MYELOMA HIGHLIGHTS FROM ASH CONFERENCE SAN DIEGO 11/30-12/4/2018

According to Jack Aiello (definitely not medically trained)

PREFACE

This is my 13th year attending ASH (American Society of Hematology), where 25,000 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 diseases, especially cancers. This year there were 939 abstracts (>100 oral presentations) 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 there were more overlapping meetings so I wasn't able to attend all the oral presentations I would have like to but have denoted them below with an **. 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. {Sat-155-M.Dimopoulus} 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 (IMF 1/10/19 tentative, MMRF to-be-scheduled) 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 (https://ash2018blogs.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 26, 2019 (register at www.lls.org). Dr. Tom Martin from UCSF 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 (SCT)**, **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 as 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. I would say this year's ASH didn't contain any surprises. New drugs like Selinexor, Venetoclax and Isatuximab continue to make their way through trials. Last year I commented on a most exciting BCMA mAb drug conjugate from GSK but this year that drug wasn't discussed in orals. However, Amgen's AMG420 BiTE (Bi-specificT-cell Engager) product was featured in an early trial.

2. There appeared to be a dozen CAR-T therapy programs presented for MM but the numbers are still small. It looks promising, but is very early in development. We still need results from more pts, a better understand of response measurement tools (for example, perhaps CAR-T cell persistence/longevity is better measure than MRD), and longer term results.

3. I appreciated that there were several studies focused on High Risk MM as well as unfit & frail MM pts, 2 groups of MM patients that really need better treatments. Both Selinexor and Melflufen showed good success for MM pts who have relapsed from 3 drug categories (e.g. IMID, PI, mAb). There seemed to be less this year on HR SMM pts because it's still early in several current studies targeting these pts.

4. Ninlaro was shown to offer help in the maintenance area. Since 30% of Rev maintenance pts have to discontinue due to Rev side effects, Ninlaro offers those folks another option, and is an oral medication just like Rev.

5. Transplants are still a very active subject for trials and still should be kept in our bag of potential treatment tools. European studies continue to show benefit of tandem over a single transplant but perhaps that's because they don't have access to as many drugs for induction as the US does. For example, most induction treatment in Europe use Thalidomide because they don't have access to Revlimid.

6. We know that BMA's (Bone Modifying Agents) such as Aredia, Zometa, and Xgeva are important bone strengtheners for MM pts. Yet, only ½ of Medicare-eligible pts use BMA's.

COMMENTS AND DISCUSSIONS I FOUND PROVOCATIVE

7. "There's an impact of immune suppression post-SCT which leads to infections and relapses. The cause could be immune suppressor cells in GCSF." Z. Al-Kadhimi (U of Nebraska Med Ctr)

8. "More than 60% of sub clonality in 17p del predicts poor outcome [so it's important to understand the level of clonality]." N. Munshi (Dana Farber)

9. "Correlation of MRD in the CAR-T setting might be different. In the initial bb2121 study 16 pts who were MRD-, 8 have relapsed. Persistence of T-cells might be a better prognosticator." E. Stadtmauer (U Penn)

10. "The best treatment should be used early so Dara may be added to VRd or KRd in the future." J San Miguel (Spain); but "MM is more like a marathon than a sprint. Consider saving more expensive treatments for later." SVRajkumar (Mayo)

11. "Rev maintenance is recommended for all Standard Risk MM and Velcade for all High Risk MM." S Kumar (Mayo)

12. "Tandem SCT is beneficial over single in both HRMM as well as SRMM." P Moreau (France)

13. "The only way to recommend treatment at R/R MM is to be in front of the patient and understand the many pt variables." J San Miguel (Spain)

14. "For a 2nd or higher relapse, you must use a triplet and at least 2 of 3 drugs the pt is not refractory." SVRajkumar (Mayo)

15. "CAR-T therapies have become much safer and effective over the last 1.5 yrs but there will still be modifications." J Mikhael (Mayo)

16. "Dex is like boosters on a rocket. They help the rocket get off but eventually the booster falls away. We want dex to fall away." J Mikhael (Mayo)

17. "At any relapse, only 50% of pts move on to the next treatment." R. Fonseco (Mayo)

18. "PFS (Progression Free Survival) below 12 mos following an SCT is a hallmark of High-Risk MM." C. Bygrave (UK)

19. "Venetoclax may be a magnifier of Carfilzomib (Kyprolis)" L. Costa (U of Alabama)

20. "In the US you can get any salvage option you can think of. Therefore the effect of a second SCT or consolidation is not as significant. SVRajkumar (Mayo) explaining the similar OS outcome results of the STAMINA clinical trial showing no OS difference among SCT, SCT-consol, and tandem SCT.

SMOLDERING MM

21. ** A Phase 2 trial of Elo-Rev-d x 8 cycles followed by Elo-R maintenance in HR SMM (PC%>10 plus any one of M protein > 30g/L, IgA, FLC > 8 but <100, PC% 50-60, 1 focal lesion, and more). HR cytogenetics (17p-, t(4;14) or 1q+) were also found in 20 of 49 pts. ORR 84% with no pts progressing to MM after 2 years but longer follow-up will be completed. {Sat-154- I Ghobrial}

22. ** A Phase 2 study of Ixa-Rev-d x 9 cycles followed by Ixa-Rev maintenance for 15 cycles for N=26 pts with at least 3 cycles, ORR = 89% (CR = 19%) with minimal toxicity and no progression to date. {Mon-804-M Bustoros

FRONTLINE (INDUCTION OR FIRST LINE) THERAPY

23. In an Education Program, for an older, unfit pt, consider RVd-Lite (15mg Rev, 1.3 mg/m2 Vel, 20mg dex) plus Zometa every 3 mos {Sat- https://ash.confex.com/ash/2018/webprogram/Session13558.html-T Wildes}

24. ** A pre-Phase 2 "run-in" study with Dara-VRd x4 induction, SCT, Dara-VRd x2 consol, 24 mos Dara-R maintenance will ultimately compare 200 randomized pts (already accrued) to a comparable VRd arm (called Griffen). So far 16 pts were several mos into the Dara maintenance and 100% achieved VGPR (63% CR) and 8 of 16 MRD- using ClonalSeq NGS 10^{-5}. Much more should be available next year. {Sat-151- P Vorhees}

25. A large UK study compared KCRd vs CTd and CRd induction followed by an SCT. Not surprising for N=1050 pts, the 4-drug regimen KCRd resulted in better >= VGPR than the others (82% vs 53% vs 65%) as well as better >= VGPR responses after the SCT (92% vs 76% vs 82%) as well as better MRD- (77% vs 53% vs 56%) and 3 yr PFS (65%, 50%, 50%). {Sun-302-G Jackson}

26. N=38 NDMM pts in a Phase 2 trial were given Dara-Ixa-Rev-dex and showed 90% ORR (29% VGPR) after 2 cycles and 100% ORR (39% VGPR) after completing 4 cycles. {Sun-304-S Kumar}

27. The Dutch presented early Phase 2 trial results of Ixa-Dara-d for both Unfit and Frail NDMM pts. The study will accrue 132 pts (66 of each) but reported on 10 U (med age 76) and 10 F (med age 82) pts. Note the dex is reduced for this trial...20 mg for cycles 1 & 2, and 10 mg for 3-6 subsequent cycles. The maintenance is weekly Ixa and Dara every 2 mos until progression or 2 years. So far for the Unfit and Frail groups after 4 cycles, >= VGPR is 30% and 20% while ORR is 100% and 80% respectively. {Mon-596-C Stege}

28. ** In the MMRD CoMMpass study, 298 pts with matched baseline characteristics who were treated with KRd vs VRd pts were compared. 12-month EFS for KRd were 95% vs 84% for VRd. In addition, ORR at 12 mos was 87% vs 68%, with CR's of 35% vs 14%, all demonstrating improvements with KRd (but should be confirmed with a Phase 3 trial). {Mon-799-O Landgren}

29. ** For N=737 non-transplant eligible pts (med age 73), DaraRd reduced the risk of disease progression or death by 44% when compared with Rd. After 28 mos, the mPFS had not been reached for the Dara arm vs 32 mos for Rd. Other responses ORR 93% vs 81%, >=CR 47% vs 24%, and MRD- 24% vs 7% all showed benefit with the DaraRd arm. {Tue-LBA-2-T Facon}

TRANSPLANTS/CONSOLIDATION

30. 474 NDMM pts were randomize to receive A) KRd induc-SCT-KRd consol or B) KRdx12 or C) KCd induc-SCT-KCd consol. ORR and MRD- favored both KRd arms over the Cytoxin arm even though the C arm included an SCT (87%, 58% vs 87%, 54% vs 74%, 42% respectively) {Sat-121-F Gay}

31. In this Ph 2 trial of 169 evaluable pts, IRd x 4 was given following an SCT and MRD- rates at 10^{-6} improved from 22% after the SCT to 32% after IRd as did VGPR (76%, 85%) but it's too early to tell about PFS & OS. {Sat-123-R Vij}

32. Tandem vs Single SCT randomizing 909 pts showed PFS benefit of 24% and 1 yr improvement in OS. The HR pts benefitted the most in this pooled analysis of European studies, which typically have less effective induction therapies. Sat-124-M Cavo}

33. ** Prolonged Rev therapy, even more than 6 cycles, does not impact PBSC mobilization for harvest. Of the nearly 300 pts, some only took GCSF, Plerixafor or both. {Sat-198-A Cowan}

TREATMENTS FOR RELAPSED/REFRACTORY (R/R) PATIENTS

34. ** For this Phase 2 trial EMN011, the first 60 pts refractory to both Rev and Vel were treated with KPd for a median of 14 mos and demonstrated an 87% ORR (31% CR). {Mon-801-P Sonneveld}

MAINTENANCE

35. A phase 3 study for N=656 pts called TOURMALINE 3 showed that after an SCT Ninlaro (Ixazomib) maintenance given once/wk for 24 mos improved PFS by 39% or 5.2 mos over a placebo (there was no SOC at the time this trial began). Further, while 1/3 of pts in both arms were MRD- after the SCT, an additional 12% vs 7% converted to MRD- during Ixa maintenance. This trial offers another oral drug for maintenance beyond Rev. {Sun-301-M Dimopoous}

36. Comparable efficiency was shown in a study of Elderly & Intermediate-Fit NDMM pts in a Phase 3 randomized trial examining A) Rd x9 followed Rev-only maintenance vs B) Continuous Rd, both till disease progression. (A) showed a slight benefit over (B) for nCR (19% vs 15%), EFS (9.9 mos vs 6 mos), 20mo PFS (43% vs 42%) and 20mo OS (84% vs 79%). With no negative impact, the elimination of Dex in this maintenance study is certainly preferred by pts who are also able to stay on maintenance for a longer period of time. {Sun-305-A Larocca}

NEW DRUGS

37. A phase 2 study with Venetoclax-Kd was given to 42 R/R MM pts, only 8 of whom who had the t(11;14) translocation. They had no prior exposure to K (Carfilzomib) but half were refractory to a PI. All 8 of the t(11;14) had an ORR (7 >= VGPR) but for the other 34 R/R pts, their ORR was 74% (50% >= VGPR). {Sun-303-L Costa)

38. Dosages and responses were determined in the Phase 1 study of Isatuximab-VRd for NDMM not eligible for SCT. Isa's first infusion time for the CD-38 mAb is 3.7 hrs, then 2.7 hrs, which is significantly less than the other CD-38 mAb Daratumumab. After a median of 6 cycles, 100% of 16 pts were in a >= VGPR (probably 5 of these in a CR but this drug has the same IgG laboratory monitoring interference issue as Dara) and 7 of 16 were MRD- (10^{-5}). This is moving on to a Phase 3 study for both TE and non-TE pts. {Mon-595-E Ocio}

39. Selinexor – Dex (S=80mg, d=20mg, both twice a week) is the STORM study in Penta-refractory pts. Pt must have had Vel, Cfz, Rev, Pom, and Dara, and been MM-refractory to at least 1 PI, 1 IMID. Dara, steroid, and their last treatment. Grade 3/4 AE's include thromcytopenia (53%), nausea (10%), fatigue (21%) and anemia (28%) but were manageable and reversible, although 1/3 of pts discontinue tx due to ASE's. For the N=123 pts, 53% were HR. ORR was 26.2% (inc 2 x sCR's) and 71% had a reduction in their M-protein. And both CRT pts achieved a PR. Median PFS and OS were 3.7 mos and 8.6 mos respectively (OS without treatment is a dismal 1.7 mos). This new agent shows promise for the heavily treated group of myeloma patients who desparately need an additional treatment option. {Mon-598-A Chari}

40. There was also a Phase 1 study examining Sel-Dara-dex for pt previously exposed to PI's and IMID's. For 24 Dara-naïve pts, ORR was 79%. {Mon-599-C Gasparetto}

41. Melflufen is another Alkylating agent (like Melphalan or Cytoxin) which has a unique action of staying in MM cells and causing cell death. It was given to RRMM pts refractory to Dara and/or Pom. Actually all 82 pts were triple-class refractory. ORR was 33% (11% >= VGPR) and med PFS was 4 mos, but 6.4 mos for pts with a PR or better. And only 13% of pts discontinued due to ASE's. With all our new "novel agents" it is good to remember that older classes of drugs (alkylators) still can be very effective. {Mon-600-P Richardson}

42. Amgen's AMG 420, a BITE connecting an MM cell's BCMA antigen with a T-cell's CD3 receptor was given to 42 RRMM pts. At the best-determined dose, 7 of 10 pts achieved ORR and 4 were MRD-. One concern, however, AMG 420 is given continuously via a pump for 4 weeks, then 2 weeks off, then 4 weeks, etc for 10 of these 4-wk pump infusions. However, I believe Amgen is working on a BITE that has a longer life not requiring continuous IV. {Mon-1010-M Topp}

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

43. Early results of "next generation" CAR-T bb21217 (the "7" represents a technique that may increase CAR-T persistence) for N=12 pts, med age 63 with a median 7 previous LOTs. CRS in 8 of 12 but only 1 Grade 3 and 0 Grade 4. 3 of 12 experienced neurotoxicity. ORR for 10 or 12 inc 3 CR's and 6 VGPR's and 4 of 4 evaluable pts were MRD-. Up to 9 mos CAR-T cell persistence. {Sun-488-N Shah}

44. China presented updated finding of their Legend-2 (License agreement with Janssen, who also makes Dara) for 57 pts at a single site with 12 month follow-up. Prior median LOT = 3, CRS = 90% but mostly Grades 1 or 2. CR=74% and MRD- = 68%. Median PFS = 15 mos but for MRD- pts, mPFS = 24 mos (only 6 mos otherwise). 12mo OS = 75% but 94% for MRD-, 29% otherwise. {Mon-955-W-H Zhao}

45. Another China study for N=20 pt, prior median LOT = 5.5 showed 85% ORR (although 3 relapsed), mPFS 15 mos. No neurotoxicity, mild CRS. CAR-T cells expand and persist well. {Mon-956-Y Liu}

46. JCARH125 was one of 3 CAR-T trials presented by MSKCC and has been chosen to proceed forward. For N=44 with mLOT=7, ORR = 82% (CR 27%, VGPR 21%) with short follow-up so far. Manageable toxicities {Mon-957-S Mailankody}

47. Another China study for N=14 with 4 previous LOTs showed 100% ORR (35% CR) plus 5 of 6 other pts at different doses also were in ORR. No neurotoxicity, only 3 CRS. {Mon-960-S Jiang}

48. From China, a therapy for HR MM (t(4;14), t(14;16), t(14;20), 17p-, 1q+): tandem auto followed by CAR-T CD-19 Day 0 followed by CAR-T BCMA Day 1, 2. All had CRS grades 1 or 2. Responses after CAR-T were 80% CR, 20% VGPR, 60% MRD- at 10^{-6}. {Mon-1009-C Fu}

49. A CAR-T therapy was given to N=11 pts with advanced stage HRMM (mLOT=11). While 100% achieved ORR, 2 have relapsed. {Mon-1011-D Green}

50. CAR-T with a "safety switch" to minimize CRS was reported for N=23 pts. They reported better ORR with higher doses, 50% at the lowest dose and 100% at the highest. There was minimal CRS so they didn't need to employ the safety switch. {Mon-1012-K Patel}

OTHER RESULTS

51. A Health Services Research study looked at 4670 Medicare MM pts during 2007-13. Of the pts who took bone-modifying agents, 83%-Zometa, 16%-Aredia, 1%-Xgeva. However, only 50% of Medicare pts treated for MM received one of these BMA's. Of note, it was indicated that this analysis confirmed the UK study showing that Zometa also extends OS by about 5 mos. {Mon-709-A Olszewski}

52. ** The VHA studied 4805 MM pts, of 1418 (29.5%) were black. They concluded survival of black patients with MM was improved compared to non-blacks in the VHA, a national comprehensive care delivery system. Black patients also received similar therapies compared to non-blacks, while presenting at a younger age with more comorbidities. {Mon-840-M Schoen}

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. Most of the induction treatments examine currently approved drugs, how best to combine them and how best to treat specific and needy patient groups such as High Risk and Frail. Thinking about Dr Fonseca's comment about only 50% of relapsed patient go onto subsequent therapy and looking at some of the trial result differences between the US and Europe, it's clear that one's initial Induction treatment is very important to the patient's ultimate success.

Look at all the new drug and CAR-T trials, especially the N (number of patients involved). Many results are early and need larger patient numbers, better understanding of dosages, longer follow-up, and perhaps better prognosis assessment tools (see CAR-T). However, there continues to be an incredible interest by researcher and clinicians to find better Myeloma treatments. Soon we'll be learning if earlier treatment in the SMM stage can offer Overall Survival benefits and even a possible cure for some. And soon MRD, an excellent prognostic measurement, will hopefully be used to help guide treatment decisions.

For someone diagnosed with stage III MM 24 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, K – 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 (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