

6th Annual IMWG 2015 Summit Vienna, Austria

* Nearly 200 members, 95 in Vienna; brainstorming session for MM; meets 2x/yr (ASH-morning breakfast, EHA-1.5 days) to develop research initiatives and guidelines. IMWG Chairmen: Drs B Durie, SV Rajkumar

Interesting Quotes

- 1) A Palumbo: "MRD is a prognostic factor but will not change the treatment of choice"
- 2) BPaiva: "Might get to using MRD to help with pt management"
- 3) JSan Miguel: "MRD+ obviously needs treatment but MRD- should also have PET-CT imaging to asses for extramedullary sites."
- 4) J San Miguel "To consider MM curable, we need to have 30-50% of pts in a 10yr continued CR [without treatment'. As with other cancers, early treatment improves the possibility of cure. Perhaps we should start by seeing if we can cure MM subgroups."
- 5) K Anderson Re high costs, "Maybe we don't need such large Ph 3 trials and not worry about minimum P values.

OPENING LECTURES

* Dr B Paiva - Pros & Cons of MRD Assessment

One reason for having a better disease assessment measure? 10% of CR pts show EARLY relapse (<1 yr).

58% of CR pts were MRD+ by NGS (Next Generation Sequencing)

39% " " " " MRD+ by 1st generation FLOW (4 color)

43% " " " " MRD+ by 2nd generation FLOW (8 color)

51% " " " " MRD+ by 3rd generation FLOW (2xpanels of 8 colors, total =10)

* Dr S Kumar - Trial Designs to Validate Role of MRD Testing

- 1) Define MRD-
- 2) Who benefits?
- 3) What to do with the information?

Can MRD move from Prognostic to Predictive? Possible trial design:

18 mos tx -> MRD- -> stop Tx or Continue Tx

-> MRD+ -> Continue Tx or Change Drug or Add Drug

Then test MRD again 1 yr later

* Dr E Terpos - Selection of Imaging Methods in Clinical Care & Trials

- Whole Body Low Dose CT (WBLDCT) superior to whole body xray
- MRI for focal lesions, at least for spine and pelvis

- PET-CT detects some lesions (30%) not detected by MRI but the reverse is also true.

* Dr G Merlini - Amyloidosis: Current Issues

For MGUS & abnormal FLC, pt needs to be monitored for Amy

GROUP PRESENTATIONS/DISCUSSIONS

* Group 1: The Challenge of Double Refractory Disease, MV Mateos

What if refractory to both Rev and Velcade? Cfz-only showed 19% ORR for these pts while Pom+d showed 31% ORR for these pts.

What if double refractory (quad) to Vel, Cfz, Rev and Pom?

- 1) Trials using KRd (ASPIRE) and Pom-Cy-d showed some ORR
- 2) SAR (Esotuximab) 32% \geq PR; Dara (Sirus trial) ORR 30%, PFS 4 mos, 1 yr OS 65%
- 3) Checkpoint inhibitors Nivolumab, Pembrolizomab
- 4) ARRY-520 (Filaesib) KSP inhibitor 16% ORR
- 5) Selinexor ORR 60% but small number of pts
- 6) Elotuzumab +/- Rd, improved PFS 4.5 mos, 2yr PFS 41% vs 27%

* Group 2: Optimal Use of SCT in Relapsed MM, S Geralt

1 yr PFS 47% for Salvage Auto

* Group 3: Genome Sequencing and Identification of New Actionable Targets for Myeloma Therapy: Current Status, P Sonneveld

Most frequently mutated gene found in only 30% of MM pts, 11 genes have most frequent mutations KRAS, NRAS,It can be difficult to target mutations due to clonal evolution.

* Group 4: New Drug Approvals and Optimizing Myeloma Therapy, S Lonai & M Gertz (two perspectives on risk versus benefit consideration)

Panobinostat w new partner drugs (Vel or Cfz) has more favorable diarrhea Adverse SE compared with Rev (3% vs 30%)

For a new drug trial, does a trial need to guarantee crossover option in the control arm?

Endpoints: PFS, OS or Hazard Ratio? Hazard ratio is "relative risk" so HR alone is useless without actual numbers. For example, HR is the same for 3/4 and 30/40 but PFS of 10 mos is much better than 1 month.

PANEL DISCUSSIONS

* What Represents "Cure" and How Can it be Achieved?

Chair: B Durie; Discussants: A Dispenzieri, S Giralt, J San Miguel

Possible defn: Sustained MRD- stats off therapy. But Sustained (how long?) MRD- (10 to -5th?) stats off (or on?) therapy.

* How do Costs and Access Impact Myeloma Care Globally?

Chair: SV Rajkumar; Discussants: JL Harousseau, WJ Chng, P Richardson

Rajkumar: Old Rx -> Older Novel Rx -> Recently approved Rx -> Rx on Horizon Doublet/Mild Triplet -> True Triplet -> Triple + New drug -> Total Wallet Failure

Costs are based on what the market will bear rather than value-based or benefit/risk ratio. We need a drug cost ceiling (e.g. 3 x Gross Domestic??). Cost is a critical problem world-wide. P Richardson noted that DCFI is paying \$2B for EPIC system.

ICER (Incremental Cost of Effectiveness Ratio) per QALY (Quality Adjusted Life Years).

* Standardization of Protocols and Optimal Strategies for Use of MRI, CT, & PET-CT in MM

Co-Chairs: M Dimopoulos, M Drake; Discussants: S Lentzsch, E Terpos, E Zamagni

Future IMWG Terpos paper d discusses WBLDCT, PET-CT (which can distinguish between active and inactive disease), MRI (excellent for spinal cord/nerve and soft tissue).

WORKING GROUP MEETINGS

I attended Group 4 (Gertz, Lonial). Goal was to develop consistent trial measures by answering questions about:

Common Endpoints, Common Reporting, Required Reporting Endpoints, AE's, QOL and COST/HTA

WORKING GROUP REPORTS AND PANEL DISCUSSION Chair J San Miguel

Group 1: Double Refractory (Mateos)

Need consensus defn but will it really help? J Mikael "I'm hesitant about adopting the phrase 'double refractory' due to lack of precision [and other drugs coming out]." H Ludwig "Time component needs to be incorporated."

Group 2: Salvage transplants (Geralt)

For transplant-eligible pts do not do a SCT up front, SCT should be a standard of care at relapse. [But do we need another trial of 300 pts to validate?] Salvage allo should be considered for pts who relapsed < 2 yrs or high risk.

Group 3: Sequencing (Sonneveld)

Should mutation analysis be included in Clinical Trials? Yes, at multipoints (dx, relapse) in order to development predictive markers. K Anderson "With small mutation numbers, we need larger collaborations in order to accrue sufficient patients."

V Rajkumar "The NCI Match Trial (by mutation) has 11 arms and will be adding MM. Europe needs to do something similar due to lack of pts per mutation."

S Lonial "Biology drugs (IMiDs, PIs, mABs) are probably more important to MM pts than mutation drugs."

Group 4: New Approvals (Gertz, Lonial)

Common Endpoints, Eligibility, Reporting

* Risk stratification criteria for NDMM * Separate trials for HRMM * Common Eligibility to include Hevylite for IgA * Relax IgA to 750 mg * Prior Rx for SMM not eligible * Report frequency to include at dx and relapse

RRMM

* Eligibility different for Ph 1 & 2 versus 3 * .5 lower M-spike * Stratify 1-3 lines and > 3 lines of prior treatment * Pts progressing on maintenance are considered to be refractory to the drug

Required reporting demographics

* ISS, LDH, B2, hycalcemia, done disease * Frailty? * Prior therapy response and failure

Endpoints

* TTR, OS @ 3yr, 5yr, PFS @ 1 or 3 yrs depending on NDMM or RRMM * Is there a better surrogate for long-term OS? * MRD * How to handle missing data, censoring, testing frequency * Relapse & PFS needs 2 consecutive measures (required by industry)

Toxicity Reporting

* Hema Grades 3 & 4 * Non-hema 2-4 * Neuro all grades * Adverse events of clinical interest

QOL

* Need for consistent QOL tool for both NDMM and RRMM * Publish in primary paper

Sample Banking & Biomarkers

* Hard to mandate at relapse * Require for Phase 3, NDMM * IRB might not approve "mandatory"

Cost/HTA (Health Technology Assessment)

* QOL impact * Admin, AE, duration costs

Group 5: Bone Disease (Terpos)

* In SMM, use WBLDCT instead of WBXR (IMF project, ASH15 abstract)

* PET-CT standardization project...paper forthcoming

* New study proposal: Zometa vs Observation after CR (although French 2006 already reported no difference)

Group 6: Long CR Project Update (S Umani)

- * Look for clinical predictors for LT Survival or Early death
- * 6500 transplant-eligible pts, majority pre-novel
- * Relative Survival = Ratio of Actual to Expected Survival
- * Cure Fraction = Proportion of pts reaching Expected Survival

Negative factors included >65, IgA, < 10 Hemaglobin, >33% plasma cells, B2M > 3.5. More to come.

FUTURE PLANNING

MRD, SCT Early vs Late, Elo & Dara, High-risk biomarkers, New staging R-ISS (Creatinine Clearance, Cytogenetics/FISH 4:14, 17p, LDH plus B2M and Albumin) uses biomarkers, not just CRAB symptoms

Others: Biomarkers in SMM, Immune Therapy, NGS, CT Reporting, Microenvironment, Cost, QOL (find FACTMM from Mike Katz).