

MYELOMA HIGHLIGHTS FROM ASH CONFERENCE “VIRTUALLY” 12/4-7/2020

According to Jack Aiello (definitely not medically trained)

PREFACE

This is my 15th 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, we all experienced ASH in a virtual conference setting, watching taped videos and interactive q&a’s of the latest research results. Both oral and poster abstracts were presented on all blood diseases, especially cancers. This year there were more than 688 abstracts on Multiple Myeloma alone, with more than 179 of these selected for oral presentation. (I did not include any details of poster abstracts below.) I’m grateful to the IMF (www.myeloma.org) and their pharma donors for registering me for 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. 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-**141**-F Gay} 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 at <https://www.myeloma.org/videos/imwg-conference-series-ash-2020>. There are scheduled webinars (IMF-1/14/21, MMRF-12/17/20) which you can listen to live or by replay. You’ll also find some patient blogs (including mine) on the IMF website (<https://ash2020blogs.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 virtual LLS Blood Cancer Conference (which includes updates from ASH) Feb 6, 2020 (register at www.lls.org). Dr. David Iberri 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”; 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 schemas are defined for stages of **Induction**, and optionally **Transplant (SCT)**, **Consolidation**, and **Maintenance** with specified **Randomization** along the way for newly diagnosed pts (**NMM**) 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...more details follow)

1. This year's ASH expanded on immunotherapies...more CAR-T's, Antibody Drug Conjugates (ADC's) and especially more BiTEs (Bi-specific T-cell Engagers) ...as well as more targets besides BCMA.
2. Studies reinforced the importance of getting the best treatment up front in order to always obtain the deepest response possible. Minimal/Measurable Residual Disease (MRD) is the best measure for response depth and an excellent prognosticator for Overall Survival.
3. With so many treatment options and available trials, getting 2nd and 3rd opinions from Myeloma experts is more important than ever. Check out my friend and fellow-patient Jim Omel's blog on the challenge of "Sequencing" drugs at: <https://ash2020blogs.myeloma.org/sequencing-of-therapy-in-myeloma/>.
4. Transplants are still a very active subject for trials and still should be kept in our bag of potential treatment tools. Both the French trial (IFM2009) and Italian trial (Forte) demonstrated that transplants get more patients into MRD- status, although these trials also showed no matter how you attained MRD-, those folks did better than MRD+ patients.
5. Cytokine Release Syndrome (CRS), a major side effect in early CAR-T trials (and perhaps BiTEs as well), seems to be much better recognized and treated quickly so that \geq Grade 3 occurrences appear very low or 0 in newer trial results.

COMMENTS AND DISCUSSIONS I FOUND PROVOCATIVE

6. "In IFM2009 where Rev maintenance was stopped after 1 year, after 5 years MRD- patients still have a 25% declining rate of PFS." K Stewart
7. "Perhaps for MRD- over 3 years, we can consider stopping maintenance." S Lentzsch
8. "Any SMM pt with $>50\%$ risk of progression (2 of 3 factors [of 20-2-20]) should be treated." SV Rajkumar
9. "We really need a trial of VRd vs DaraRd to determine which is better." SV Rajkumar
10. "We need a Compass to find the best treatment for any patient that considers these 4 points: 1) Disease-related factors; 2) Patient-related factors; 3) Efficacy & toxicity of prior treatments; and 4) Future options." J San-Miguel
11. "BiTEs are the prom queen of ASH2020." S Usmani
12. "We need somethings besides BCMA so fortunately there are BiTEs and CAR-T's targeting other antigens." SV Rajkumar
13. "We are so blessed in MM to have so many treatment options for Relapsed/Refractory patients." K Anderson

14. “Side effects for Selinexor are both more manageable and not unexpected now that Seli is being given weekly (60 or 80 mg) instead of twice a week.” J Shah
15. “Molecular markers and circulating plasma cells may need to be incorporated into our 20-2-20 algorithm for better prognosis to progression for SMM patients.” MV Mateos. “Practically, how will we do this?” T Martin
16. “To D or not to D? That is the question. Adding Dara adds minimal toxicity but significant efficacy.” T Martin
17. “With MRD, hopefully we’ll have stopping rules.” J Mikhael
18. “If a patient progresses with any amount of Rev, I consider them to be refractory.” J Mikhael (T Martin agreed)
19. “Saving the best for last is good for a Hallmark movie but not for treating MM patients.” J Mikhael
20. “Amazing responses to heavily pretreated patients means we have to bring CAR-T up front.” T Martin
21. “Given the long OS (34 mos compared with 10 mos PFS in bb2121 CAR-T), maybe CAR-T re-sensitizes patients to prior therapies.” MV Mateos
22. “All cancer patients, even if on immunosuppressants, should get the Covid vaccine. Some protection is better than none.” A. Fauci

SMOLDERING MM

23. KRd-R: Ph 2, N=54; NIH study for HR SMM. KRd (x 8) followed by Rev maintenance (2 yrs) with a goal to prevent symptomatic MM. Results: 8yr PFS – 91%; 8yr OS-100%, ORR 100% (\geq VGPR 94%) and MRD- at 10^{-5} 70%. So after 8 years, only 10% developed MM whereas with no treatment, historical rates show that 75% would have progressed. {Mon-548-D Kazandjian}
24. APOBEC: N=32 (18 MGUS, 14 SMM) compared with N=80 MM. When the enzyme called APOBEC is mutated in MGUS or SMM, this led to higher progression within 2 yrs to MM (80%) versus normal APOBEC activity showed lower progression (13%). {Mon-602-B Oben}

FRONTLINE (INDUCTION OR FIRST LINE) THERAPY

TRANSPLANT-Eligible

25. Forte, MRD: Ph 3, N=474, NDMM; KRd-SCT vs KCd-SCT vs KRd x 12 followed by R or KR maintenance till progression. Despite similar responses, KRd-SCT significantly improved MRD 10^{-5} of 68% (vs 45%, 54%) and 3yr PFS 78% (58%, 66%). KR prolonged 30 mo PFS 81% (vs 68%). {Sat-141-F Gay} {Sun-491-S Olivia}
26. IFM2009: Ph 3, N=700, NDMM; RVd (x3 cycles)-SCT-Rvd (x2) vs RVd (x8) followed by 1 yr R maintenance. With 8 years of follow-up, there was no Overall Survival benefit (or PFS2). Rather, the benefit was seen in patients who achieve MRD-negativity (30% for SCT, 20% RVd alone), no matter

how you got there (transplant up-front, delayed, or none at all). About 48% of RVd arm got a delayed SCT. SCT pts also got more SPM's (9.7% vs 7.7%) {Sat-[143-A](#) Perro}

27. IRd: Ph 2, N=120 NDMM of which 48% were HR. This all-oral regimen (except SCT) of Ixa-Rev-dex followed by SCT followed by IRd consolidation followed by Rev for Standard risk and IxaRev for High Risk resulted in good efficacy with limited follow-up (13 mos). ORR = 93% after induction; 54 >= VGPR after consolidation, and 53% MRD- at 10^{-5} for 32 pts in CR. {Sat-[144-R](#) Helena}
28. Griffen: Ph 2, N=207; This is the trial examining the benefit of 4-drug induction adding Dara at every stage except SCT: VRd-SCT-VRd consol-R maint and comparing these 2 arms after 12 mos of maintenance. The Dara arm favored all comparisons: 10^{-5} MRD- 62% vs 27%; CR 82% vs 61%, although magnitude of benefit was less for High risk than Standard risk pts. At 27 mos f/u, there's no difference yet in 1-yr PFS or 1-yr OS. {Mon-[549-J](#) Kaufman}

MAINTENANCE

29. EMN02/HO95: Ph 3, N=878; VCd-randomize SCT or VMP, then randomize again to consolidation RVd (2 cycles), followed by Rev maintenance till progression. Results focus on "consolidation or not". Consolidation showed benefits for 5-yr PFS (50% vs 42%), med PFS (59 vs 43 mos), and 6-yr OS (75% vs 69%), all calculated from start of maintenance. {Mon-[550-P](#) Sonneveld}

TRANSPLANT-Ineligible

30. Tourmaline-MM2 Ph 3, N=705. All-oral IRd vs PlaceboRd, 18 cycles followed by dose reductions cycles till progression improved PFS by 13 mos (35 vs 22 mos). ORR 82% vs 80% similar but deeper responses shown by CR 26% vs 14%. The presenter indicated that this all-oral therapy was comparable to VRd but that DaraRd was probably better. {Mon-[551-T](#) Facon}

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

31. Apollo: Ph 3, N=304; DaraSubQ+Pom+d vs Pom+d resulting in benefit for both 12mos PFS (52% vs 35%) and OS (69% vs 44%). Nearly half the pts were refractory to both Vel and Rev. {Sun-[412-M](#) Dimopoulos}
32. Dara-Cytosin-dex +/- Pom: Ph 2, Arms A, B, and then C=Add Pom to B arm at progression. N=120 (Arm C = 45). ORR= 89%, 51%, 58% for the 3 arms. Follow-up is 25 mos so med PFS was Not Reached (but expected > 30 mos), 9 mos, and 21 mos respectively. Conclusion: If patients progressed on the DCd arm, adding Pom helped many. {Sun-[413-M](#) Sebag}
33. IKEMA: Ph 3, N=302. Carfilzomib (K)-dex +/- Isatuximab. Benefits in the Isa arm include ORR (87% vs 83%), MRD- at 10^{-5} (30% vs 13%), and "adjusted-for-Isa-interference-with-M-protein" CR (46% vs 28%). Note that previous non-refractory Dara pts were allowed on this study. {Sun-[414-T](#) Martin}
34. GEM-KyCyDex: Ph 2, N=198. K-d +/- Cytosin. Similar response rates but KdC showed particular PFS benefit for the Rev-refractory patients (26 vs 9 mos). {Sun-[415-MV](#) Mateos}
35. Algonquin: N=37, Ph 1, Part 1; Belamaf+Pom-dex for RRMM, prior Pom pts excluded. ORR 88% but 100% for 2.5 mg dose given every 4 weeks. However, keratopathy (corneal changes, blurry, vision

changes) was 76% including 51% G3 (although about 15% actually experienced visual changes), so alternative dosing schedules (e.g. every 8 or 12 weeks?) are being investigated. {Mon-725-S Trudel}

36. Xpovio (Selinexor): N=85, Ph 1; Seli+Pom+d (SPd) all oral arm of STOMP trial. Seli RP2D dosage 60mg once weekly given to N=20. ORR's were 54% (Pom naïve or non-refractory, 36% (Pom refractory), and 60% (RP2D). Med PFS was 1 yr for all pts but NR for RP2D pts. (In another meeting, it was noted that Seli side effects are much more manageable without surprises at the 60-80 weekly dosage rather than twice a week.) {Mon-726-C Chen}

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

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

37. Allo: N=35, half HR pts; ORR 60% with a short median follow-up (f/u) of 3 months. Small numbers but encouraging. {Sat-129-S Mailankody}
38. CRB-402, bb21217: N=35 at RP2D. ORR=68% but recent manufacturing changes have improved treatment efficacy. {Sat-130-M Alsina}
39. Ida-cell (bb2121, KarMMA), QoL: For 62 patients with 18 mos median f/u, ORR=76%, median PFS and OS 9 and 34 months respectively. This CAR-T platform has been submitted to FDA for approval which many folks believe will occur Q1'2021. Quality-of-Life results were assessed over the first 15 mos and were generally stable or improved, demonstrating meaningful QoL benefits. It's important to understand that many trials these days include an analysis of Patient Reported Outcomes (PRO's) which is valuable to all future patients. {Sat-131-Y Lin} {Sun-437-N Shah}
40. CT053, Lummicar-2: N=24, 87% ORR (79% CR), med PFS 19 mos. Med T-cell persistence 161 days, with the longest persistence being 510 days and counting. {Sat-132-S Hao} 94% ORR (17 of 18 ps). {Sat-133-S Kumar}
41. P-BCMA-101: N=53, 67% ORR {Sat-134-C Costello}
42. Cilta-cel (CARTITUDE): N=97 pts, med LOT=6. ORR=97% (inc sCR=67%); 1yr PFS and OS were 77% and 89% respectively. MRD at 10^{-5} = 93%. This was the show-stopper at ASH19 when an astounding 100% ORR was reported. With another year of evaluation this CAR-T treatment continues to provide excellent effectiveness and durability, may well be the next CAR-T submitted for FDA approval. {Sat-177-D Madduri}
43. GC012F Fast: N=16 (15 were HR). Has Dual targets BCMA and CD19. 94% ORR (100% at dose level 3). Manufacturing time of 24-36 hrs results in med 17 days from apheresis to infusion. This shorter manufacturing time is an important departure over the typical 3-4 weeks time needed to produce other CAR-T products, thus reducing the "bridging" period. {Sat-178-H Jiang}
44. C-CAR088: N=23, 1/3 of pts over 65 yo, half of pts had 2 High Risk abnormalities. ORR 96% (44% CR, 48% VGPR), 6 mos PFS 65%. {Sat-182-P Lu}

BiTES (myeloma cell X t-cell)

45. Teclistamab: Ph 1, BCMA x CD3. ORR = 73% at higher doses, which included “step-dosing”. Both IV (N=84) and SubQ (N=65) formulations being tested. No CRS in 149 pts. {Sat-**180**-A Garfall}
46. AMG701: Ph 1, 26% ORR but 5 of 6 pts ORR in most recent evaluable cohort, and 6 of 7 pts MRD-. Starting N=85, med LOT=6, 64 pts discontinued, most due to progression but 8 pts had CRS Gr 3. {Sat-**181**-S Harrison}
47. Talquetamab: Ph 1, GPRC5D (not BCMA) x CD3. Testing both IV (N=102) and subQ (N=55) formulations but perhaps going with subQ for which higher-dose (N=19) ORR=69% (>= VGPR 39%), 8 responders continue to respond longer than 12 mos. {Sat-**290**-A Chari}
48. REGN458: Ph 1, BCMA x CD3. 95% >= VGPR (18 of 19 pts). 32 of 49 pts discontinued treatment. ORR for extramedullary plasmacytomas was 17%. {Sat-**291**-D Madduri}
49. Cevostamab: Ph 1, FcRH5 (not BCMA) x CD3. For N=51, ORR = 53% for active dosage, which included 5/8 responses from prior BCMA patients (CAR-T or Blenrep). Had a patient who discontinued Cevostamab over 1 yr ago and is still in CR. {Sat-**292**-A Cohen}
50. TNB-383B: Ph 1, BCMA x CD3. N=58. 80% ORR at target dosing (N=15). {Sat-**293**-C Rodriguez}

ADC's (Antibody Drug Conjugate)

51. MEDI2228: ORR=66% but 74% ORR for 17/23 pts on dose expansion phase. BCMA-targeted. No keratopathy but photophobia (sensitivity to light) which was reversible. {Sat-**179**-S Kumar}

OTHER Drugs

52. GMMG-Birma: Since about 8% of RRMM pts have a BRAF mutation, N=12 pts were given BRAF and MEK inhibitors resulting 83% ORR (CR=25%, VGPR=50%). Interestingly they used drugs encorafenib (BRAF inhibitor) and binimetinib (MEK inhibitor) that are also used in Melanoma. Note all-oral and dex-free. {Sat-**294**-M Raab}
53. ANCHOR: Ph 1/2a, Melflufen+dex combined with either Dara (N=33 pts) or Vel (N=13). Melflufen RP2D will be 30mg for the Dara arm and has not yet been determined for the Velcade arm. Arms showed ORR of 73% and 60% respectively and the med PFS for the Dara arm was 13 mos. {Sun-**417**-E Ocio}
(Note: Has also applied for FDA approval based on Horizon study Melflufen+dex for triple-refractory as well as EMD...about 25% ORR.)
54. Iberdomide: The first results of Iberdomide (CC-220) + dex, with either Dara (N=27) or Vel (N=23) for RRMM were presented although numbers are small. Importantly Iber (which binds to Cereblon) was shown to be effective in patients who were refractory to Rev and Pom. The ORR for the Dara and Vel arms were 42% and 61% respectively. {Mon-**724**-N Van De Donk}

OTHER RESULTS

55. F Gay and L Rosinol discussed difficult cases: 1) Renal Failure: Dose-reduce Rev but not necessary for Pom, PI's, and mAb's and SCT can be effective. 2) EMD: Vel, DCEP treatments 3) CNS: Unusual (1-2%) but radiation, dex, IMiDs, Selinexor cross the blood-brain barrier and can be effective.

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. And importantly, other targets besides BCMA and mechanisms of action, e.g. dual targets, are being investigated.

For someone diagnosed with stage III MM 26 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 10 more approvals and many combination therapies. And we'll likely have more FDA approvals in 2021. 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)

<p><u>Drug (brand names) by Drug Class/Category</u></p> <p><u>IMID – Immunomodulatory Drug</u> T – Thalidomide R – (Lenalidomide) Revlimid Pom – Pomalidomide (Pomalyst)</p> <p><u>PI – Proteasome Inhibitor</u> V- Velcade (Bortezomib) Cfz, K – Carfilzomib (Kyprolis) I, Ixa – Ixazomib (Ninlaro)</p> <p><u>mAb – Monoclonal Antibody</u> D, Dara – Daratumumab (Darzalex) E, Elo – Elotuzumab (Empliciti) Isa – Isatuximab (SAR650984)</p> <p><u>HDAC - histone deacetylase inhibitors</u> Pano – Panobinostat (Farydak)</p> <p><u>Steroids</u> P – Prednisone D or d - Dexamethasone</p> <p><u>Chemotherapy Drugs</u> C – Cyclophosphamide (Cytoxan) M – Melphalan</p> <p><u>Treatment Measurements</u> 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</p>	<p><u>Treatment Response</u> 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)</p> <p><u>Side Effects</u> 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</p> <p><u>Tests/When to treat?/Other</u> CRAB – High Calcium, Renal, Anemia, and Bone... CRABi – CRAB + “i” increased infections FLC – Free Light Chain</p> <p>SCT – Auto stem cell transplant. TE, NTE – Transplant Eligible of Not TE</p> <p>LOT – Lines of Therapy</p> <p>TE, nTE – Transplant eligible or non-TE</p>
<p>“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</p>	