MYELOMA HIGHLIGHTS FROM ASH CONFERENCE SAN DIEGO 12/2-6/2016

According to Jack Aiello (definitely not medically trained)

PREFACE

This is my 11th 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 cancers. This year there were nearly 700 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. 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. {Mon-**675**-T. Zimmerman} and clicking on the abstract number will take you to the actual abstract.]

There are other ways to learn more about results from this conference. There are scheduled webinars (MMRF 1/11/17, IMF 1/12/17) 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://ash2016blogs.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) Feb 4, 2017 (Register Now). Dr. Jeff Wolf of 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 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).

HIGHLIGHTS (e.g. My Takeaways)

1. In Nov 2015, 3 new drugs were approved for Myeloma...Daratumumab, Elotumumab (both mAb's) and Ixazomib (oral PI). At this ASH, trials were presented that provided results for **using these drugs beyond their current FDA-approved indications** such as Dara in combinations and Ixa before and after transplant.

2. Speaking of **transplants** (SCT), there were lots of abstracts on specific SCT usage...some contradictory. For example, one trial showed SCT plus consolidation benefitting MM pts while another trial showed no difference whether being treated with a single SCT, SCT + consolidation, or a tandem SCT.

3. There were 3 new drugs of interest: **Nelfinivar, Selinexar and Venetoclax**. Most impressive is that they were particularly effective in certain scenarios: Nelfinivar (with Velcade) for Vel-refractory pts; Selinexar alone for t(11;14) pts; and Ventoclax + dex for quad- and penta-refractory pts. Quad means refractory to Rev, Vel, Pom and Cfz, while Penta include Dara.

4. **Minimum Residual Disease (MRD)** testing is still not ready for prime time, but one doctor googled "Myeloma + MRD" and found 45 abstracts. MRD tests are certainly being added and reported in trials and while there's good correlation between PFS/OS and MRD, it's still not being used to determine subsequent treatment. Since MRD has the potential to guide therapy, stop therapy and change therapy, it's something we patients need to keep on our radar.

5. There were several presentations on **Immunotherapies** (mAb's, CAR-T's and checkpoint inhibitors). However other than mAb's like Dara, Elo, and Isatuximab (not yet approved), CAR-T and checkpoint inhibitors are still in a very early stage of evaluation.

6. More on **checkpoint inhibitors**. Dr Don Benson (OSU) explained that MM suppresses the immune system from doing its job. Inhibitors of the KIR ligand and PD1/PDL1 pathways enable NK cells and T-cells respectively to do a better job of finding and destroying MM cells. The concern, however, is that normal cells also have these built in checkpoints and you wouldn't want the immune system destroying these cells as well. One doctor even mentioned that these are still "scary".

COMMENTS AND DISCUSSIONS I FOUND PROVOCATIVE

7. "For **patients in a CR**, half will be MRD- and half will be MRD+." B. Durie (IMF)

8. "I always see **SMM patients** again 1 month after diagnosis. It's more important to know the tempo of their disease than risk factors." S. Lonial (Emory)

9. "I'm afraid that some might interpret **MRD-** as a cure, which is not true." J. Mikhael (Mayo)

10. "Half of **SMM patients** have MGUS-like disease and half are more like MM. If we only knew which patients were which, we would know who to treat." S. V. Rajkumar (Mayo)

11. "It's becoming more difficult to select the best treatment option for **R/R MM patients**." P. Moreau (France)

12. When discussing the management of **ND HRMM pts**, Dr A. Dispenzieri (Mayo) reminded attendees that "high risk" not only includes chromosome abnormalities but also fitness/frailty assessment and access/cost of treatment. Whether TE or nTE, these patients should consider Velcade-based induction and maintenance. TE pts should consider Tandem SCT. And for renal-impaired, Velcade triplet is more effective than a Velcade-doublet.

13. "Although **CR and MRD-** should be the goal, not all patients get there and this needs to be considered." N. Raje (UMass)

14. "For relapsed patients, doctors must consider **previous treatments and responses**. R/R MM pts should consider including POM." N. Raje (UMass)

15. "Every 5 years, folks ask if **SCT** is dead. But it isn't...not yet". P. McCarthy (Roswell-NY)

16. "Today we are curing a subset of patients. We just don't know who they are." S. Lonial (Emory)

SMOLDERING MM

17. n=270 in 2 trials demonstrated that **multiparameter flow cytometry** may represent a better way (actually a "biomarker") to classify HR SMM. Specifically this test classified these patients as MGUS-like (17%), Intermediate between MGUS & MM (66%) and MM-like (18%). Then 2-yr median Time-to-Progression (TTP) to MM/risk % was shown to be "not reached"/4%, 57 mos/25%, and 16 mos/58% respectively. {Sun-**373**-B. Paiva}

18. n=34 Elo (weekly)-Rev-dex in **High Risk** SMM, where HR is based on cytogenetics t(4:14), t(14:16, 17p- or +1q amplification. ORR was 82% (including CR 9%) and thus far no pts have progressed to active MM during or after protocol therapy. {Mon-**976**-I. Ghobrial}

FRONTLINE THERAPY FOR TRANSPLANT INELIGIBLE (NTE) PATIENTS

19. Ph 3, n=1600 NDMM pts, final PFS & OS results of the FIRST trial were presented comparing Rd continuous vs Rd 18 mos vs MPT. 4-yr PFS % (33 vs 14 vs 14) and median OS mos (59 vs 62 vs 49) and other factors showed overall **benefit for continuous Rd**. {Sat-**241**-T. Facon }

TRANSPLANTS

20. Ph 3, n=1400 NDMM pts, EMN02/HO95 MM trial VCD (R1) VMP or SCT (R2) VRD consolidation or none followed by Rev maintenance till progression, examined the impact of consolidation, which benefitted std but not HR pts. Best news was that **3yr OS from R2 was 86% and 87%** respectively.{Sat-**242**-P. Sonneveld}

21. Additional analysis was provided from the EMN02/HO95 MM trial shown above. Specifically, the SCT arm did show benefit over the VMP arm for all pts, e.g. ORR 86% vs 75% and 3yr PFS 65% vs 57%; for HR pts 3yr PFS was 52% vs 30%. So ultimately **HR MM pts benefitted by SCT but not from consolidation** (above). {Mon-**673**-M. Cavo}

22. Ph 3, n=581 Myeloma XI study investigated a **response-adapted approach to induction**. Specifically if pts achieved less than VGPR to induction (IMID regimen), they would be randomized to be given an additional regimen (PI based) before SCT. The consolidation side improved median PFS from 20 to 30 mos. For those having a transplant, the PFS was even better (31 mos versus 55 mos). However even Transplant Ineligible pts showed PFS benefit with consolidation of 14 vs 20 mos. {Sat-**244**-G. Jackson}

23. n=42, Ph 2. IxaRd –> SCT -> IxaRd -> Ixa maintenance for NDMM pts. Note this **all-oral therapy** (except for SCT). VGPR (CR) or better at the end of Induction, SCT and Consolidation were 36% (12%), 78% (38%), and 77% (44%) respectively. Adverse events were well-tolerated with no grade 3/4 neuropathy. If the future Dara may be added to this regimen. {Mon-**674**-P. Moreau}

24. n=76, Ph 2. KRdx4 -> SCT -> KRdx4 -> KRd maintenance (x10) -> Rev maintenance. Analysis were done after cycles 4, 8, and 18. At C18, ORR was 94% with a very high 86% in CR. [BTW, with no SCT for another group of 53 pts, C18 ORR/CR was 90%/40%.] MRD was done by both Flow and NGS. At C8 and C18 MRD- was 86%/64% and 97%/71% respectively by each method. For HRMM pts, ORR was 96% (81% CR) and C18 MRD- was 90%/63%. And 3yr PFS/OS was 86%/95%. When asked to compare this **KRd regimen with the IxaRd regimen** results above, the speaker said KRd speeds up response but has higher toxicity. {Mon-**675**-T. Zimmerman}

25. n = 46, KRdx4 -> SCT -> KRdx4 -> Rev maintenance (**nearly the same as above**) resulted in similar outcomes sCR = 57%, >= VGPR = 91%, MRD- = 70% with no neuropathy. {Mon-**1142**-G. Jackson}

26. n=111, Ph 2. KTdx4 -> SCT –> KTd x4 (T lowered from 200mg to 50mg). ORR after consolidation was 95% (CR=64%). **Overall 3yr PFS and OS were 68% and 90%** respectively. For HR pts, responses and OS were about the same while PFS was less. {Mon-**1141**-R. Wester}

27. n=750 pts were randomized into 3 arms. Arm 1, denote ACM, received one auto SCT, 4 cycles of RVD consolidation, then Rev maintenance until progression. Arm 2, denoted TAM, received a tandem (two) SCT's and Rev maintenance until progression. Finally Arm 3, denoted AM, received a single auto SCT, then Rev maintenance until progression. **After 38 months, the PFS (57%/56%/52%) and OS (86%/82%/63%) were comparable in all three groups.** Furthermore, when looking at subgroups such as High Risk, there was no differences (all about 24% PFS and 75% OS). Even overall secondary primary cancers (SPMs) were all about 5%. {Tue-**LBA-1**-E. Stadtmauer}

TREATMENTS FOR RELAPSED/REFRACTORY (R/R) PATIENTS

28. MRD results were presented for the recent **POLLUX** (DaraRd vs Rd) and **CASTOR** (DaraVd vs Vd) trials, which **resulted in FDA approval of using Dara with Rev or Vel**. MRD- outcomes were typically about 3x in the Dara arms versus the non-Dara arms. Further, MRD- for Dara-Rd was about 2x compared with the Dara-Vd arm (25% vs 10% evaluated by NGS with 10^{-5} sensitivity). {Sat-**246**-H. Avet-loiseau}

29. Another update of the **Pollux** study (DRd vs Rd) for RRMM pts showed benefits in ORR (94% vs 77%), 18 mos PFS (77% vs 50%), and MRD- (25% vs 6%). ORR for HRMM was 89% vs 67%. {Sun-**489**-P. Moreau}

30. n=41 RRMM pts on Dara-Pom-dex trial also examined **"retreatment" with Dara**. ORR 89% for Dara & Pom naïve but nearly 35% ORR for pts refractory to both Dara and Pom {Sun-**492**-A. Nooka}

TARGETED THERAPY

31. Ph 3, n-432. Tourmaline-MM1 study Ixa-Rd vx Rd for RR MM pts that resulted in Ixazomib approval Nov 2015. This **sub-analysis examined patient expression level of c-MYC** (proto-oncogene regulation cell proliferation & cell death. High c-MYC expression pts showed a 6 month PFS benefit on the Ixa-Rd over Rd. {Sat- **243**-A. Di Bacco}

NEW DRUGS

32. n=34 **Nelfinavir** is an approved, generic oral drug, and HIV protease inhibitor used to treat AIDS. When **combined with Vel-dex** (NVd) for Vel-refractory pts (and 76% were also Rev-refractory), ORR = 65% include 5 pts achieving VGPR. {Sun-**487**-C. Driessen}

33. n=66 (inc 30 pts had t(11;14) MM. Ph 1. **Venetoclax**, BCL-2 inhibitor, **single agent** for RRMM showed 21% ORR but 40% ORR for t(11;14) pts (88% if also high BCL-2 expression). {Sun-**488**-S. Kumar}

34. n=65 **Venetoclax + Vel-d** for RRMM pts. Overall ORR 67% with best responses ORR=97% for Vel non-refractor and 1-3 prior tx lines. Worst ORR for >6 tx lines (20%) or Velcade-refractory (31%). Likely Ph 3 to be Ven-Vd vs Vd. Higher BCL-2 expression means better ORR. {Mon-**975**-P. Moreau}

35. n=45, Ph 2 **Pembrolizumab** (checkpoint inhibitor Keytruda) **+ Pom-dex** for RRMM, all refractory to Rev, 73% double refractory. ORR 65% (inc 27% >= VGPR and median PFS 17 mos. However ASE's included 40% grade 3 neutropenic and ½ pts required dose reduction. {Sun-**490**-A. Badros}

36. n=79 including 48 quad (Rev-Vel-Pom-Cfz) and 31 penta (quad + Dara) refractory. **Selinexor** (80 mg 2x/wk) (oral XPO1 inhibitor) **and dex** (20 mg 2x/wk) regimen (Sd) goes by the name STORM study. ORR was about 20% for both quad and penta but also had grade 3/4 hematological events. Median OS was 9.3 mos. {Sun-**491**-D. Vogl}

37. n=12, Phase 1 study of **Selinexor-Cfz-d** in RRMM pts. These 12 pts were also refractory to Cfz. ORR for this group was 67% (15% >= VGPR) with 3.7 mos PFS. {Mon-**973**-A. Jakubowiak}

38. n=22, Ph 1b/2 study of **Selinexor** (100 mg/wk)**-Vel-d** (SdB) for RR MM pts, including those refractory to Vel (STOMP trial). Overall ORR=77% (inc 9% CR, 18% VGPR). For Vel-refractory, ORR=67%, while Vel-exposed/naïve had 100% ORR. {Mon-**977**-N. Bahlis}

39. n=12, Pilot Study of **CAR-T CD19** in conjunction with salvage (2^{nd}) SCT for advanced MM. Method: 2 weeks after the SCT, 5 x 10^7 CAR-T cells are infused. Of these 12 pts, 3 pts had a VGPR and longer PFS than from their first SCT. One patient (featured on the cover of Parade Magazine several months ago) had a 16 mos PFS but then relapsed and is now in a 12-mos CR with Dara. Only one episode of cytokine release for these 12 pts. {Mon-**974**-A. Garfall}

OTHER RESULTS

40. n=113 **For Light Chain MM patients** who follow their disease with 24-hr urine analysis (UPEP), the Serum Free Light Chain test offered better correlation with clinical outcomes (e.g. PFS) than urine assessments....and is certainly easier on these patients. {Sun-**376**-T. Dejoie}

41. There were several presentations on **racial disparities**. These included {Mon-**844**-M. Fiala}and {Mon-**846**-A. Rosenberg}that examined the usage of SCT's by African American MM pts. The first concluded that when elimininating health disparities and postential access barriers, black pts are will 37% less likely to utilize an SCT. The second focus was on California patients but came up with a similar number 30%. This poster {Sun-**3544**-S. Ailawadhi}examined MM complications (CRAB symptoms) among different racial groups with blacks having the highest rate of complications, perhaps being due to reduced access to drugs/supplemental insurance coverage.

42. An interesting study for Myeloma Cast Nephropathy (**kidney impairment**) comparing Haemodialysis with High Cut-off vs Standard High Flux Dialyzer in pts receiving Velcade-based therapies. With Haemodialysis, 1/2 the pts became dialysis-free versus only 1/3 in the Standard control group. {Mon-**978**-JP Fermand}

43. n=41 This trial study the efficacy and side effects from administration of **Daratumumab via sub-Q injection** in R/R MM pts. For pts on the recommended dose of 1800mg given over 30 minutes, the ORR was 41% and Infusion Reaction Rates were lower than with Dara IV infusion. And when asked about pain or bruising at the infusion site, Dr Usmani said that neither were problems. This has the potential to reduce infusion times from six or eight hours to 30 minutes. {Mon-**1149**-S. Usmani}

SUMMARY

For someone diagnosed with stage III MM 22 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 accurate 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