

IMWG/GMAN/BMT CTN 2016  
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June 2016 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. As you know, Daratumumab (Darzalex), the recently approved CD-38 mAb, showed over 33% response as a single agent for relapsed/refractory MM patients. Dr. Antonio Palumbo presented CASTOR Phase 3 trial results for R/R MM pts at ASCO which examined Vel-dex +/- Dara. The Dara arm resulted in a 61% reduction in disease progression, while doubling the CR and VGPR rates from 10-20% and 30-60% respectively. And at EHA, Dr. Meletios Dimopoulos announced results of the POLLUX Phase 3 trial for the same category of pts which compared Rev-dex +/- Dara. The Dara arm resulted in a 63% reduction in disease progression, with 93% (vs 76%) of the R/R patients achieving at least a PR (43% vs 19% getting a CR). I mention these 2 trials because the success of these Dara results impacted some of the discussions in the meetings I did attend.

IMWG Summary

The IMWG (International Myeloma Working Group) held its 7<sup>th</sup> annual meeting in Copenhagen (where EHA was held). The IMWG consists of nearly 200 MM experts, of which 100 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, Antonio Palumbo, S. Vincent Rajkumar, and Jesus San Miguel, an impressive group of world-wide MM experts. The meeting format started with opening lectures, debates, and working group meetings with lots of time for discussion throughout.

Interesting Quotes from IMWG

- 1) V Rajkumar: "[With the aforementioned success of Dara] Is there a role for Elotuzumab (Empliciti)?"
- 2) J Mikhael: "We now have 4 pillars of treatments: Proteasome Inhibitors, IMiDs, mAb's, and Alkylators plus more coming such as HDAC, Selinexor, Checkpoints, Vaccines and CAR-T's."
- 3) B Paiva: "A CR without MRD- is no better than a PR."
- 4) J San Miguel: "Is cure a dream worth trying to make a reality?" "My definition of a curative treatment is that 1/3 of patients remain MM-free for 10+ years."
- 5) S Giralt: "SCT is a choice, not a necessity. However, delaying an SCT has consequences."
- 6) S Lonial: "When you only had alkylators and steroids, more alkylators [for SCT] made sense. Today there are so many options."
- 7) P Moreau: "What is the optimal treatment option for a specific patient? We don't know."
- 8) V Rajkumar: "Besides trials to get drugs to markets, we need trials to provide best treatment for groups of patients or situations (e.g. first relapse)."

## (SOME OF THE) OPENING LECTURES & DISCUSSIONS

### \*S Kristinsson – Screening for MGUS: Are we ready?

This is an IMF Black Swan project iStopMM which will screen the whole population over 40 yo (n=140K) in Iceland for MGUS/SMM patients (expect 4500-5K pts). They'll be randomized to the arms "No treatment", "Follow IMWG guidelines", or "Intervention" to learn the impact of early screening, QOL, and possibly cure Iceland of MM. See the #AskDr.Durie 4-minute video at <http://myeloma.org/ArticlePage.action?articleId=4815> for more details.

### \*B Paiva - Role of MRD Detection in Myeloma

It was noted that MRD results for  $10^{-5}$  (NGFlow) and  $10^{-6}$  (NGSequencing) produce similar results and that higher MRD- predicts better outcomes. However, 5-10% of VGPR pts are MRD- due to the long life of the immunoglobulin. Dr Rajkumar asked if 5-10% of the general population >65 yo would be MRD+ (reflecting MGUS expectations).

### \* J Mikhael – How do we best use new immune therapies in Myeloma?

He noted that the SAR trial (Isatuximab), the other CD-38 mAb, will be starting soon in Dara-refractory patients and also mentioned that SAR has a shorter infusion time than Dara. Dr Mikhael also mentioned that a clinical trial measuring the effectiveness of subQ Dara is also in progress and is expected to conclude in 2018. I believe the infusion time is about ½ hr.

### \* JS Miguel & S Kumar - Can we Cure Myeloma?

To achieve a cure, one requires excellent measuring tools (MRD plus Imaging) and a treatment protocol to eradicate any tumor clone:

Induction: VTD (or KRD) + Dara

Transplant: SCT or no SCT

CR? Yes: Maintenance Rev +/- Ninlaro

No: Consolidation: RVD -> Maintenance Rev +/- Ninlaro

HRMM needs experimental therapies.

We need to identify types of MM in order to possibly cure some.

### \* SV Rajkumar – Approach to the Patient with MRD Positive Disease

Lisa Paik, SR VP at the IMF, role-played a patient who learned she was MRD+ (even though she was in a CR). This prompted a discussion about various questions: 1) Should a Dr provide MRD test results without knowing what to do with the results? 2) Should a patient be asked if they want an MRD test? 3) Should the Dr tell a patient that test results may not change treatment? Answer: "MRD test is still experimental."

## DEBATE AND PANEL DISCUSSIONS

### \* Debate - Early vs. Delayed Transplant S Giralt – Pro; S Lonial – Against

It was noted that an SCT only costs \$72K/QALY (Quality Adjusted Life Years), cheap when compared with various 3-drug regimens. Dr Giralt said that MRD- after induction might be the one exception to early SCT.

### \* Panel Session – New Combinations, New Issues: How to Use Them, How to Develop Them?

P Moreau: Proposal and Presentation of Evidence

Panel: B Durie, P Moreau, A Palumbo, SV Rajkumar

Access and cost issues were discussed in this session as well as in the breakout working group. Most European countries cannot give Revlimid maintenance due to both access (not approved in their countries) & cost. Dr Rajkumar suggested accumulating a huge MM registry (“tens of thousands”) in terms of treatment and responses, perhaps being faster and more beneficial than randomized trials.

## WORKING GROUP REPORTS Chair: Brian Durie

### Group 1: Optimal Imaging – Bone Group (E Terpos)

This group reported on open issues. For example, for SMM patients, there’s a need to define focal lesion, when reevaluation should be done for MRI positive (every 6 mos?) or negative (yearly?), and follow-up with “diffuse pattern”. For MM, we need to have criteria and standardization of proposed PET/CT.

### Group 2: Cost and Value in Myeloma Therapy (P Moreau/J Luc Harousseau)

- Access concerns. (High cost implying inability for payers (insurance or country) resulting in unavailability of drug.)
- Cost of drugs only part of the problem. Overall healthcare cost, especially end of life cost needs to be taken into consideration. Why are drug costs so high...claims of R&D, high risk of failure, bureaucracy. However, high R&D costs doesn’t explain why Gleevec introduced in 2001 has increased 5-fold. We do have high development costs due to large trials being needed to show small benefit. The cost of a trial may not be high if the drug is highly effective. Other cost drivers discussed was one high drug price in Myeloma for example, paying the R&D cost for another drug of a different cancer/malignancy.
- Need transparency from Pharma companies on their R&D and other costs that make drug prices high.
- Need value-based pricing, based on perceived value by the customer (e.g. patient, not payer)
- Prices clearly based on what the market will bear.

- ICER (Institute for Clinical and Economic Review) should be a tool, not a philosophy to define “fair” price. It needs to include overall impact, for example maybe 4-6 cycles of a very expensive protocol Dara + RVd may eliminate/decrease the need for maintenance till progression. And it needs to also include non-health QOL such as convenience and ability to integrate into everyday life.
- Guideline: 1) Therapeutic strategy at each disease step; 2) Define objective criteria for clinical value of a new drug; 3) Add “efficiency” (e.g. treatment duration) in Clinical Trials. 4) Focus on investigator studies
- Discussions included whether or not Price should be based on GNP (for example 2 or 3 times GNP) but would this encourage shipping across border? And do we need the cost of getting drug approvals at every stage (e.g. R/R 3 times, 1 time, newly diagnosed, etc)?
- For more insight into ICER’s recent report, see Dr. Durie’s blog at: <http://brianduriemd.myeloma.org/?q=content%2Ficer-blinks-and-patients-benefit>

#### Group 3: Role of MRD (B Paiva)

NGF & NGS should both be used until further conclusions. Guidelines should include 1) PET-CT; 2) Incorporation of MRD in trials, ie when, 2) Not a biomarker for prognosis but rather for treatment decisions. Dr Rajkumar then asked a very insightful question: “Are there Trials where equal MRD results are then randomized to treatments, e.g. if MRD-, then randomize to Tx1 or Tx2?” Not currently but in process of being developed.

#### Group 4: Optimal Use of Immune Therapy (J Mikhael)

We have lots of choices, with more coming, but do not yet know “optimal use”.

#### Group 5: Plasma Cell Leukemia, Extramedullary Disease (J Blade)

Guidelines are forthcoming.

My summary of this IMWG meeting is that much of the focus, and correctly so in my opinion, was on MRD and Cost of Care. In the future, MRD results will be used to guide subsequent treatment. And more doctors today, when given a choice of two similarly effective drug treatment protocols, need to consider drug costs when recommending a treatment. Finally, Dr. Rajkumar of the Mayo Clinic-Rochester, MN was presented the prestigious Robert A. Kyle Award for his valuable Myeloma research as well as providing excellent patient care. With the urging of Patient Advocate Mike Katz, Dr. Rajkumar was Primary Investigator on the now famous clinical trial that concluded less Dex is better than more Dex.

#### GMAN Summary

GMAN (Global Myeloma Action Network) is an advocacy initiative of the IMF and its mission is to improve lives of myeloma patients around the world. In attendance during the 1.5 day meeting were nearly 40 individuals from 25 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) 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. Or, in Australia, only one drug can be used at a time (with a steroid) instead of combination therapies.

Attendees learned about new drugs from Dr. Rafat Abonour as well as drugs in the pipeline from pharma sponsors BMS (checkpoint inhibitor Nivolumab), Novartis (AKT inhibitor PIM447), Amgen (Oral PI Oprozomib as well as AMG176, 232 and 224), Takeda (Ninlaro maintenance trials) and Celgene (checkpoint inhibitor Durvalumab)

We also spent time viewing a proposed GMAN Patient Charter consisting of expectations the MM patients have a right to expect of themselves, their government, health care providers and the pharmaceutical industry. Together with a similar charter from the IMWG, this would represent a strong voice within the myeloma health care industry.

Finally, we discussed ways to increase MM Awareness (perhaps a worldwide Myeloma day in 2017?), Access that involves educating pharma, payers, and government, and Action, including raising dollars, changing legislation, improving QOL, and creating better Clinical Trial design.

#### BMT CTN Myeloma Intergroup Meeting Summary

While the IMWG and GMAN meetings were in Copenhagen, this 1-day BMT CTN meeting was in Minneapolis at the NMDP/Be-The-Match headquarters. I attend this meeting as a result of being on the Consumer Advocacy Council (CAC) of the Center for International Blood and Marrow Transplant Research (CIBMTR...www.cibmtr.org). BMT CTN (Blood and Marrow Transplant Clinical Trials Network) is the clinical trial arm of CIBMTR. And the CIBMTR itself is a research collaboration between the Nation Marrow Donor Program (NMDP, Be-The-Match) and Medical College of Wisconsin (MCW). The BMT CTN Myeloma Intergroup meets 1-2 times/per year and their goal is to develop clinical trials and/or support clinical trials from the other NCTN groups Alliance, ECOG. And SWOG.

On-going trials include: 1) a long term study of #702 (2<sup>nd</sup> SCT + Maintenance vs Consolidation + Maintenance vs Maintenance-only; 2) DFCI/IFM2009 (DETERMINATION early vs delayed SCT). Note the French results have shown that 6 pts (11%) of deaths in the early SCT arm were due to Secondary AML compared with only 1 pt (2%) in the non-SCT arm; and 3) 1302 (Allo +/- Ninlaro Maintenance for HRMM n=110) but is on hold due to 2 early deaths. Also the Dendritic Vaccine trial #1401 randomizing maintenance after an SCT to a) Rev+GCSF+Vaccine, b) Rev+GCSF, or c) Rev-only. Note for n=132, the randomization ratio is 2:1:1 and this trial will activate June/July 2016.

There was also considerable discussion about the NCI-approved SWOG 1606 trial that compares Rev +/- Ninlaro Maintenance and whether or not this trial made sense for BMT CTN to endorse. To get NCI approval, SWOG had to change the primary endpoint to Overall Survival for n=1400 pts, so results probably wouldn't be known for 10 yrs, possibly making it irrelevant by then.

The meeting then considered proposals in 4 areas called Study Concepts: 1) Upfront/Conditioning regimens; 2) Maintenance Therapy; 3) Salvage Therapy; and 4)

Immunotherapy/Cell Based. Included among the proposals were a randomized study of 3 different condition regimens (P Hari) as well as a DETERMINATION2 study that incorporates Dara (P McCarthy). A maintenance proposal for AL Amyloidosis using the mAb NEOD001 (E. Scott) as well as a Salvage proposal (P Hari) using a 2<sup>nd</sup> SCT/Maintenance approach (Cfz & Dara involved) were well-received. And a Pembrolizomib (checkpt inhibitor) synergistic with Rev would be given to post SCT pts who achieve  $\leq$  VGPR after the SCT.

The meeting concluded with attendees voting on these and other proposals as well as creating action items required to move forward.