-highlights-from-the-2021-american-society-of-hematology-ash-annual-meeting/) which you can listen to live or by replay. You'll also find some patient blogs (including mine) on the IMF website (https://ash2021blogs.myeloma.org/), Patient Power (www.patientpower.info), and Myeloma Crowd/HealthTree (www.myelomacrowd.org) among others. One of the excellent blogs I'll make reference to was written by Yelak Biru, long-time MM patient, advocate, great friend, and now the new CEO of IMF. See this link for a listing of many of the trial names and schemas: https://ash2021blogs.myeloma.org/ash21-trial-design-acronyms/. And all of us in the SF Bay Area should attend the virtual LLS Blood Cancer Conference (which includes updates from ASH) Feb 5, 2021 (register at www.lls.org). Dr. Michaela Liedtke from Stanford will do a great job presenting the latest information.

Even virtually, presentations of clinical trial results followed the same format: Background (including hypothesis), Study Objective, Design & Treatment schema, Patient Characteristics & Cohorts, Responses (include high-risk cytogenetics), Toxicity (hematological and non-hematological), Conclusion, and Next Step. Remember, the goal of Phase I (typically handful of patients) is to determine "Maximum Tolerated Dose" and/or Recommended Ph2 Dose (RP2D); Phase I/II and II (typically 25-75 pts) continue to measure dosage escalation and safety while looking at responses; and finally Phase III (several hundred patients) compares response rates between new and current standard of care (SOC) treatments.

Treatment schemas are defined for stages of **Induction**, and optionally **Transplant (SCT)**, **Consolidation**, and **Maintenance** with specified **Randomization** along the way for newly diagnosed pts (**NDMM**) relapsed/refractory pts (**RRMM**). Dosage amounts and scheduling are provided for each drug along with optimum number of treatment cycles (typically 28 days). **Risk stratification** correlates various techniques such as cytogenetics-FISH analysis (e.g. chromosome deletions and translocations) and gene-expression profiling (GEP). And while all these details are provided in the actual abstract, I don't necessarily list them below.

HIGHLIGHTS (e.g. My Takeaways)

1. This year's ASH expanded on immunotherapies…more CAR-T's and Bi-specific Antibodies (BiABs) …as well as more targets besides BCMA. Since BCMA is a prominent target but can shed from tumor cells, I appreciated something called a gamma secretase inhibitor (GSI) that can actually increase BCMA density and potentially be combined with the immunotherapy.

2. The iSTOPMM study focus on adults over 40 and asks if screening for MGUS should be done. The PROMISE study screens high-risk adults, both Blacks or those who have first degree relatives with MM. While these studies are early, the iSTOPMM study already determined that the rate of SMM among adults over 40 is .5%. We already know that MGUS rates for adults over 50 is 3%. While we don't have definitive treatments for these patients, a recommendation to follow these patients may result in diagnosing myeloma earlier.

3. My friend Yelak Biru commented that transplants will likely be around for 10 years. While that seems long to me given the immunotherapy results, he brings up a valid point that head-to-head studies may be required.

4. "Quads", that is induction with 4 drugs such as Dara-RVd, appear here to stay based on a number of trials that show adding Daratumumab or Isatuximab (both CD-38 mAb's) to 3 drugs results in better outcomes.

5. Cytokine Release Syndrome (CRS) and Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS), can be potential major side effect in early CAR-T and Bi-specific Antibodies (BiABs) treatment. However, with more treatment experience, these seem to be much better recognized and treated quickly so that almost all occurrences are categorized as Grades 1 or 2 rather than the more severe Grade 3 and higher.

6. We know that MRD (Minimal/Measurable Residual Disease) is an excellent prognosticator for treatment efficacy. However, it's value as a guide to treatment (when to stop, continue or change treatment) is being tested in various clinical trials. In addition, Mass Spectrometry results via blood test are being favorably compared with MRD and is certainly favored by patients who want to avoid that painful bone marrow biopsy/aspirate.

COMMENTS AND DISCUSSIONS I FOUND PROVOCATIVE

7. "While there's no specific treatment for HRMM, our goals should be to provide continuous therapy and focus on getting MRD (Minimum Residual Disease) as low as possible." M-V Mateos

8. "An important study from Dr R Fonseca looking at patients from 2000-2018 showed "that 57% of non-transplant eligible patients only get 1 Line of Therapy, so many patients are not getting newer

treatments." S Lentzsch [Note, Dr Fonseca's paper can be seen at https://bmccancer.biomedcentral.com/track/pdf/10.1186/s12885-020-07503-y.pdf.]

9. Dr N Biran, when treating relapsed MM, suggested using the TRAP algorithm when making subsequent treatment decisions. T=Timing of relapse; R=Response from prior therapy; A=Aggressiveness of disease; and P=Performance status. This algorithm was reiterated by Dr SV Rajkumar.

10. "Triplets outperform doublets in early relapse." N Biran

11. For Non transplant eligible patients, Dr Moreau noted "I think DaraRd till progression [Maia study] is the best treatment for elderly patients. Dr SV Rajkumar countered "But VRd for 6 mos, then Rev maintenance is more cost effective, easier on the patient, and also provides excellent results so either treatment choice is ok."

12. Dr Rajkumar's principles for selecting treatments for relapsed MM: 1) use a triplet; 2) change 2 drugs; 3) consider a transplant; 4) consider a clinical trial.

13. "Ultimately bi-specifics will be used in all lines of therapy and CAR-T will replace transplant." predicted T Martin

14. "If Blenrep is working, don't give up due to ocular side effects. Rather, try dose adjustment, give less frequently, even adding prednisone has helped with eye effects…don't give up." M Gertz

15. For triple class refractory patients both Drs Martin and Gertz commented that the alkylating agent Cytoxin should be considered if it hasn't been previously used

16. "Mass spec will be rolled out in the next year or so as a blood test called Exent from the Binding Site" B Durie

17. "We at UCSF are considering 4-drug therapy Griffin (Dara + RVd) to be the new standard of care for transplant-eligible MM pts, pending insurance coverage for the Dara." T Martin

18. "Celmods such as Iberdomide will replace IMIDs Revlimid and Pomalyst." MV Mateos

19. "We've seen poor responses to Covid vaccine for patients on anti-BCMA and anti-CD38 treatments but some patients have efficacy after their booster shot. Stopping CD-38 treatment for a period of time doesn't appear to improve booster benefit." T Martin

MGUS & SMOLDERING MM (early screening)

20. In iStopMM, over 75,000 individuals were screened with nearly 4,000 MGUS patients found and after 3 years of follow-up some have become SMM and myeloma patients. {Sat-156- Kristinsson} While this is a long-term study, several interesting outcomes have already been determined: 1) SMM occurs in 0.5% in persons 40 years or older but according to today's risk stratification, only 1/3 of these SMM patients are considered intermediate or high risk; {Sat-151-A Thorsteinsdottir} 2) There is no relationship between MGUS and the susceptibility of either getting COVID-19 or the severity of it. {Sat-154-S Rognvaldsson}

21. The PROMISE study examines potentially high-risk individuals, specifically Black/AA (N=2439) and those with first degree relative dx with hema malignancy or precursor to MM (N=3866). MGUS screening via both SPEP (6%) and Mass Spec (13%) both confirmed higher rates as well as increased sensitivity with Mass Spec. {Sat-152-H El-Khoury}

22. An update for the Cesar study for HR SMM KRd -> SCT -> KRd ->Rd maintenance up to 2 years. For N=90, 52% are MRD- (10^{-5}) after maintenance and at 5 yrs, 94% are alive and progression-free. {Sat-1829-MV Mateos}

FRONTLINE (INDUCTION OR FIRST LINE) THERAPY

TRANSPLANT-Eligible

23. Darzalex® (daratumumab) or Sarclisa® (isatuximab) (both CD-38 monoclonal antibodies) provides benefit when considering outcomes such as responses, minimal residual disease (MRD) rates, PFS, and or OS. Example include Abstracts {Sun-463-H Goldschmidt} (Isa + RVd induction), {Sun-464-A Perrot} (Dara + IxRd induction), and {Sun-465-M Kaiser} (Dara + CyBorD + Rev (5 drugs!) for ultra high-risk (>1 HR factor) MM.

24. Master Trial: Dara-KRd -> SCT -> D-KRd -> D-KRd -> R maintenance. MRD is tested after each treatment and 2 successive MRD- at 10^{-5} results moves the patient into an MRD-SURE category to stop treatment (observation only with continued MRD surveillance). Results were presented for SR, HR and UltraHR (>1 HR factor) patients. 2-yr PFS and OS were in the 90%+ for SR and HR but only 58% and 76% respectively for UHR pts. And 84 pts (72%) achieve MRD-SURE. {Sun-481-L Costa}

25. An update with a follow-up of 2 years after maintenance was provided for the Griffin study: [Dara]RVd -> SCT -> [D]RVd -> [D]R maintenance (2 yr). Dara arm had superior outcomes: MRD- (10^{-5}) 81% vs 44% after 2 yrs maintenance, CR 82% vs 61%, 3yr PFS 89 vs 81% and improved rates of durable MRD- lasting >12 mos 44% vs 13%. {Sat-79-J Laubach}

MAINTENANCE

26. This resulted in a negative study, comparing Ninlaro® (ixazomib) added to Revlimid® (lenalidomide) + dexamethasone (IRd) maintenance versus Rd alone and concluding that the Ixa arm did not result in improved progression free survival (PFS). {Sun-466-L Rosinol}

TRANSPLANT-Ineligible

27. In another negative study, the addition of Empliciti® (elotuzumab) to Revlimid, Velcade® (bortezomib), and dex (ERVd) induction/consolidation and Rev maintenance did not result in improved PFS or OS. {Sun-486-H Goldschmidt}

CURRENT TREATMENTS FOR RELAPSED/REFRACTORY (R/R) PATIENTS

28. Xpovio (Selinexor): There were several abstracts that looked at Selinexor efficacy in combinations XPd {Sun-2748-D White} and XVd {Mon-3793–S Jagannath}. And another study examined a negative correlation between Dara and Selinexor. Specifically, it suggested that sequencing Selinexor directly after a patient relapsed on Dara may improve Selinexor efficacy. {Mon-893-P Sudalagunta}

NEW DRUGS: CAR-T, BiABs, ADC's, and Other Drugs

CAR-T STUDIES, ALL PTS RRMM, ALL TARGETING BCMA UNLESS OTHERWISE NOTED

29. CAR-T Universal Allo-715: N=43 pts; ORR 71% (CR 25%). Low grade CRS and neurotoxicity but 10 pts had grades 3-5 infections. {Mon-651-S Mailankody}

30. Results were presented for a CAR-T study of MCARH109 that targets GPRC5D (not BCMA) and CD3, and eligible patients included those with prior BCMA therapy (inc CAR-T as well as allo-SCT). N is small at 16 but 69% had ORR (inc 25% CR) with similar ORR for prior BCMA/CAR-T. {Mon-827-S Mailankody}

31. ARI0002h CAR T appears unique because some of a patient's CAR-T cells are given up front and then as a subsequent booster dose. For N=30, ORR=100 and CR=60% and the mPFS is estimated to be 18 months. {Sun-552-A Oliver-Caldes}

32. bb21217 CAR-T for N=72 included 40% HR and 22% EMD patients. Results showed 69% ORR (28% CR) and mDOR of 2 yrs. The design focus of bb21217 was to increase persistence over bb2121 (Ida-cel, Abecma) which appears successful. {Sun-548-N Raje}

33. CARTITUDE-1 CAR-T updated results after 2-year follow-up for N=97. ORR 98%, CR 83%; 2-yr PFS and OS were 61% and 74% respectively and even higher for those with sustained MRD-. MRD- at 10^{-5} was achieved by 92% of pts. For 6 mos and 12 mos sustained MRD, 2-yr PFS was 95% and 100% respectively. And even more interesting sCR rates have improved yr 2 over yr 1. {Sun-549-T Martin}

34. CT103A CAR-T from China demonstrated (N=79) 95% ORR with 58% CR and mPFS of 25 months. The first enrolled patient is still in stringent complete remission (sCR) at 34 months. And for 13 patients who had previous CAR-T, ORR was 77% and CR 39%. {Sun-547-C Li}

Bi Specific Antibodies (myeloma cell X t-cell)

35. Updated results were provided for Teclistamab from a study called MajesTEC-1. For N=165, ORR=62%, CR=29%, 9-mos PFS=59% and MRD- is 17% (10^{-6}). Dosage is .06 -> .3 mg/kg, using a step-up dosing to minimize side effects such as cytokine release syndrome (CRS), which were all grade 1/2. {Mon-896-P Moreau}

36. Talquetamab (GPRC5D x CD3) given SubQ to N=55 pts resulted in ORR 67-70%. {Sat-158-A Krishnan} And combining Talquetamab with Dara N=21 showed an ORR 77-85% (no dara within prior 90 days). {Sat-161-A Chari}

37. REGN458 (BCMAxCD3) for N=73 provided ORR = 75% at the combined 200-800mg dose levels. {Sat-160-J Zonder}

38. Cevostamab (FcRH5 marker on the MM cell x CD3 on the T cell) given every 3 weeks to N=161 patients (pts) heavily pre-treated (including prior BCMA) resulted in ORR of 57% and mDOR of 11.5 mos for dosing 132-198mg via IV. {Sat-157-S Trudel}

39. This study examined outcomes of N=57 RRMM pts following treatment of bispecific antibodies and concluded that getting another T cell directed therapy significantly improves median progression free survival (PFS) (mPFS:19 vs 2 months) and OS (NR vs 12 mos) [821 {Mon-821-T Mouhieddine}

40. For N=55, this bispecific called Elranatamab from Pfizer given SubQ achieved 69% ORR at the recommended phase 2 dosage (RP2D). {Mon-895-M Sebag}

41. Another bispecifc ABBV-383 (previously called TNB-3838) targets BCMAxCD3. For N=76 at the RP2D (40mg via IV), ORR was 81% with >= VGPR of 69%, although for triple-class refractory, ORR dropped to 53%. {Mon-900-S Kumar}

ADC's (Antibody Drug Conjugate)

42. The DREAMM-5 study showed that combining Blenrep® (belantamab mafodotin) with a T cell Co-stimulator Agonist aICOS resulted in increasing single agent Blenrep ORR from 32% to 52% without increasing side effects. {Sun-897-N Callander] And the DREAMM-9 early results for N=36 with lower doses of Blenrep + RVd showed ORR=94% (CR=36%), all for RRMM pts. {Sun-2738-S.Usmani}

OTHER Drugs

43. This study presented early results for N=41 t(11;14) RRMM from a trial comparing Venetoclax plus Dara and dexamethasone (VenDd) vs Velcade®(bortezomib) plus Dara-dex (VelDd) and showed an overall response rate (ORR) improvement of 20+ points (87% vs 63%) {Mon-817-J Kaufmann}

44. Iberdomide (a CELMod) + dex demonstrates efficacy in triple-refractory patients, including those 100% refractory to IMIDs, ORR 26% N=26 and pts with previous BCMA, ORR 25% N=24. {Sat-162-S Lonial}

OTHER RESULTS

45. This study examined racial and ethnic differences in MM patients. The presenter remarked that "Blacks are getting one-half the benefit of improved survival outcomes compared with whites. However, similar access to care results in similar outcomes." As a society, we need to do more to accrue a diverse population in our clinical trials and then provide better access to new treatments. {Sun-402-S Gillis}

46. This study examined the impact of chromosome 1 gain (3 copies), amplification (>3 copies) and deletion, conferring inferior PFS compared with standard risk patients. Kyprolis® (carfilzomib), Revlimid, and dex (KRd) may overcome negative OS for gain1 and del1 but not necessarily amp1. {Sun-467-T Schmidt}

47. In another chromosome abstract, the presenter noted that 17p deletion is long-considered to be a high-risk factor. But how important is the clone size (17del seen in >60% plasma cells) when treated with a single vs tandem transplant? While the results demonstrated tandem transplant compared with a single transplant improves outcomes, a clone >60% may negatively impact outcomes. {Sun-460-A De La Torre}

48. An oral Gamma Secretase Inhibitor to increase BCMA expression may be used in the future with BCMA-directed therapies. {Sun-551-A Cowan}

49. For clinical trials, it was proposed that PFS and QoL measures be co-primary endpoints rather than just PFS since many MM patients favor one over the other. Mon-836-AFlescher}

50. Finally, there were a couple of interesting abstracts that assessed the cost of saving stem cells for a 2nd transplant {Mon-665-F Yassine} and the cost /wait times for doing blood draws (CBC and chem panel) before every Velcade infusion as part of RVd treatment {Mon-666-E Inyang}. At Mayo Clinic-Florida, only 2% of patients get a 2nd transplant but the cost of harvest and cryopreservation totals $8 million for all their patients (average 4 years storage). And changing protocols to perform blood draws only once per cycle can save $1,500 and 3-4 hours wait time per draw times the number of draws previously done per cycle.

SUMMARY

This year's ASH continued to amaze me with so many studies in Myeloma, focusing on all stages from Smoldering Myeloma to MM Induction through Relapse. Clearly immunotherapy treatments, CAR-T's and Bi-specific T-cell engagers were predominant among the oral presentations I attended, providing longer-term data on these new treatments. And importantly, other targets besides BCMA and improved T-cell persistence are being investigated.

For someone diagnosed with stage III MM 27 years ago with only 2 treatment options available (MP or VAD-SCT) and given 2-3 years expected survival, I've seen incredible progress since 2003 when Velcade was first approved followed by 12 more approvals and many combination therapies. And we'll likely have more FDA approvals in 2022…likely CARTITUDE-1 CAR-T and perhaps a Bi-specific (Teclistamab?). While there continues to be unanswered questions, we now have many more effective treatments for MM, providing patients with better opportunities to manage their disease.

GLOSSARY (according to Jack)

Drug (brand names) by Drug Class/Category

IMID – Immunomodulary Drug
T – Thalidomide
R – (Lenalidomide) Revlimid
Pom – Pomalidomide (Pomalyst)

PI – Proteasome Inhibitor
V- Velcade (Bortezomib)
Cfz, K – Carfilzomib (Kyprolis)
I, Ixa – Ixazomib (Ninlaro)

mAb – Monocloncal Antibody
D, Dara – Daratumumab (Darzalex)
E, Elo – Elotuzumab (Empliciti)
Isa – Isatuximab

HDAC - histone deacetylase inhibitors
Pano – Panobinostat (Farydak) but no longer FDA approved in the US

Steroids
P – Prednisone
D or d - Dexamethasone

Chemotherapy Drugs
C – Cyclophosphamide (Cytoxan)
M – Melphalan

Treatment Measurements
EFS – Event-free Survival
ORR – Overall response (>=PR)
OS – Overall Survival
PD – Progressive Disease
PFS – Progression-free Survival
PFS2 – PFS + next-line treatment PFS
TTP - Time to Progression
TTR - Time to Respond

Treatment Response
CR – Complete Response: No sign of MM (0 M-spike)
nCR – Near CR (positive M-spike, may be same as VGPR)
MR – Marginal Response: 0-50% reduction in MM
PR- Partial Response: 50% reduction in MM
SD – Stable Disease i.e. no response but also not worse
sCR-Stringent CR: CR+ normal FLC & no clonal cells
VGPR – 90% reduction in MM
MRD – Minimum Residual Disease typically by Flow Cytometry (NGF) or DNA sequencing (NGS) to provide more sensitive measure of MM (e.g. 10^{-5} or 10^{-6})

Side Effects
AE (ASE) – Adverse Event (Adverse Side Effects)
DVT - Deep Vein Thrombosis (blood clots)
MTD – Maximum Tolerated Dose
ONJ – Osteonecrosis of the Jaw
PE – Pulmonary Embolism
PN – Peripheral Neuropathy
QOL – Quality Of Life
VTE - Venous Thromboembolism (PE + DVT)
CRS – Cytokine Release Syndrome

Tests/When to treat?/Other
CRAB – High Calcium, Renal, Anemia, and Bone…
CRABi – CRAB + "i" increased infections
FLC – Free Light Chain

SCT – Auto stem cell transplant.
TE, NTE – Transplant Eligible of Not TE

LOT – Lines of Therapy

TE, nTE – Transplant eligible or non-TE

"d" and "D" – Typically both mean Low-dose Dex (40 mg/week) these days
MGUS – Monoclonal Gammopathy of Undetermined Significance
SMM – Smoldering MM
Pt(s) – Patient(s)
n - Number of pts
R/R- Relapsed/Refractory, Ref defined progressing while on Tx or within 60 days.
HR – High Risk
RP2D – Recommended Phase 2 Dosage