IMWG/GMAN 2018 Jack Aiello

June 2018 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 one view the IMWG Conference Series video made just after the IMWG meeting. It can be watched at: https://www.myeloma.org/videos/imwg-conference-series-stockholm-sweden.

IMWG Meeting Summary

The IMWG (International Myeloma Working Group) held its 9th annual meeting in Stockholm (where EHA (European Health Association, like ASH) was held). <u>The IMWG consists of 234</u> <u>MM experts, of which 100 attended this brainstorming session for MM</u>. They meet 2x/yr (ASH-morning breakfast, EHA- 2 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 an <u>evening talk</u>, then 1.5 days of <u>plenary session</u>, <u>major topic presentations/panel discussions</u>, and <u>working group meetings</u> with lots of time for audience discussion throughout. The topic subjects were:

- 1) CRISPR in Myeloma A Wiita (UCSF)
- 2) MASS Spectrometry D Murray
- 3) Do I Need A Transplant SV Rajkumar, J-L Haroussseau, N Raje, patient Y Biru
- 4) CAR-T & Other Immune Therapies in MM Y Lin
- 5) MRD in 2018: Open Questions J Mikhael, A Orfao, P Moreau, N Munshi
- 6) Early Relapse: Treatment Decisions P Moreau
- 7) New Drugs in MM: Access & Pricing in Europe J-L Haroussseau
- 7a) Causes & impact of high prices on drug access P Moreau, patient L Eriksson, Celgene
- 7b) Value-based pricing in Europe Janssen, HTA (Health Technology Assessment) and
- HAS (French National Authority for Health) Reps

And working group topics were:

- 1) Mass Spectrometry SV Rajkumar, D Murrary, S Kristinsson, B Durie
- 2) Bone & Imaging J Hillengass, S Usmani, S Lentzsch
- 3) CAR-T & Other Immune Therapies J Berdeja, A Cohen, Y Lin, S Trudel, J Kaufman (I attended this breakout)
- 4) Smoldering MM M-V Mateos, S Kumar, J San Miguel
- 5) Cost of MM Therapy J-L Haroussseau

Interesting Quotes/Discussions from IMWG

- An Exchange on the topic of Transplants: N Raje "We don't know the answer for individual pts. We haven't shown that SCT results in living longer." J-L Haroussseau "In medicine, there's what we hope and what we know." N Raje "After 4 yrs, French data has not shown OS benefits." J-L Haroussseau "Need to wait longer to see OS benefit." SV Rajkumar "The final Answer might also vary by country (access/cost) and QoL."
- 2) On MRD: A Orfao "MRD- is associated with PFS and OS and is one of the strongest prognostic factors. Even with MRD- to 10⁻⁶, there are still relapses so we may need to increase sensitivity for cure. Circulating Tumor Cells (CTC) in the blood are associated with shorter progression." N Munshi "CTC is 2 log less sensitive than bone marrow."
- 3) On Early Relapse: J-L Haroussseau "What does Revlimid-refractory truly mean when dosages vary between 10mg versus 25 mg?"

NOTES FROM DISCUSSION TOPICS AND WORKING GROUPS

CRISPR in Myeloma - A Wiita (UCSF)

CRISPR is a technology that can cut DNA strands so, for example, when the DNA tries to repair itself from a "cut" mutation, the repaired DNA knocks out the mutated gene. Or it can be used as a technique to build CAR-T cells. Perhaps CRISPR can also be used to increase (or decrease) CD38 expression, thus making a CD-38 antibody like Daratumumab more effective. However, there are caveats such as off-target effects and ethical considerations. This is very new and something to pay attention to for the future.

MASS Spectrometry – D Murray

This technique is being used at the Mayo and replaces SPEP and IFE tests. It doubles throughput in the lab and produces superior analytical results but may be several years away from general use. Mass Spec can also overcome M-spike misreads seen by SPEP for patients on Dara.

CAR-T & Other Immune Therapies in MM – Y Lin

CAR-T has been the hottest treatment topic discussion the past year and continues to be so as more trials (all BCMA studies) and patient numbers are increased. From ASCO and at the IMWG meeting, the largest trial reviewed was the bb2121 trial. With 43 patients reporting results, 63% of pts achieve a CR and median PFS was nearly 1 year for these heavily treatment patients. It also turns out that BCMA expression levels do not correlate with responses and should no longer be an inclusion criterion. However, 10 pts in this trial have relapsed so it becomes important to understand why...low BCMA levels? low CAR-T levels? And since CAR-T responses can be very quick (2 wks or 4 mos) compared with today's treatments, should the response timeframe criteria be changed, say to at least 6 weeks?

And more unanswered CAR-T questions: Combination therapies such as Revlimid or Checkpoint Inhibitors with CAR-T? Maintenance with CAR-T? Pre-emptive reinfusions similar to donor leukocyte infusions (DLI)?

Other immune therapies, mAb conjugates (ADC's such as GSK2857916 Ph2 FDA registration trial) and Bi-specific mAb's (BITEs) were mentioned but no details provided.

MRD in 2018: Open Questions - J Mikhael, A Orfao, P Moreau, N Munshi

The audience of IMWG members was polled several questions and % responses are shown:

- 1) Maintenance Strategy: Stop Tx after 2 yrs-13%, Treat till Progression-46%, Use MRD to Guide-41%. After talk, "Stop" decreased by 6% and "MRD as Guide" increase by 6%
- 2) MRD a Valid Endpoint? Yes-77%, No-11%, Don't Know-11%
- 3) Which MRD? NGS-32%, NGF-24%, Both-42%, Neither-1%, Don't Know-1%
- 4) Is 10^{-6} Beneficial? Yes-89%, No-4%, Don't Know-7%
- 5) Stop Maintenance after single MRD-? Yes-8%, No-76%, Don't Know-35%

6) MRD+? Continue Tx with No Changes-34%, Stop/Change-31%, Don't Know-35% There was a discussion of several trials focusing on confirming the validity of MRD, sustained MRD (is 1 yr apart enough?) and the usage of MRD to guide treatment. These trials include Cassiopia & GEM14 in Europe and DraMMatic, MASTER, and Optimum in the US. For example, the DraMMatic study compares Rev vs Rev+Dara maintenance. After 2 yrs, for MRDpatients in both arms are randomized to Stop or Continue treatment till progression and patients will be followed for 7 years.

The <u>I2TEAMM</u> (International Independent Team for Endpoint Approval of Myeloma MRD) is examining 7 groups and 14 trials, working with the FDA to validate MRD as a surrogate endpoint for Clinical Trials.

Early Relapse: Treatment Decisions - P Moreau

- Rev-refractory options: Kd, DaraVd, PomVd
- Vel-refractory options: IxaRd, KRd, Dara+Rd

Bone & Imaging

Bone surveys should no longer be used because they're not sensitive enough. Imaging Guideline suggested:

	Positive> N	> MM Work-up		
HRMGUS -> WBLDCT ->	Inconclusive -> BM MRI	+	$\wedge \wedge \wedge$	
		-	VVV	
	Negative> F	> Follow-up 1 yr		

sitive> MM Work-up	
Positive -> MM	Work-up
onclusive or Negative -> BM MRI >1 Lesion -> M	M work-up
Negative -> Foll	ow-up 1 yr
Positive -> MM Positive -> MM onclusive or Negative -> BM MRI >1 Lesion -> M Negative -> Foll	Work-up M work-u ow-up 1 y

<u>Current Treatment Algorithms (see Mayo's www.msmart.org) and Trials</u> For SMM, studies trying to determine when to initiate treatment and whether or not early treatment delays MM or perhaps offers cure. Example:

EA173 Ph 3, DETER for SMM: Randomize Rd +/- Dara ->CR/PR/Stable -> Continue 2 yrs Progression -> Off treatment

E1A11: ENDURANCE Trial examines MM Induction effectiveness & Maintenance length Randomize: VRd vs. KRd -> Randomized Rev 2 yrs vs until progression

IFM 2019: French follow-up to IFM 2009 Determination Trial (Transplant or not?) for both HR and non-HR MM:

HR: KRd+Dara(6) -> SCT -> KRd+Dara(4) -> SCT -> Rev+Dara (2 yrs) with MRD each year Primary Objective: 30% PFS increase compared with IFM 2009

NonHR: Randomize to Non-adaptive vs Adaptive Therapy Non-Adaptive: IRd+Dara(6) -> SCT -> IRd+Dara(4) -> Rev (2 yrs)

Adaptive: IRd+Dara(6) -> MRD -> + SCT -> KPd+Dara (4) -> MRD ->+ SCT -> R+Dara 2yrs - Rev 2yrs - SCT -> IRd+Dara (4) -> MRD -> + SCT -> R+Dara 2yrs - Rev 2yrs

Primary Objective: MRD3 at end of therapy increases 45% to 55% PFS with adaptive therapy Secondary Objectives: PFS, OS Operational cure (i.e. MRD3, 4, 5, 6 all neg each year)

GMAN Summary

GMAN, in its 6th 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 <u>55 individuals from 37 different countries and pharma (10)</u>, 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, MM awareness, 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. The meeting began with Dr. B Durie identifying global priorities: drug <u>access</u>, best <u>guidelines</u> (specific to where you live) and community <u>support</u>. For example, he identified KRd frontline only being available in the US, Germany & Japan. VRd frontline is available in Taiwan, Japan and some of Europe (not Italy or Spain). However, VCd and VTd are widely available.

<u>Black Swan Research Initiative "Dedicated to Finding a Cure"</u>
MGUS: Prevention by CESAR trial (Spain)
SMM: Early Intervention by KRd(6) -> SCT -> KRd(2) -> Rd (2 yrs); ASCENT adds Dara; iSTOPMM KRd treatment
MM: New Therapies for MRD+

2017 Susie Novis Grant Reports

Spain: Smartphone app for MM lifestyle, food Israel: Use of social network and publicity to increase awareness Canada: Advocacy program tool called "MAP" raises awareness for pts, cgs and healthcare providers

ASCO and EHA highlights (provide by Dr J Mikhael) Repurposing drugs: Dara in frontline, Cfz weekly (higher dose), Pom/Vel

New Drugs: 1) Selinexor (oral, increases tumor suppress cells) in STORM (Sel-dex) showed 22% ORR for penta-refractory. Now in trials SVd, SDara, SPd; 2) Venetoclax + Cfz synergistic; 3) CD38 mAb's Isatuximab and MOR202; 4) CAR-T; 5) GSK2857916

Throughout the meeting Pharma Cos presented: Janssen (Dara, which has both direct tumor effect and immunomodularity effect); <u>Takeda</u> (Velcade, Ninlaro, TAK-573 Anti-CD38 with interferon, TAK-079 CD38 mAb; <u>Celgene</u> (Rev, Pom, Thal, CAR-T bb2121 plus Juno acquisition with a different CAR-T technology); <u>BMS</u> (Elo, Nivolumab Anti-PD1 checkpoint inhibitor); and <u>Karyopharm</u> (Selinexor in STORM Sel-dex, STOMP Sel with Rd, Pd, Vd, Kd, and Dara+d, and BOSTON SVd vs Vd with crossover studies).

I always appreciate reconnecting with GMAN 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 <u>fortunate MM patients are by comparison living in the US, even though MM is a global disease that knows no borders.</u>