GMAN/IMWG 2017
Jack Aiello

June 2017 was an active month for Myeloma meetings. In fact, there were 2 other meetings ASCO (American Society of Clinical Oncology) and EHA (European Hematology Organization) that I didn't attend. Rather, this report covers the GMAN (Global Myeloma Action Network) and IMWG (International Myeloma Working Group) meetings in which I was fortunate to participate.

GMAN Summary

GMAN, in its 5th year, is an advocacy initiative of the IMF (International Myeloma Foundation), and its mission is to improve lives of myeloma patients around the world. In attendance during the 2 day meeting were nearly 40 individuals from 26 different countries, mostly from Europe but also from South Korea and Australia as well as North and South America. Advocates from these countries share what works for them as well as what issues they have. While cost of drugs may be our most serious issue in the US, for other countries it may be access to drugs or education. For example, the EMA (European Medical Agency, similar to our FDA) may approve a new medicine but then each country's government, which pays for the drug, decides whether or not to make it available in their country.

Meeting goals were well-articulated by Yelak Biru (MM Patient Advocate, Arkansas) to Improve the Lives of MM Patients Around the World by 1) raising the profile of advocacy groups; 2) increasing MM awareness; and 3) improving access to treatments. Specifically Access was defined as being equal to Approval minus Cost minus Coverage, and the only way to expand Access was to engage with Policymakers, Payers, and Pharma.

Also in attendance were Myeloma expert Drs. Rafat Abonour (Indiana University), who answered many treatment-related questions and Jean-Luc Harousseau (University of Nantes, France). Dr Harousseau spoke about Healthcare costs (also at the IMWG meeting) where he reminded attendees that drug costs amount to only 15% of healthcare expenditures, but it's perhaps the fastest growing segment. He noted that the SOC (Standard of Care) costs for an MM patient's treatment averages $.5M and relapsed patients $1M. He provided monthly cost examples for Velcade ($4K), Revlimid ($10K), Pomalyst ($13K), Carfilzomib ($11.5K) and Elotuzumab ($19K), Panobinostat ($11K), Ninlaro ($11.5K), Dara ($18K). Treatment costs are high because of 1) treat till progression; 2) combination treatment; and 3) longer survival. This is such a complex issue because how should a final price be determined? Price needs to incorporate production costs, R&D, high risk of failure, and limited life duration (generics, biosimilars) but should also include added value when compared with existing treatments.

The final group of attendees were Pharma co-sponsors Takeda (Velcade, Ninlaro), Bristol Myers Squibb (Elotuzumab, Nivolumab-checkpoint inhibitor), Amgen (Carfilzomib, Denosumab), and Celgene (IMIDs, Durvalumab-checkpoint inhibitor, bb2121 with Bluebird-anti BCMA CAR) which provided company updates.

Breakout sessions on access to novel therapies, more effective advocacy, and clinical trial navigation were facilitated and reported on by Yelak Biru, Dr Durhane Wong-Rieger, and Jack Aiello respectively. Finally various advocacy updates were provided for France, Columbia, Brazil, Korea, and Canada followed by Susie Novis Grant 2016 reports and 2017 awardees made to Armenia, Croatia, and Paraguay.

I always appreciate reconnecting with these advocates who play such a critical role in improving the lives of MM patients in their countries while facing a variety of challenges. I'm reminded how fortunate MM patients are by comparison living in the US, even though MM is a global disease that know no borders.

IMWG Summary

The IMWG (International Myeloma Working Group) held its 8th annual meeting in Madrid (where EHA (European Health Association, like ASH) was held). The IMWG consists of 226 MM experts, of which 96 attended this brainstorming session for MM. They meet 2x/yr (ASH-morning breakfast, EHA-1.5 days) in order to develop research initiatives and guidelines for doctors and patients. At this meeting, the IMWG Chairmen were Drs. Brian Durie, Philippe Moreau, S. Vincent Rajkumar, and Jesus San Miguel, an impressive group of world-wide MM experts. The meeting format started with a plenary session, major topic presentations/panel discussions, and working group meetings with lots of time for audience discussion throughout. These topic subjects were:

1) Pathogenesis of MM – L Bergsagel
2) Front-line Therapy – B Durie
3) Role of Transplant – G Cook
4) MRD Assessment in MM – H Avet-Loiseau (P & C of NGS), J San-Miguel (P & C of NGF)
5) Making sense of New mAb's – M Dimopoulus
6) Cost of MM Therapy & Access - J-L Haroussseau

And working group topics were:

1) Cost of MM Therapy - J-L Haroussseau
2) Bone & Imaging – E Terpos, E Zamgni
3) Immunotherapy – I Ghobrial, A Cohen
4) Smoldering MM – M-V Mateos, S Kumar (I attended this breakout)

Interesting Quotes/Discussions from IMWG

1) On the topic of Pathogenesis - L Bergsagel: "MM is a disease of enhancer-driven-oncogenetics-regulation. We need to target super enhancers such as Ikaros and ETV4, derugulating MYC. It's difficult to target MYC directly."

2) D Vesole: "At ASCO, Dara-KRd and Elo-VRd results were not impressive compared with non mAb counterparts." This statement generated significant conversation including the small size of these Phase 1/2 studies and that Europe has a 1000 patient study examining Dara +/- VTd.

3) On the subject of Transplants - M. Gertz: "Carfilzomib comes along and we want to add. Dara comes along and we want to add. For SCT, we always try to delete. SOC (Standard of Care) has to be Induction plus SCT." S Geralt: "80% of patients benefits from an SCT. Why don't the other 20%?" V Rajkumar: "Timing of SCT (early of late) is not clear due to no OS benefit based on 4 trials." S Usmani: In response "But follow-up has not been long enough to determine possible OS benefit."

4) On the topic of MRD Assessment - H Avet-Loiseau: NGS Pro's over NGF– Only needs 2M (rather than 20M) cells; NGS is already standardized; Can use frozen rather than fresh (<48 hrs) sample. J San-Miguel: "Negative PET-CT plus MRD- is better than either Neg PET-CT or MRD- alone." V Rajkumar: "Yesterday we knew MRD was prognostic. Today we must prove MRD can be used as a surrogate for OS in Clinical Trials. Tomorrow we need a trial that shows MRD can be used to effect practice."

5) On the subject of mAb's - M Dimopoulus: "Can we combine Dara (or Isatuximab) with Elo?" K Anderson: "HDAC inhibitors can upregulate CD38 so should we combine with Dara?" V Rajkumar: "Are any patients using Elo instead of Dara?" K Anderson: "Checkpoint monitoring of patients is a whole new world. We need to watch patients carefully for autoimmune response."

6) On the topic of Costs - J-L Haroussseau (see GMAN notes above): "High costs harm patients due to lower compliance, lower survival, lower socio-economic group." "After FDA approval in the US, there's no value assessment which results in the highest $$. We need both Health Technology Assessment (HTA) and Value/Benefit measures." M Gertz: "Public utilities and banks are public companies but are regulated because services are necessary. Doesn't pharma also provide a necessary service? We have a failure in the US Government regulations." V Rajkumar: "Things we can do: 1) Strict guidelines, e.g. Velcade before Carfilzomib; 2) Speak up publicly; 3) Education of oncologists."

7) SMM Breakout- M-V Mateos: "How do we evaluate risk of progression from SMM to MM...plasma%, cyogenetics, FLC, PET/MRI." R Kyle: "We don't need to know on day 1 if a patient is at high risk of progression, 'watch & wait' can help." S Kumar: "Ideally we whittle away SMM on both sides, treating more as either MGUS or MM. While standard MGUS progresses at 1% per year, there are high-risk MGUS patients progressing at 60% over 15 years."

WORKING GROUP REPORTS Chairs: B Durie, JS Miguel

Group 1: Cost of MM Therapy - J-L Haroussseau

- Cost of drugs only part of the problem but rising the fastest.
- Cost of combo's a great concern, "break the bank"
- Not just an MM issue but other cancers as well, e.g. checkpoint inhibitors
- Government and payers must spread their money
- Different problems in different countries but US prices drive other country prices
- Need to introduce the assessment of drugs, added value.
- Consider the roles of regulators & HCA
- Pay for Performance
- Determine the price relative to GDP
- Role of lobbying: Patient advocacy group, with cooperative groups like the IMF, with other cancer orgs, taking the lead to bring a "consortium of stakeholders" for an issue/solution discussion

Group 2: Bone & Imaging – E Terpos, E Zamgni

- PET-CT most effective imaging (but uses radiation) vs DWI MRI (Diffused Weighted Imaging) (but no standardization)
- Study proposal to compare and determine the best for MRD testing

Group 3: Immunotherapy – I Ghobrial, A Cohen

- Checkpoint Inhibitors: 30 trials but only 3 have reported data so not enough data to know which patients might benefit
- CAR-T: 8 x BCMA trials, 4 reporting 44-100% response but durability not known. Definitely monitoring responses
- Need to determine biomarkers of Response and Resistance

Group 4: Smoldering MM – M-V Mateos, S Kumar

- Need new Risk Assessment model to better understand the "type" (e.g. renal) of progression
- Clinical Trial endpoints will vary depending on if the goal is to Cure vs Delay Progression
- Better screening, including for HR MGUS

How Best to Treat High Risk MM – S Usmani

All agreed that there is no standard answer to this question, and as such, is an unmet need. Dr Usmani presented 7 categories of myeloma based on molecular subtype, which resulted in different cytogenetics/FISH, elevated genes, and risk-of-relapse outcomes. While there's work being done in this area at the in vitro (pre-clinical) level, he suggested a clinical trial treatment approach for HR ND Transplant eligible patients: RVd -> Early SCT -> Either t(4:14) Velcade maintenance OR Del 17p, other HR features RVd maintenance. [I find it interesting that Venetoclax, which has shown initial efficacy in t(4;14) pts wasn't mentioned in this proposal although it was discussed later.]

Some Conclusions:

- Recognize MM as not one disease so do small enrichment design clinical trials
- Achieving MRD- matters for HR MM
- T (4:14): choose best PI for up front and maintenance
- Del 17p: Pom may overcome poor prognosis; need to evaluate as part of induction and maintenance
- Future strategies: CAR-T (BCMA, SLAMF7, CD38...), BITE (BCMA), Antibody-drug conjugates, Immune modulation

Current Portfolio of Phase 3 (mostly) Clinical Trials – SV Rajkumar, P Moreau, WJ Chng

These 3 doctors presented current phase 3 trials (only Phase 2 in the Asia Myeloma Network). These can be found on www.clinicaltrials.gov. But a couple of key takeaways were: 1) the question asked by SV Rajkumar "Can KRd improve on VRd, specifically helping HRMM?" and 2) Many of the European studies include MRD assessments. And future ideas included 1) a meta-analysis of maintenance treatment and 2) the need for a trial where patients become MRD+ and how to treat.