MYELOMA HIGHLIGHTS FROM ASH CONFERENCE ATLANTA 12/8-12/2017

According to Jack Aiello (definitely not medically trained)

PREFACE

This is my 12th year attending ASH (American Society of Hematology), where 26,000 attendees from all over the world (hematologists/oncologists, lab researchers, oncology nurses, scientists & 300 pharma companies) present the latest research results via both oral presentations (1000) as well as posters (3000) on all blood cancers. This year there were 981 abstracts (>100 clinical) on Myeloma alone, many of which were selected for oral presentation. I'm grateful to the IMF (www.myeloma.org) and their pharma donors for sending me to ASH so that I can learn and 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. Even at that, there are overlapping MM oral sessions as well as 4'x6' posters without reprints, so it's always possible that I have not included something of interest to you or made a typo because I can't read my own writing as detailed powerpoint slides are presented quickly. And this year snow caused me to miss additional presentations. You might want to view the published abstracts at www.hematology.org and various press releases. [Wherever possible, I've listed Day-Abstract#-Lead Investigator after the trial results, e.g. {Sun-510-S. Zweegman} and clicking on the abstract number will take you to the actual abstract. 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 are scheduled webinars (MMRF 1/10/18, IMF 1/11/18) which you can listen to live or by replay. You'll also find some patient blogs (including mine) as well as MM expert video interviews posted on the IMF website (http://ash2017blogs.myeloma.org), Patient Power (www.patientpower.info), and Myeloma Crowd (www.myelomacrowd.org) among others. And all of us in the SF Bay Area should attend the LLS Blood Cancer Conference (which includes updates from ASH) Jan 27, 2018 (register at www.lls.org). Dr. Ken Anderson from Dana Farber Institute in Boston will do a great job presenting the latest information.

Presentations and posters of clinical trial results follow 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"; Phase I/II and II (typically 25-75 pts) continues 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 schedules are defined for stages of **Induction**, and optionally **Transplant**, **Consolidation**, and **Maintenance** with specified **Randomization** along the way; 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 cytogentics-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...more details follow)

1. The most exciting presentation for me was the new BCMA mAb drug conjugate from GSK that resulted in 60% ORR for RRMM pts. Besides this presentation, I didn't see much on new drugs such Venetoclax, Selinexor, Isatuximab or others which received more discussion last year.

2. CAR-T therapy programs were presented but the numbers are still small. It looks promising, but is very early in development.

3. I appreciated that 2 QOL presentations showed 1) MM pts would benefit from the High dose flu vaccine plus a booster rather than the standard of care and 2) Prophylactic use of 12 weeks Levofloxacin (Levoquin) when undergoing treatment reduced fevers and deaths without increasing infections. However, I'm also told that Levofloxacin is not an innocuous drug. It has strange side effects including muscle weakness and tendon ruptures in some patients!

4. An exciting oral presentation showed good early results for Dara being given as a 3-5 minute injection in the skin instead of in a vein.

5. There was considerable focus on High Risk SMM patients and it will be interesting to see if early treatment of just Dara or the intense CESAR protocol or something else will be best to delay the onset of MM (and maybe be curative for some?).

6. MRD status was on everybody's lips and trial results but it's still frustrating that there isn't an agreed-upon standard. Maybe it doesn't matter if we use NGF or NGS but sensitivity does matter and it appears that 10^{-6} should be the standard along with using PET-CT.

7. Transplants are still a very active subject for trials and still should be kept in our bag of potential treatment tools.

8. I saw good results for RRMM patients using various regimens that included Cytoxin: KCd, VCd (also known as CyBorD), RCd, and PomCd.

COMMENTS AND DISCUSSIONS I FOUND PROVOCATIVE

9. "To me, [we] should replace "uncertain significance" (in MGUS) and low-risk SMM with "Monoclonal Gammapathy". Intermediate Risk SMM should be called "Indolent MM". And High Risk SMM should be denoted as MM (early detection)." O. Landgren (MSKCC)

10. "I look forward to the day when we have MGUS (no treatment) and MM (treat) and no SMM." J Mikhael (Mayo). Dr. B. Durie (IMF) noted the iStopMM Iceland project that screens adults >40 for MGUS/SMM will help answer this question.

11. "[For MRD testing] it seems likely that both a bone marrow and whole-body imaging will be required to accurately assess remission status." F. Davies (UAMS)

12. "For HR SMM, the pt choice is between aggressive and non-aggressive treatment. We don't know which is the best but treatment should be done within a study." B. Paiva (Spain)

13. "We need trials and new drugs but understanding the mechanisms that pin this disease is critical to treatment." J Mikhael (Mayo)

14. "If you get to MRD-, it doesn't matter how you get there and enables us to tailor our treatment." P. Richardson (Dana Farber)

15. "Maintenance therapy is the SOC." J Mikhael (Mayo)

16. "Maybe if you're MRD-, you continue maintenance and if you're MRD+ add to maintenance treatment." B. Durie (IMF)

17. At the IMF symposium when the question, "If a patient is MRD- three years past maintenance, is the patient cured?" was asked, a distinguished group of MM expert panelists all said "not sure" or "no." They commented that some patients may be cured and others not.

18. "Regarding CAR-T therapy, it's a high-nuanced approach so small changes can make big differences." P. Richardson (Dana Farber)

19. "We still have some 'early-model' CAR's. I'm nervous about those folks who have relapsed. J Mikhael (Mayo)

SMOLDERING MM

20. Preliminary results for GEM-CESAR trial for HR SMM pts: KRd->SCT->KRd Consolidation-> Rd Maintenance for n=43 evaluable pts. The Primary Objective for this trial is MRD. Both MRD- and ORR improved after Induction (31%, 71%), SCT (50%, 100%), Consolidation (60%, 100%) and Maintenance (NA, 100%) and while OS is encouraging, it's much too early to say if this is curative for some SMM patients. {Sun-402-MV Mateos}

21. Dara monotherapy "CENTAURUS" study for HR SMM pts for long, intermediate and short durations among n=123 pts. Longest duration was best (56% ORR and 95% 1 yr PFS) and will likely result in a Ph3 study{Sun-510-C. Hofmeister}

22. MYC translocations (structural variants) may be used as a genetic marker correlating to progression of SMM to MM. For n=128 pts, no MYC SV were detected in MGUS, SMM non-progressors at > 5yr or SMM progressors between 2-5 yrs. By contrast, MYC SV were detected in 49% of SMM pts that progress within 2 yrs. {Sun-393-N. Keane}

FRONTLINE THERAPY FOR TRANSPLANT INELIGIBLE (NTE) PATIENTS

23. At the IMF Symposium, Dr. S. Vincent Rajkumar presented preferred induction for the following cases:

1. Standard risk, 62yo: RVd
2. Standard risk, 75yo: RVd or RVd-Lite
3. High-risk, del 17p: KRd for younger patients; RVd for older patients
4. Renal-compromised patients: CyBorD should be chosen over Rev-based regimen

24. A Td +/- Ixa induction therapy [followed by Ixa or no maintenance] and showed ORR=81% benefit after induction for all 120 patients, HR pts, Fit/Unfit/Frail pts. {Sun-433-S. Zweegman}

25. Initial results of the Phase 3 ALCYONE trial comparing VMP (Velcade, Melphalan & Prednisone) +/- Dara. The Dara arm produced better results for n=706 pts: ORR (91 vs 74%, CR 43 vs 24%), MRD- (22 vs 6% where MRD used NGS 10^{-5}). PFS has not yet been reached for the Dara arm vs 18 mos so Dara may well get approved for induction therapy, and could especially benefit non-transplant eligible pts. {Tue-LBA-4-MV Mateos}

TRANSPLANTS

26. Last year, the STAMINA trial compared stem cell transplant (SCT) compared to SCT + consolidation, and compared to tandem (SCT). In all of these scenarios, the initial treatment is followed by maintenance. The results showed that there was essentially no progression-free survival or overall survival differences amongst the three arms. And yet at my BMT CTN session examining MRD at pre-SCT, pre-maintenance, and one-year post-maintenance did show MRD- differences for arm 1 (42%, 77%, 78%); arm 2 (40%, 76%, 85%); and arm 3 (47%, 83%, 92%), indicating benefit in the transplant arms.

27. Second Primary Malignancies (SPMs) were studied in MM pts with and without an SCT and concluded the risks of developing an SPM was similar for both 5-yr (4.8% vs 4.7%) and 10-yr (9.1% vs 7.5%) analysis. {Sun-332-A. Rosenberg}

28. The EMN02/HO95 trial compared 3 arms VMP consolidation, SCT, Tandem SCT after VMP induction. In particular the SCT arms showed significant 3-yr OS benefit over VMP (70-75% vs 45%). In addition 2 SCT's were better than a single SCT when examining 3-year PFS (72% vs 64%) and OS (89% vs 82%). When asked about why the STAMINA trial with similar consolidation, 1 SCT or 2 SCT's arms showed no real difference, the answer was that there were significant trial schema differences in the induction used (drugs and cycles). {Sun-397 & 401-M Cavo}

TREATMENTS FOR RELAPSED/REFRACTORY (R/R) PATIENTS

29. At the IMF Symposium Dr. San Miguel reminded folks that treatments at first relapse could be the following three choices: 1) KRd...The ASPIRE trial showed 8 months OS improvement over Rd; 2) RCd ...a Dutch trial will show 72% ORR; and 3) Dara combinations.

30. Phase 2 trial studying efficacy of dara + poma + dex in second- or third-line treatment who have failed Rev treatment, and found ORR=72%. {Sat-1811-D. Siegel}

31. The POLLUX trial: Rd +/- Dara for RRMM patients was updated with a median follow-up of 33 months for n=579 patients. The Dara arm significantly improved PFS (not reached vs 18 months) and ORR (93% vs 76%). The 30-month PFS was 58% vs 34%. Also noted was 7% SPM's for both arms. {Mon-739-M. Dimopoulus}

32. Final results from the ASPIRE Ph 3 trial KRd vs Rd for RR MM patients. KRd benefits over Rd included PFS (26 vs 17 mos), OS (48 vs 40 mos), ORR for High Risk patients (79 vs 60%), and a 23% reduction in risk of death. {Mon-743-K. Stewart}

MAINTENANCE

33. A network meta-analysis across six large trials of maintenance treatment for newly diagnosed multiple myeloma patients following a stem cell transplant concluded that Rev maintenance provides both superior PFS (avg 20 mos benefit) and OS (22 mos or 10% benefit looking at 3-, 4-, or 5-yr%) when compared with no maintenance {Sat-1832-S. Schmitz}

34. Ixa-Rev maintenance showed 100% ORR (34% CR) and 2 yr PFS of 81%. However, 8 of 16 High-risk MM pts have progressed. {Sun-437-K. Patel}

35. Elo-Rev-dex maintenance improved responses by 36% (20% converted to CR); also 31% of patients experienced Grade 3 neutropenia for this Phase 2 n=68 trial. {Mon-840-S. Thomas}

MRD

36. At the BMT CTN meeting Dr. Nikhil Munshi described the i²TEAM Initiative, an international retrospective study that will use 7 large trials, n=4500 patients to evaluate differences between MRD+ and MRD- results, with the goal of establishing MRD as a surrogate endpoint.

37. MRD was examined for the large IFM2009 trial (RVD +/- SCT -> Consol->Maint. He concluded that MRD should be considered as a surrogate biomarker if 10^{-6} sensitivity is used but that "it's probably still important to include PET-CT". MRD- patients did well on both arms. {Sun-435-H. Avet-Loiseau}

38. From BMT CTN meeting, stay tuned for future SWOG S1804 trial, PI is Dr Amrita Krishnan (City of Hope) called DRAMMATIC which incorporates NGS MRD testing after 2 years of maintenance. If MRD-, pt is randomized to stop or continue treatment.

NEW DRUGS

39. A Phase 1b study of isatuximab (a CD38 mAb) plus Pom + dex in R/R MM pts confirmed a 60+% ORR. {Sat-1887-P. Richardson}

40. Results were provided from a Ph2 study of Pembrolizumab (checkpoint inhibitor) combined with low-dose Rev maintenance after an SCT. However, since the FDA stopped the trial early, only 29 patients (rather than 46 patients) were accrued. OS at 18 months is 100%. So while numbers look good, it's unclear how much Pembro added to the benefit of getting Rev maintenance. {Sun-339-A.Pawarode }

41. Results from varying dosages of a BCMA CAR-T +/- Cytoxin for 24 pts across 3 arms. Cytokines Release Syndrome (CRS) was experienced by 20 pts and there was 1 death. 11of 24 pts (10 of 19 in the 2 preferred arms) showed responses and interestingly BCMA expression amount did not correlate with responses. The longest survivor so far is at 24 mos. {Sun-505-A.Cohen }

42. A pilot study giving 10 patients both BCMA-CART and CD19-CAR-T infusions. CRS typically came on at about 14 hrs and lasted 3 days but none had to go to the ICU. And 9 of 10 have shown responses. {Sun-506-Dr. Fu}

43. A report of the multi-center bb2121 anti-BCMA CAR-T therapy for n=21 patients who had a median 7 lines of prior treatment. There was 94% ORR (56% CR) and 9 of evaluable 10 patients were MRD-. But there were also 5 deaths (3 on the lowest dose) and 4 patients progressed (3 had been VGPR's). {Mon-740- J. Kochenderfer }

44. 35 RR MM patients were treated with monotherapy GSK2857916, an mAb drug conjugate against BCMA, dosed once every 3 weeks over 1 hr. 60% achieved ORR with only 4 patients progressing. All patients had at least 1 Adverse Event, the most frequent (63%) being corneal events (blurry vision, dry eyes) mostly Grade 1/2 and reversible. {Mon-741- S. Trudel}

45. Folks were reminded that at last year's ASH they were testing Dara-MD (Mix & Deliver) using a syringe pump for 30 minute infusions. This year's abstract discussed a new Dara-SQ (manual injection) taking only 3–5 minutes!! A phase 3 study is planned. {Mon-838-A. Chari}

OTHER RESULTS

46. The rate of multiple myeloma patients using hospice has doubled between 2000 and 2013, with a high percentage enrolling within 3 days of death, although the median length of hospice is 13 days. {Sun-346-E. Meier}

47. 2 doses (45 days apart) of high-dose flu shots offer twice the immune protection compared to the single standard-of-care flu shot. {Sun-438-A. Branagan}

48. The antibiotic Levofloxacin was given as a prophylactic for 12 weeks to nearly 1000 pts randomized to the antibiotic or a placebo. A significant benefit for the use of levofloxacin with 19% (including 4 deaths) versus 27% (including15 deaths on the placebo arm as well as many fewer "febrile" (fever) episodes, as well 20% fewer infections. {Mon-903-M. Drayson}

SUMMARY

Perhaps this ASH didn't have as much excitement for MM patients as the last 2 ASH conferences but how are you going to compete with 4 drugs approved in 2015 and additional regulatory approvals in 2016? Many new trials have been started but are awaiting more patients as well as "readouts". Interestingly, readouts refers to events such as when a drug stops working. And the longer these treatments work, the longer it takes for enough readouts to occur before trial results can be reported. Confused? Trust me, this is actually good news.

For someone diagnosed with stage III MM 23 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. 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 – Carfilzomib (Kyprolis)
I, Ixa – Ixazomib (Ninlaro)

mAb – Monocloncal Antibody
D, Dara – Daratumumab (Darzalex)
E, Elo – Elotuzumab (Empliciti)
Isa – Isatuximab (SAR650984)

HDAC - histone deacetylase inhibitors
Pano – Panobinostat (Farydak)

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.

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)

Tests/When to treat?
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

"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