

IMWG/GMAN 2019  
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June 2019 was an active month for Myeloma meetings. There were ASCO (American Society of Clinical Oncology) and EHA (European Hematology Organization) which I didn't attend. Rather, this report covers the IMWG (International Myeloma Working Group) and GMAN (Global Myeloma Action Network) meetings in which I was fortunate to participate. The comments below are my takeaways but I'd suggest that you view the IMWG Conference Series video made just after the IMWG meeting. The video slides are downloadable and provides a great talk featuring Dr. B Durie, J Mikhael, and P Moreau. It can be watched at: <https://www.myeloma.org/videos/imwg-conference-series-amsterdam-netherlands>

IMWG MEETING SUMMARY

The IMWG, founded by the IMF (International Myeloma Foundation), consists of 243 MM (Multiple Myeloma) experts, of which 100 attended the 10th annual meeting in Europe, typically scheduled around the European Hematology Association (EHA) conference, similar to the ASH meeting in the US. They actually meet twice a year (ASH- morning breakfast, EHA- 2 days) to collaborate on myeloma projects that will benefit both patients and physicians who treat them. At this meeting, the IMWG Chairmen were Drs. Brian Durie, Philippe Moreau (France), S. Vincent Rajkumar (Mayo), and Jesus San Miguel (Spain), an impressive group of world-wide MM experts.



The meeting format started with an evening talk examining Machine Learning & Artificial Intelligence (very futuristic possible application to Myeloma), then 1.5 days of major topic presentations/panel discussions, and working group meetings with lots of time for audience discussion throughout. The major topics were:

- 1) Who should we treat with Smoldering MM - J San Miguel, S. Kumar, MV Mateos
- 2) Next Generation of Frontline Therapies– SV Rajkumar, T Facon, P Richardson
- 3) CAR-T Therapies/BiTes: Role for the Future – T Martin, Y Lin, P Moreau
- 4) MRD in 2019: Current Status, use in trials, and clinical practice – B Durie, J San Miguel, N Munshi
- 5) High Risk Disease: Classification & Treatment – P Sonneveld, WJ Chng, S Usmani

- 6) Unraveling the Complexities of Relapsed Treatment Options - SV Rajkumar, P Moreau, P Richardson
- 7) Portfolio of Phase 3 trials world-wide: S Lonial, F Gay, K Kim

And working group topics were:

- 1) Mass Spectrometry - SV Rajkumar, D Murrar
- 2) Bone & Imaging – E Zamagni, E Terpos
- 3) CAR-T, BiTcs & Other Immunotherapies – T Martin, Y Lin (I attended this breakout)
- 4) Smoldering MM – M-V Mateos, S Kumar
- 5) New idea about Drug Access - J-L Harousseau, S Zweegman

### Who should we treat with SMM

Our meeting began with a discussion of Smoldering Multiple Myeloma (SMM), including risk stratification and if/when any SMM pts should be treated. Referring to the 20-2-20 (20% plasma percentage, 2 g/dL M-spike, and 20 FLC (Free-light chain) ratio) and even further risk-scoring classification that included FISH abnormalities, SMM can be categorized into low (4% chance of 2 yr progression to MM), low-intermediate (25%), intermediate (49%) and high (73%). Two recent trials for HR SMM patients have shown improved survival with preventative (delay?) approaches treating with Rev (or Rd, one trial treated for fixed length, the other to progression), and currently curative trials with more intensive therapies (4-drugs PI, Imid, mAb, Dex, SCT) CESAR (has accrued) and ASCENT (is accruing) patients. In fact, Dr MariaV Mateos noted there are currently more than 50 SMM trials. A trial just opened comparing Rev-dex +/- Dara will also prove interesting for these patients. As such, should these HR SMM pts be treated today, and if so, which treatment (preventive or similar to MM), and will insurance cover? These are certainly discussions SMM patients should have with their doctors.

There was a comment by Dr. Sagar Lonial that paraphrased said “We should help the immune system to ‘control’ the myeloma versus trying to eradicate the myeloma, the latter of which might also reduce the immune system’s chance of controlling the myeloma.”

And for the first time, I heard the phrase “Relapsed SMM”. Are they still smoldering when they progress or should they wait for CRAB features? Which clinical trials will they be eligible for...SMM, Newly Diagnosed or Relapsed-Refractory myeloma? Are they then considered to have had one line of treatment?

### Next Generation of Frontline Therapies

This topic is probably the best understood and yet not without controversy. VRd is quite common but VTd (in countries where Rev is not available or reimbursed), VCd (renal failure), KRd (HR MM in US) and others (VDT-PACE, PAD, and VMP) are all used. However, can the VRd triplet be improved? As Dara makes its way to frontline, perhaps Dara-Rd or a quadruplet Dara-VRd could be used (cost, toxicity?). One important point mentioned by Dr Paul Richardson is that treatments should not increase mutations, although he pointed to an analysis that showed 5K mutations at first line treatments but 12K at 2nd-3rd lines. He also noted that there are still

not enough “events” after 4 years of the Determination trial (Early vs Late SCT), probably due to maintenance till progression. That’s good news for MM patients indicating good PFS prognosis.

Within the Bone & Imaging working group, it was noted that DWI (Diffused Weighted Imaging)-MRI could replace PET-CT.

#### CAR-T Therapies/BiTes: Role for the Future

Currently on [www.clinicaltrials.gov](http://www.clinicaltrials.gov), almost 50 CAR-T trials are listed and it’s thought that MM is likely the next disease indication in CAR-T for regulatory agency review. These trials are now being examined in earlier disease setting, looking at combination treatments such as CAR-T + Rev, targeting different antigens beside BCMA, and even off-the-shelf (allo) CAR-T. Mechanisms of resistance such as “antigen escape” and T-cell persistence are being studied. It’s also interesting to note that MRD- status (no myeloma in the bone marrow) can be reached before CR response.

Several ADC’s (Antibody Drug Conjugates) are on the horizon with the one furthest along being GSK 916 in their DREAMM-1 study showing a 12 mos PFS as a single agent (roughly the same as CAR-T). And the best known BiTe (Bi-specific T-cell engagers) is Amgen’s AMG420, however it’s given 4 weeks continuous infusion, the 2 weeks off and repeat. Fortunately an HLE (Half-Life Extender) BiTe is also in development.

The working group decided to design & maintain a database for sharing CAR-T & BiTe experiences. There was consensus that (1) Most CAR-T today are not curative for most since many patients relapse 12-18 months after treatment; and (2) More studies are needed to be done so that CAR-T treated patients are not eliminated from future clinical trials.

#### MRD in 2019: Current Status, use in trials, and clinical practice

MRD (Minimal/Measurable Residual Disease) has shown to be a good prognosticator for PFS and OS but has yet to be approved to guide treatment decisions or as a surrogate objective for clinical trials. Fortunately there are trials in Europe and US that examine the use MRD to guide treatment. And the I2TEAMM is working closely with the FDA to provide data in order to obtain approval of MRD as a surrogate. MRD by Flow and MRD by NGS also had some discussion. The nodding agreement was, it did not matter as long as the trial or study specified the degree of accuracy of the test 1:100,000 or 1:1,000,000 (although 1:1,000,000 is more sensitive).

Within the Mass Spec working group, it was noted that at Mayo, Mass Spec has replaced SPEP & IFE with faster throughput. Since it’s also more sensitive, perhaps 1/3 of CR patients would be categorized as VGPR. And someday maybe it might be used for MRD (although would need to first be correlated with NGS/NGF).

Two of the most pertinent comments for me came from Dr. Ken Anderson: (1) “What can we do to ensure persistent MRD-?”; and (2) “As leading investigators in this field, we need to think ‘What’s beyond MRD?’ ”.

## High Risk Disease: Classification & Treatment

There are different risk stratification approaches for HRMM but all include del17p, t(4;14), and t(14;16). Some others include add1q, del1p, GEP (Gene Expression Profiling), and more. While HRMM still has a poor prognosis, some newer drugs such as Cbz, Ixa, Pom and Dara may partly abrogate poor PFS and OS. Specifically, Cbz may improve PFS for del17p. PI's improve PFS/OS for t(4;14) but may make matters worse for t(14;16). IMiDs don't improve PFS/OS for t(4;14) but Pom may improve these for Del17p. And currently tandem SCT seems to improve outcomes along with PI induction and maintenance. However, new therapeutic strategies and clinical trials are needed for this subgroup of patients.

## Unraveling the Complexities of Relapsed Treatment Options

Dr Rajkumar began this talk with summarizing Mayo's treatment approach at first relapse: If non-refractory to Rev, then DaraRd; if refractory to Rev, then DaraVd or DaraPd. Of course there are other alternatives as well. He also made the point that just because you progress while on maintenance of 10-15mg of Rev, does not mean you're refractory to Rev. You're not refractory to Rev until you relapse at the 25mg level. And at 2<sup>nd</sup> or higher relapse, Mayo suggests "Any first relapse options that have not been tried (2 new drugs, triplet preferred). IMWG proposed writing a guidelines paper for treating RR patients, including the consideration of drug availability. It was also noted that pts relapsing from CAR-T are very difficult to treat.

## Portfolio of Phase 3 (mostly) trials world-wide

I won't go into details here. Dr Lonial presented 9 US trials, Dr Gay listed 13 in Europe and Dr Kim from Asia listed 4 trials in earlier phases.

## GMAN MEETING SUMMARY

The mission of GMAN (Global Myeloma Action Network) is to improve the lives of myeloma patients around the world. Founded in 2013 by the IMF, GMAN is a group of myeloma patient organizations around the world who share best practices that address mutual areas of concern such as access to drugs/treatments and awareness of myeloma. This year, GMAN was attended by 35 advocates representing 5 continents and 23 countries. The meeting was facilitated by Serdar Erdogan, Myeloma advocate from Turkey, and Director of GMAN, Europe & Middle East Patient Programs. Serdar presented a survey summary of important topics previously filled out by country advocates and these results drove the development of our agenda.

Dr. Brian Durie (IMF co-founder) began the meeting by sharing Clinical Trials of the IMF. These included trials for High Risk Smoldering MM (HR SMM) patients called CESAR (Europe) and ASCENT (US) as well as the AMN (Asian Myeloma Network), very important since Asia represents 60% of the world (and myeloma) population. HR SMM factors has been most recently defined by 20-2-20: 20% plasma %, 2 M-spike g/dL, and 20 FLC (Free-light chain) ratio. Having any 2 of these will on average result in 46% of patients progressing to MM within 2 years. Since recent trials for HR SMM patients have shown that treatments such as Revlimid can delay the progression to MM, I asked "Should HR SMM patients now be treated?" Dr Durie suggested that we should continue with trials for now but watch these patients closely.

He reminded us: 1) we don't know what treatment is best...Rev-only, VRd, SCT, etc; and that 2) insurance would likely not cover since treatment for HR SMM is not within the NCCN Guidelines.

Later in the meeting Dr Rafat Abonour (IMF Medical Advisor, Indiana University) presented trial updates for Newly Dx MM and Relapsed-Refractory patients. For NDMM, Forte (KRd +/- SCT showing SCT benefit for HRMM), MIAI (Rd +/- Dara showed better ORR & MRD-) and Cassiopeia (VTd +/- Dara -> SCT -> VTd +/- Dara showed improved PFS in Dara arm). And for RRMM pts, Venetoclax, Selinexor, Pom-d +/- Isatuximab, Sub-Q Dara, BiTEs and CAR-T were all discussed.

Each year at this meeting the prior year's Susie Novis Durie (IMF co-founder) Grant recipients present their results. Advocates from Spain (MiMOVE smart phone app), Canada (Myeloma Advocacy Program) and Israel (Awareness education campaign for early diagnosis) shared their works. And 2019 awards were announced to Columbia (Digital Awareness), S. Korea (Healing Walk) and Sweden (Toolkit for Patient Preferences).

Robin (IMF VP of Support groups and caregiver) and hubby Michael Tuohy (19-yr myeloma survivor) presented their stories as caregiver and survivor, particularly focusing on the former because GMAN members had requested more information and tools for caregiving. They discussed the importance of living with myeloma, how to talk to your children about cancer and myeloma, the shared decision model, the ups and downs of treatment, quality of life management. GMAN attendees then divided into working groups listing what programs could help caregivers in different countries. There was a consensus that while caregivers are a critical component of the patient journey, there was no effort to engage with them as a group because: (1) they are forgotten during the doctor visit (especially in Europe); (2) Caregivers generally don't live in close proximity to each other; and (3) Caregivers have "a life outside of myeloma". It was also agreed that a working group needs to create a consensus guideline that member organizations can customize to each of their country characteristics.

Next Miko Santos (IMF Web producer) presented the Support Group Leaders Toolkit used by US Support Group Leaders and again various working groups provided items that would be helpful in a future global toolkit.

One of the most interesting topics was Improving Clinical Trials in Europe led by Dr Jean-Luc Harousseau (IMF Medical Advisor, France) and Mimi Choon-Quinones (IMF Sr VP Global Advocacy). The question at hand was how can Clinical Trials expand in smaller European countries? This can involve country advocates meeting with their Ministry of Health, develop relationships with potential Primary Investigators, go through training, and provide site qualification...quite an undertaking but something Mimi and the IMF plan to support. The success of AMN (Asian Myeloma Network) bringing clinical trial and novel therapies through clinical trials to Asian countries was discussed.

During the meeting, representatives from Takeda (future drug TAK 573 ADC), Celgene (Iberdomide IMiD), Sanofi (Isatuximab CD38 mAb) & Amgen (AMG420 BCMA BiTE) presented updates on their myeloma product pipeline as well as other myeloma related industry

current event, e.g. Celgene being acquired by BMS, Sanofi's value pricing model, Takeda's INSIGHT trial, and other Amgen products.