MYELOMA HIGHLIGHTS FROM ASH CONFERENCE ATLANTA 12/6-10/2013

According to Jack Aiello (definitely not medically trained)

PREFACE

This is my 8th year attending ASH (American Society of Hematology), where over 20,000 attendees from all over the world (hematologists/oncologists, lab researchers, scientists & 300 pharma companies) present latest research results via both oral presentations (1000) as well as posters (3000) on all blood cancers. This year there were 835 abstracts (>100 clinical) on Myeloma alone, many of which were selected for oral presentation.

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. [I've listed Day-Abstract#-Lead Investigator after the trial results, e.g. {Mon-**405**-M.Dimopoulos}.]

There are other ways to learn more about results from this conference. The IMF and Patient Power were conducting video interviews of MM experts for postings on their site. Some have also scheduled webinars (MMRF 12/18/13, IMF 1/16/14) which you can listen to live or by replay. You'll also find some patient blogs (including mine) posted on the IMF website. And all of us in the SF bay area should attend the Emerging Therapies-LLS ASH Review Jan 25, 2013 in SF (bit.ly/emergingtherapies or call 866-450-0669 to register). 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, Goal, Treatment plan, 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 and FISH analysis (e.g. chromosome deletions and translocations) gene-expression profiling (GEP) and flow cytometry with patient responses.

OVERALL IMPRESSIONS

- **Monoclonal Antibodies** This seems to be the next area beyond Proteasome Inhibitors (e.g. Velcade) and IMIDs (e.g. Revlimid) that will yield targeted drug therapies. Daratumumab, Elotuzumab, and SAR650984 are already in trials but I saw others which have showed success in the labs and mouse models that are heading to Phase 1 clinical trials. These mAb's are designed to attack a specific antigen expressed by the Myeloma cell, thus causing cell death. Might we see a PI-IMID-mAb combination?

- **Fit/Unfit/Frail** A way of using age, comorbidities (e.g. diabetis, cardio disease), and physical disabilities (e.g. arthritis) that will help determine a best treatment for older patients while focusing on quality of life.

- **Smoldering Multiple Myeloma** There's a belief that, like other cancers, earlier treatment means longer term success. While the standard treatment for SMM (M-spike >= 3g/dL and/or plasma% >= 10% but no CRAB damage) is watch-and-wait, there's a portion of SMM patients that are high risk (defined as "and", high free light ratio or flow cytometry that analyzes plasma cells and results in median TTP to MM < 2yrs) and will likely progress to full-blown MM within a couple of years. Perhaps treatment for high risk SMM patients can significantly delay the on-set of MM, thus preventing earlier organ damage. Treatment regimens such as Rev-only, Rev-dex, and Cfz-Rev-dex are all being studied in High-risk SMM. Perhaps MM will be redefined to include high-risk SMM and both will be treated the same.

- **Cytoxin instead of Melphalan** Since Cytoxin is less likely to damage your bone marrow and blood counts, several presenters recommended using Cytoxin as the alkylating agent in treatment rather than Melphalan. For example, CyBorD (Cy-Vel-dex) would be a better choice than MVP.

- **So many options** In general better responses result in better survivals. The list of treatment options since last year's ASH continues to grow now that we have Carfilzomib and Pomalidomide, although I've listed new patient treatments involving these drugs under the "New drugs" category since they are only approved for relapsed/refractory pts. There are clinical trials for every diagnosis phase...smoldering thru high-risk MM, newly diagnosed thru relapsed/refractory. Trials are so important because that's how we move possible treatments and new drugs. Perhaps you want to ask your MM doc if there's a trial that's beneficial for you.

- **Maintenance** This is still a hot topic. Most agree that maintenance (a better name might be "continued treatment") improves progression-free survival. But does it extend overall survival? More maintenance studies are necessary before there's full agreement on the benefit.

Of course, there are still so many unanswered questions such as:

- **Best treatment** for me as a newly diagnosed or R/R patient? What if I'm standard or high-risk [del 17, t(4;14), t(14;16) about 20% of pts]?
- For **transplant**-eligible,do it **now, later or never**?
- Length and type of **maintenance**?

Yet, I'm very encouraged by the continued progress to understand everything about MM, determine new MM cell targets, and learn what treatments work best.

COMMENTS I FOUND PROVOCATIVE

1. "Maintenance is really Continued Treatment." A. Palumbo, Italy. Or stated another way "Maintenance after an SCT removes the allure of a treatment-free benefit." S. V. Rajkumar

2. Discussing whether or not to do a transplant, S. Kumar (Mayo) said "While an SCT can clearly help some patients, we don't know who they are."

3. O. Landren suggested that one might think of Myeloma as a metastatic disease that evolves from a Solitary Plasmacytoma (passing through the MGUS and SMM phases).

4. "While all treatments are available to Fit patients, dose reduction should be considered for Unfit patients while those who are Frail prefer oral meds and should avoid melphalan." M-V. Mateos (Spain) A. Palumbo (Italy) categorized older patients via a geriatric assessment and suggested that Fit patients use 3-drug combinations, Unfit use 2-drug, and Frail use dose-reduced 2-drug regimens.

5. More on Maintenance: "The benefit of Revlimid maintenance is an early benefit so one can stop after 2 years." M.Attal. While P.Singh said "We don't know the subset of pts who will benefit most be Rev maintenance." To summarize, "We still need more study on maintenance." P. Richardson

TREATMENTS FOR NEWLY DIAGNOSED PATIENTS

6. This plenary session attended by 10, 000 examined a Phase 3 trial results for 1623 (!) pts at least 65 yrs old randomized into 3 study arms: (A) Rev-dex until disease progression; (B) Rev-dex for a fixed 18 cycles (72 weeks); and (C) Mel-Pred-Thal for a fixed 12 cycles (72 weeks). ORR % (75-73-62), PFS mos (26-21-21) and Median 4-yr OS % (59-56-51) appear close. However, there were differences. For example, PFS curves for (A) and (B) were very close through 18 months but then the curve separation became apparent and expanded. And while Arms (A) and (B) both had about 28% grade 3-4 neutropenia (low white count), Arm (C) had 45%. {Sun-**2**-T.Facon}

7. Outcomes for Velcade-Cytoxin-Dex (CyBorD) versus Velcade-Revlimid-Dex (VRD) were examined. Besides comparable PFS (70% vs 68% at 2 yrs) and OS (92% vs 85% at 2yrs), cost was also analyzed. The cost for 4 cycles CyBorD versus VRD was $37K vs $67K. {Sun-**3178**-S.Kumar}

8. Another poster for CyBorD induction determined that 81% of standard risk pts are alive at 5 years. {Sun-**3192**-C.Reeder}

9. This poster examined patient (n=283) responses to Revlimid in newly diagnosed patients with and without continuous therapy. It demonstrated that patients stopping Revlimid after 1 year and achieving a VGPR or better can result in long-term (4 yrs) disease control and can be considered a treatment strategy. {Sun-**3209**-T.Kourelis}

10. A Phase 2 study compared sequential (9 + 9 cycles) versus alternating (18 cycles) treatments of VMP and Rd. After 18 cycles, 60 vs 69% ORR but after 20 mos OS and PFS were similar. AE's also similar. High risk pts responded similarly to std risk. {Mon-**403**-M-V.Mateos}

TREATMENTS FOR RELAPSED/REFRACTORY (R/R) PATIENTS

11. Bendamustine-Vel-Dex (BVD) in 73 elderly patients in first relapse provided a high ORR 70% (CR 14%) {Sat-**1971**-P.Rodon} In another Phase 2 study of 70 RRMM pts, BVD showed 77% ORR (20% CR, 20% VGPR, and 37% PR) {Sat-**1974**-M.Offidani}

12. Bendamustine-dex-Rev (BdL) in a Phase 1/2 for 37 pts showed a 45% ORR (inc 11% CR), 74% 1-yr OS, and 45% 1-yr PFS. {Sun-**3212**-S.Pozzi}

13. Phase 1/2 trial (n=21) of Rev+Cytoxin (Endoxan)+Pred (REP) in 100% Rev-refractory pts (76% also refractory to Vel) showed 67% ORR, 6 mos PFS and 16 mos OS

14. Pom-Dex-Doxil in a Phase 1/2 trial demonstrated early ORR of 22% for Rev-refractory pts. {Sun-**3218**-J.Berenson}

15. Pom-dex for high-risk pts with 17del [a] and/or t(4;14) [b] produced: 1) 22% ORR (32% [a]; 16% [b]); 2) duration of response 6 mos (8 [a]; 2 [b]); and 3) median OS of 12 mos (12 mos [a]; 9 mos [b]), so Pom-dex is more beneficial for 17del than t(4;14). {Mon-**689**-X.Leleu}

16. Good results from two early trials Pom-Vel-Dex (PVD) for pts resistant of refractory to Rev and Vel-exposed (Richardson) have been incorporated in a Phase 3 trial comparing PVD with VD. {Sat-**1969**-P.Richardson, Sat-**1940**-J.Mikhael}

17. This Phase 1/2 trial analyzed Car-Pom-d for rev-refractory and prior velcade pts (n=67), which resulted in 70% ORR (28% >= VGPR) and median PFS and OS of 12 and 16 mos. Responses were similar for high-risk 17p deletion. {Mon-**690**-J.Shah}

TRANSPLANTS

18. This study examined SCT's in age groups (A) > 70, (B) 60-69, and (C) 18-59 yrs of age for more than 1200 pts. 3-yr OS & PFS were 72/33%, 75/38% and 78/42% respectively. In summary, survival differences are driven partly by higher co-morbidities and lower post relapse survival. {Mon-**416**-M.Sharma}

19. This interim randomized study (n=47) compared Rex-dex (8 cycles) versus Rex-dex (4 cycles) + SCT, both followed by 2 yrs Rev maintenance. After 3 yrs analysis, while the SCT had better ORR (77 vs 96%), this didn't translate into significant differences in median PFS (25 vs 17mos) or OS (not yet reached vs 58 mos). {Sun-**3180**-S.Lentzsch}

MAINTENANCE (including CONSOLIDATION)

20. In this long-term study, PFS2 was examined for regimens MPR-R (40 mos), MPR (28 mos), and MP (29 mos) but OS was similar. {Mon-**405**-M.Dimopoulos}. In another study after SCT's, pts were entered into arms (A) Rev vs (B) no maintenance. While PFS (46 vs 24 mos) was better for (A), OS was the same (81 vs 82 mos). It was shown that the 2nd PFS was shorter for (A) suggesting that it's more difficult to treat pts who have progressed while on maintenance, thus introducing quite a maintenance controversy that needs more study. {Mon-**406**-M.Attal}.

21. Phase 3 study (n=425) of newly diagnosed elderly pts who were randomize to VD, VTD, or VMP (8 cycles) all followed by 5 cycles of Vel maintenance. ORR's were 70-80% (CR/nCR 30-40%). Median PFS 15-17 mos and OS 50-53 mos. VD was just as effective with less toxicity. {Sat-**1966**-R.Niesvizky}

22. This is a Phase 3 (n=413) study of PAD (Vel-dox-dex) followed by SCT followed by 2 yrs maintenance of either daily Thal (50mg) or 2 Vel infusions per month. ORR 91% (CR 49%, VGPR 226%). Median OS after 7+ years not yet reached. {Mon-**404**-P.Sonneveld}

23. This Phase 3 (n=243) SCT pts looked at maintenance with (A) indefinite pred (50 mg every other day) or (B) in combination with 12 mos of thal consolidation (100-200mg). 5 yr PFS rates were 15/27% and 5 yr OS was 47/66% respectively. However, if >=VGPR was obtained by SCT, Thal arm did not show PFS/OS benefit. {Mon-**537**-A.Kalff}

24. Good Phase 2 trial results from the maintenance of an all oral regimen MLN9708 + Rev after an SCT is leading to a Phase 3 trial comparing is to Rev-only. {Sat-**1983**-J.Shah}

NEW DRUGS FOR NEWLY DIAGNOSED PATIENTS

25. Carfilzomib plus Melphalan and Prednisone for elderly patients is a promising therapy. In a Phase I/II trial, it showed and Overall Response Rate (ORR) of 91%, including 10% CR and 45% VGPR. {Sat-**1933**-P.Moreau}

26. Phase 2 (n=45, ages 40-88, median 60 yrs old) Cfz-Rev-Dex followed by Rev 2-yr maintenance (CRD-R) resulted in 67% CR and 98% ORR with PFS at 18 mos of 91%. Using flow cytometry, all 27 CR/nCR patients were MRD-negative. {Mon-**538**-N.Korde}

27. This Phase 1/2 trial examined the all-oral regimen of MLN9708 (Ixazomib)-Rev-dex. A 21-day cycle Phase 2 dosage is MLN9708 3mg (d 1,4,8,11), Rev 25mg (d 1-14), and dex 20/10mg (cycles 1-8/9-16; d 1,2,4,5,8,9,11,12). For Phase 2 (n=57) ORR was 95% (CR 27%, VGPR 48%). Worst Grade 3/4 AE was rash (11%) and there were no Grade 4 AE's. {Mon-**535**-P.Richardson}

28. CYCLONE [Cytoxin-Cfz-Thal-Dex] (don't ask me where the Thal-Dex fits in) in a Phase 1/2 after 4 cycles showed 96% ORR (76% >= VGPR) and 2-yr PFS & OS of 77% and 98% respectively. (Only grade 1 neuropathy even though daily Thal of 100mg.) {Sun-**3179**-

J.Mikhael} In a similar trial after 4 cycles of Cytoxin-Cfz-Dex (but no Thal), CCd showed 92% ORR (67% >= VGPR) and 2-yr PFS & OS of 76% and 87% respectively. {Mon-**685**-S.Bringhen} And a third trial Cfz-Thal-dex (no cytoxin) showed 93% ORR (60% >= VGPR). {Mon-**688**-P.Sonneveld}.

NEW DRUGS FOR RELAPSED/REFRACTORY (R/R) PATIENTS

29. MLN9708 (Ixazomib) as a single agent in a Phase 2 trial (n=32) not refractory to Velcade showed 16% >= PR after 4 cycles and is expected to improve. {Sat-**1944**-S.Kumar}

30. ARRY-520 (KSP Inhibitor) plus Velcade in a Phase I suggested >= 1.25 mg/m2 dosage is quite effective, resulting in 30% ORR for Vel-refractory and 63% ORR for Velcade-sensitive, or 42% ORR overall. {Sat-**1938**-A.Chari} Another presentation showed an inverse correlation between ARRY-520 and Acid Glycoprotein (AAG) levels suggesting that single agent ARRY-520 is more effective with low AAG (e.g. OS 23 vs 4.5 mos). {Mon-**285**-J.Kaufman (S.Lonial not available)}

31. A phase III poster showed that Perifosine with Velcade plus Dex in patients previously treated with Velcade showed no benefit in PFS or ORR {Sun-**3189**-P.Richardson}

32. An oral AKT inhibitor Afuresertib (GSK2110183) has previously shown single agent activity. Given together with Vel-dex (n=37) showed 65% ORR, although these were Vel-naive/relapsed but not refractory. However, Vel-refractory pts in a Part 1 study also showed a response. Grade 3/4 >10% AE's were thrombocytopenia (27%), diarrhea (14%), skin rash (13%) and anemia (10%). {Mon- **283**-P.Voorhees}

33. Panobinostat, an HDAC inhibitor, is combined with Vel-Dex (PANORAMA) in a Phase 2 trial of Vel-refractory pts and showed a PFS and OS of 5.4 mos and 17.5 mos respectively. {Sat-**1970**-P.Richardson}

34. SAR650984 is a CD38 mAb in a Phase 1 trial (n=24) showed no hematological Grade 3/4 AE's, while providing a single agent ORR of 31% with dosage >= 10mg/kg. These pts averaged 5 lines prior therapies, all Vel & rev, some Cfz & Pom. {Mon-**284**-J.Mikhael (T. Martin not available)}

OTHER RESULTS

35. If a solitary plasmacytoma has abnormal PET-CT scans and serum Free-Light-Chain values, perhaps MM treatment should start after appropriate surgery/radiation. {Sat-**1888**-G.Fouquet}

36. This poster looked at 1018 MM pts during the 2002-2009 timeframe from the VA Registry who took either Zometa or Aredia but not both. Zometa improved OS by showing a reduced risk of death by 16%. {Sun-**3182**-K.Sanfilippo}

37. Several trials integrated Minimum Residual Disease (MRD) testing, which is important as part of the IMF's Black Swan Research Initiative. There still needs to be a consistent definition of MRD but this is the first year I remember seeing it at all. Abstracts included **535**, **538**, **762**, **2077**, **3126**, **3152**, **3220**, **3223**, and **4647**.

SUMMARY

For someone diagnosed with stage III MM 19 years ago with only 2 treatment options (MP or VAD-SCT) and given 2-3 years expected survival, I've seen incredible progress since 2000. While there are many 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 Class/Category
IMID – Immunomodulary Drug
PI – Proteasome Inhibitor
mAb – Monocloncal Antibody

Drugs
B - Bendamustine
C - Cytoxin
Cfz - Carfilzomib
Dox - Doxil
E - Elotuzumab
M – Melphalan
P – Prednisone
Pom - Pomalidomide
R – Revlimid
T – Thalidomide
V- Velcade
Vor-Vorinostat (Zolinza®)

Treatment Success 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 (further defn needed); Immunophenotypic CR uses Flow Cytometry and is an example of a possible MRD defn.

Side Effects
AE – Adverse Event (aka Side Effects)
DVT - Deep Vein Thrombosis (blood clots)
MTD – Maximum Tolerated Dose
ONJ – Osteonecrosis of the Jaw
PE – Pulmunary 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.

"d" and "D" – Typically both mean Low-dose Dex (40 mg/week) these days
MGUS – Monoclonal Gammopathy of Undetermined Significance
R/R- Relapsed/Refractory Ref defined progressing while on Tx or within 60 days.
SMM – Smoldering MM