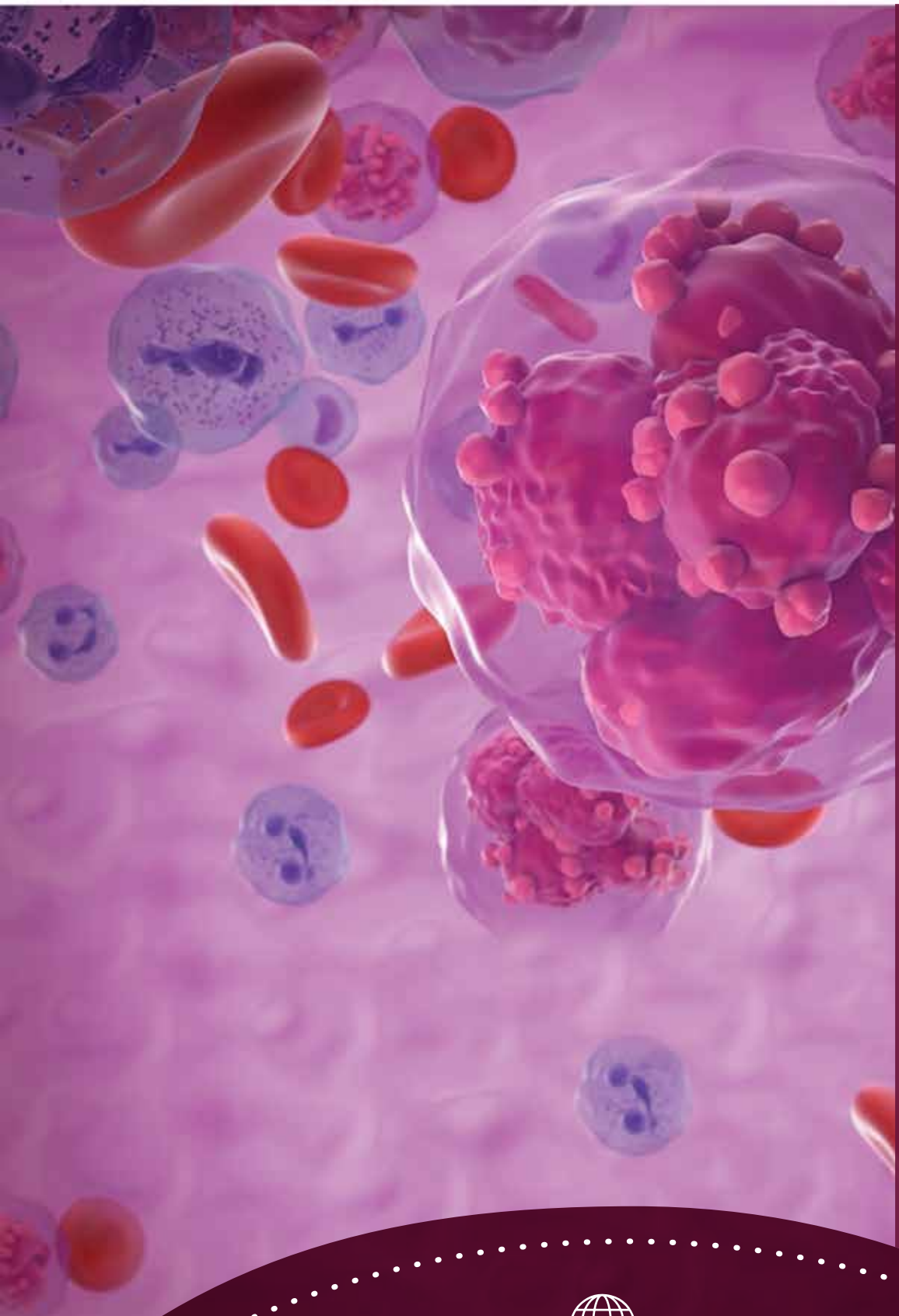
NEWSLETTER

Issue no-03 | Month-October | Year-2023

An Indian Myeloma Academic Groupe Publication (IMAGe)



JOURNAL CLUB

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Preface

*This newsletter was born out of sincere efforts of the **IMAGE Groupe** to serve a quarterly academic feast to all myeloma connoisseurs and novitiates with a platter of translational research work update, neuron tickling trivia, cherishable accomplishments of our members and highlights of past and upcoming academic events in the realm of myeloma. A blitzkrieg of brainstorming zoom sessions followed by pounding and grinding of intellect and prose by five geeks over weeks led to fruition of the first edition on new year eve and a greater hard work to bring forth this snippet on myeloma activities across country as second edition.*

- From Editorial Team

This bulletin will be a ready reckoner for those grappling to keep up with the progress on myeloma. As it summarizes journal clubs that paved the way for the holy grail of truth based on evidence, the eagle eye gives the synopsis of the critical thinking prowess shown by the myeloma prodigies. The rest of the sections gives us a glance at what is happening around us. The team has done a spectacular job in putting this together. Of course, not to mention the turbocharger, Dr Uday.

- Newsletter Committee

"Inshorts- Through expert's lens" Journal Club

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Friedrich MJ, Neri P, Kehl N, Michel J, Steiger S, Kilian M, Leblay N, Maity R, et al. The pre-existing T cell landscape determines the response to bispecific T cell engagers in multiple myeloma patients. CancerCell. 2023 Mar 9:S1535-6108(23)00036-3. doi:10.1016/j.ccell.2023.02.008. PMID: 36898378.

Background: A cancer cell tries to evade immune system by various mechanism which are- Loss of antigen presentation- Loss of MHC expression, suppressive ligand- PDL1 , LAG-3, TIM-3, suppressive cell population-CD4 Tregs, MDSC, Suppressive cytokines-IL-10, IL-12, TGF-beta,suppressive cell population and cytokines creates an exhausted T cell phenotype which has less cell killing capacity. T cell engager therapy (BiTE) can overcome few resistance mechanism like antigen presention, however exhausted phenotype can lead to poor response even if there is engagement between T cells and tumour cells by a T- cell engager.
Multiple myeloma as a model to understand this mechanism is unique because 1. It is closely associated with the bone marrow immune microenvironment, 2. Serial BM aspiration biopsies are possible to understand the interaction and 3. Biopsy can be done from same site (marked) of iliac crest to avoid intra-individual variations in different site. Here, 30 bone marrow samples were studied longitudinally (healthy sample=5, newly diagnosed=7 and RR myeloma=18 samples). Transcriptome and TCR repertoire bone marrow-associated immune cells was done. T cell clones were traced over time using their TCR amino acid sequence as an individual barcode. Longitudinal site matched bone marrow samples taken at various time points during therapy (Pre, early(post C-1), late(post Cycle-4)
Results: After stringent quality control and filtering, a total of 325,571 bone marrow-associated immune cells were obtained from 30 BM samples. They were further grouped into 63,374 distinct clonotypes by matching both α and β chain pairs and matched with periperal blood bulk TCRβ-sequencing of patients. This could allow to track clonal lineages and measure overlap and dynamics of single clones in bone marrow and blood.
Important observations were- 1)T regs are not increased at relapse 2)In responders, there was consistent proportional increase in CD8 effector CX3CR1 cells.3)Proportion of pre-existing exhausted-like CD8+ clones before therapy start was significantly increased in Non responder vs. responder patients.4) Clonal expansion was significantly reduced by MHC class I blockade.
Commentary: Two important modes of resistance to T cell engager therapy was evident from this analysis-
1. GZMK+ CD8 T cells expressing exhaustion markers like PDCD1 and LAG3 – exhausted Effector CD8 T cells – _negative predictor of response.
2. Loss of MHC-1 loss of as a potential mechanism of TCE- mediated tumor immune escape beyond loss the target antigen (BCMA) .
Two potential clinical implications-
Choosing between TCE versus CAR-T cell therapy?
An exhausted T cell phenotype is negative predictor of response to TCE as opposed to CAR-T cell therapy.
Modulations causing synergism with TCE?
Stimulation of naïve T cells an alternative route of TCE induced immune response by allowing MHC class I:TCR interactions. Immunogenic cell death sensitize tumors to TCEs e.g Bortezomib/carfilzomib or irradiated extramedullary disease e.g Bortezomib/carfilzomib or irradiated extramedullary disease.

"Inshorts-Through expert's lens" Journal Club

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Mina R, Musto P, Rota-Scalabrini D et al, Carfilzomib induction, consolidation, and maintenance with or without autologous stem-cell transplantation in patients with newly diagnosed multiple myeloma: preplanned cytogenetic subgroup analysis of the randomised, phase 2 FORTE trial. Lancet Oncol. 2023 Jan;24(1):64-76. doi: 10.1016/S1470-2045(22)00693-3. Epub 2022 Dec 14. Erratum in: Lancet Oncol.2023 Feb;24(2):e72. PMID: 36528035.

Summary: FORTE trial was an Italian study which looked at outcomes associated with high-risk cytogenetic abnormalities (HRCAs) across treatment groups receiving carfilzomib-containing induction, consolidation, and maintenance regimens in comparison with carfilzomib, cyclophosphamide, and dexamethasone for NDMM were assessed.

Study Details: Four seventy-seven patients were randomly assigned 1:1:1 to receive four KRd induction cycles, melphalan and ASCT and four 28-day KRd consolidation cycles, twelve 28-day KRd cycles; or four 28-day KCd induction cycles, melphalan, and ASCT, and four 28-day KCd consolidation cycles. Second randomisation was done before maintenance to KR and R arm.

Key results: Median follow-up from first randomization was 51 months. Four-year PFS from first randomization was 71% in no HRCAs, 60% in one HRCA and 39% in two or more HRCAs. Four-year OS from first randomization was 94% in no HRCAs, 83% in one HRCA, and 63% in two or more HRCAs.Three-year PFS from second randomization was 80% in no HRCAs, 68% in one HRCA, and 53% in those with two or more HRCAs. In the context of maintenance therapy, PFS continued to be influenced by HRCA status, with patients with two or more HRCAs having the poorest outcome. The investigators concluded that carfilzomib-based induction–intensification–consolidation regimens are effective strategies in patients with standard and high-risk (one HRCA)myeloma with similar rates of PFS. Patients with ultra-high-risk disease (those with two or more HRCAs) still have poor outcomes.

Commentary:

Strengths: 1. Clinical Relevance: Study addresses NDMM patients with HRCA, which is an unmet medical need.
2. Randomized control study design.
3. In-Depth Analysis: Also looked at MRD negativity along with PFS and OS.

Limitations: 1. Limited Generalizability: The study was conducted in Italian centres, which may limit its generalizability to broader populations. **2. Small Sample Size:** The phase 2 trial had a relatively small sample size, especially when stratified by cytogenetic risk. **3. Short Follow-Up:** The median follow-up of 51 months is relatively short for a disease like multiple myeloma. Longer follow-up would provide a more comprehensive understanding of treatment outcomes. **4. Financial implications:** There was no significant difference in the PFS or OS between the KRd or KCD arm in patients with 0 HRCA or 1 HRCA group. So standard risk patients and patients with 1 HRCA can receive still receive VRD or VCD in resource constraint setting, though there is no head-to-head comparison

Overall Assessment: While the study provides valuable insights into the treatment of multiple myeloma, especially in the context of cytogenetic risk, it has some limitations and lacks generalisability. Patients classified as standard risk or having only one HRCA may receive more intensive treatment, potentially leading to increased complications.

"Inshorts-Through expert's lens" Journal Club

Yong, Kwee et al, Upfront autologous haematopoietic stem-cell transplantation versus carfilzomib-cyclophosphamide-dexamethasone consolidation with carfilzomib maintenance in patients with newly diagnosed multiple myeloma in England and Wales (CARDAMON): a randomised, phase 2, non-inferiority trial ; Lancet Haematol. 2023 Feb;10(2):e93-e106. doi: 10.1016/S2352-3026(22)00350-7. Epub 2022 Dec 15. PMID: 36529145.

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In NDMM the aim was to evaluate whether an IMID-free carfilzomib-based induction, consolidation, and maintenance protocol without autologous HSCT was non-inferior to the same induction regimen followed by autologous HSCT and maintenance.

Summary: CARDAMON is a randomised, open-label, phase 2 trial in 19 hospitals in the UK. ND, transplantation-eligible patients with MM aged more than 18 years with an ECOG PS of 0–2 received four 28-day cycles of KCd [carfilzomib (56 mg/m² intravenously on days 1, 2, 8, 9, 15, and 16), cyclophosphamide (500 mg orally on days 1, 8, and 15), and dexamethasone (40 mg orally on days 1, 8, 15, and 22)], followed by PB stem cell mobilisation. Patients with at least a PR were randomly assigned (1:1) to either HD melphalan and ASCT or four cycles of KCd. All randomised patients received 18 cycles of carfilzomib maintenance. The primary outcomes were the proportion of patients with at least a VGPR after induction and difference in PFS rate at 2 years from randomisation (non-inferiority margin 10%). In the trial period 281 patients were enrolled, with 218 proceeding to randomisation, 109 assigned to both the arms. Median follow-up from randomisation was 40·2 months .After induction, 162 of 281 patients had at least a VGPR. The 2-year PFS was 75% in the HSCT group versus 68% in the KCd group, exceeding the non-inferiority margin. The most common grade 3–4 events during KCd induction and consolidation were lymphocytopenia(Induction [26%] and consolidation [14%]) and infection([18%] for induction; [14%] for consolidation). During maintenance it was hypertension and infections.Treatment-related serious adverse events at any point during the trial were reported in 39 % patients who started induction, with infections [29%] being the most common. Treatment-emergent deaths were reported 2% patients during induction and one during maintenance after autologous HSCT

Commentary: The study group sought to assess if ongoing treatment with KCd was non-inferior to KCd induction followed by autologous HSCT in NDMM who were transplant eligible, with both groups receiving carfilzomib maintenance. Results show that KCd consolidation did not meet the criteria for non-inferiority when compared with upfront transplantation. However, the non-inferiority margin was only exceeded by a small amount (confidence limit –11·1%, prespecified margin –10%). The observed median PFS from randomisation was 33·8 months in the KCd consolidation group versus 42·4 months in the HSCT group (HR 1·35). MRD-negative rates were higher in the HSCT group for both patients with high risk and patients with standard risk than in the KCd consolidation group, with little difference between patients with high risk and patients with standard risk. Despite this finding, patients with high-risk genetics had inferior PFS compared with patients with standard risk.The restricted duration of maintenance carfilzomib (18 months) and the absence of consolidation after autologous HSCT would explain the inferior results. In this study, there was no clear benefit of HSCT in patients who had an MRD-negative response after induction, whereas for individuals who are MRD positive, autologous HSCT could be beneficial. The study also

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Yong, Kwee et al, Upfront autologous haematopoietic stem-cell transplantation versus carfilzomib-cyclophosphamide-dexamethasone consolidation with carfilzomib maintenance in patients with newly diagnosed multiple myeloma in England and Wales (CARDAMON): a randomised, phase 2, non-inferiority trial ; Lancet Haematol. 2023 Feb;10(2):e93-e106. doi: 10.1016/S2352-3026(22)00350-7. Epub 2022 Dec 15. PMID: 36529145.

showed that there was no difference in PFS between the autologous HSCT and consolidation groups for patients with an MRD-negative response after autologous HSCT or consolidation.

Conclusions: The CARDAMON trial provides preliminary evidence that MRD assessment after induction could be used to guide treatment choice. Future trials that stratify by a composite of genetic risk and depth of response will be able to accurately identify patients likely to benefit from autologous HSCT, leading to a personalised treatment approach.

Limitations: 1. Due to the non-inferiority design of CARDAMON, no comments on the superiority of autologous HSCT in the context of this study was possible. 2. Furthermore, to keep the trial at a feasible size, it was not powered to assess non-inferiority in subgroup analyses and there might be additional subpopulations that deserve further evaluation.

Transplantation related events were not reported. There was an inability to make a direct comparison of toxicity between treatment groups during the randomised phase of treatment. The reported rate of patients who received a deferred transplant after disease progression might be an underestimation of the true value, as these data are collected on long-term follow-up forms

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"Inshorts- Through expert's lens" Journal Club

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Dimopoulos MA, Moreau P et al; Overall Survival With Daratumumab, Lenalidomide, and Dexamethasone in Previously Treated Multiple Myeloma (POLLUX): A Randomized, Open-Label, Phase III Trial. J Clin Oncol. 2023 Mar 10;41(8):1590-1599. doi: 10.1200/JCO.22.00940. Epub 2023 Jan 4. PMID: 36599114; PMCID: PMC10022849

Summary: The Pollux trial was a multicenter, randomized, open-label, phase III study investigating the efficacy and safety of Daratumumab in combination with lenalidomide and dexamethasone (D-Rd) versus lenalidomide and dexamethasone (Rd) alone in patients with relapsed or refractory multiple myeloma. The present journal reports updated efficacy and safety results during the final overall survival (OS) analysis of the POLLUX trial after a follow-up of 6.5 years. D-Rd significantly extended OS versus Rd alone. The median OS was 67.6 months in the D-Rd arm versus 51.8 months in the Rd arm. Moreover, the improvement in OS was observed with D-Rd in nearly all subgroups regardless of age, ISS disease stage, cytogenetic risk, prior PI (Proteasome Inhibitor) exposure, or refractoriness to PI or the last line of previous therapy. MRD negativity rates (10–5 sensitivity threshold) were significantly higher with D-Rd than Rd. There were no new safety concerns in the updated results. The POLLUX trial reported the most extended OS for relapsed refractory multiple myeloma patients of 5.5 years compared to most of the previously published studies on Relapsed refractory multiple myeloma patients.

Commentary: Despite these impressive results, it is crucial to appraise the article critically. The authors have detailed the study design, methodology, and statistical analysis explicitly. Despite the increasing attrition with extended follow-up, the trial still sets a new benchmark of increased OS and deeper response achievement in the D-Rd arm.

One potential limitation is the potential for selection bias, as patients included in the trial may not be representative of the broader population with relapsed or refractory multiple myeloma. Furthermore, the trial employed lenalidomide and dexamethasone as the comparing arm. This may not reflect the more widely used triplet regimens as the standard of care for Myeloma patients with relapsed refractory disease. Besides, most relapsed refractory myeloma patients from India may not tolerate Lenalidomide 25mg for 21 days. Not to mention the economic strain in Daratumumab's affordability in an out-of-clinical trial setting among Indian Patients.These limitations may limit the generalizability of the trial findings to real-world clinical practice in India.

However, despite these limitations, the Pollux trial provides valuable evidence supporting the use of daratumumab in combination with lenalidomide and dexamethasone. It also encourages using Daratumumab as a Standard of Care Regimen early to achieve deep and sustained responses and prolonged disease control. The observed improvement in OS is encouraging and suggests a potential for a more significant impact on patient outcomes.

"Original research publications from India"
Publications from Indian Faculty from Macrh 2023 - September 2023

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"Original research publications from India"

Publications from Indian Faculty from Macrh 2023 - September 2023

- Sathya P, Kayal S, Srinivas BH, Hamide A, Kar R. Quantification of circulating clonal plasma cells by multiparametric flow cytometry as a prognostic marker in patients with newly diagnosed multiple myeloma. Int J Lab Hematol. 2023 Aug 25. doi: 10.1111/ijlh.14156. Epub ahead of print. PMID: 37632156.
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"Original research publications from India"
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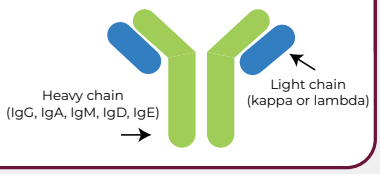
Q1.

Which of these organisations/expert group on plasma cell dyscrasia use an ensign that is epicentered on the immune globulin structure ?

A. IMWG
B. European Myeloma Network (EMN)
C. IKMG
D. International Myeloma Foundation (IMF)



Q2.

Which one of the following is an incorrect statement based on the findings of Friedrich etal study analysing the longitudinal profile of T cell repertoire in MM patients receiving BiTEs ?

A. Single-cell TCR tracing identifies conserved T cell responses to BiTEs in humans
B. Clonal expansion of effector CD8+ T cells is an immunological driver of TCE therapy
C. Naive T cells require additional MHC class II signal and differentiate upon TCE activation
D. The abundance of exhausted CD8+ clones predicts response failure in multiple myeloma

Q3.

As per the study protocol by Friedrich etal what clone size threshold defined a large clonotype in TCE cohort ?

A. 10 % B. 30 % C. 1 % D. 50 %

Q4.

Which of these option is incorrectly matched positivity threshold and cytogenetic abnormality by FISH as per Schavgoulidze etal study of impact of del 1p32 in NDMM ?

A. Del 17 p : 55 % B. t(4;14) : 30 %
C. Del 1p32 : 30 % D. Gain 1q : 50 %

Q5.

Which of the following statements is incorrect in the light of findings of Schavgoulidze etal study of impact of del 1p32 in NDMM ?

A. The OS and PFS is significantly inferior compared with patients without del(1p32)
B. Biallelic deletion of 1p32 dramatically worsens the prognosis compared with a monoallelic loss
C. Melphalan based auto HCT upfront mitigates the adverse risk conferred by 1p32 loss
D. Patients without HR CAs had a lower PFS and OS when they carried del(1p32)

MYELOMA QUIZ

MYELOMA QUIZ

APR 2023

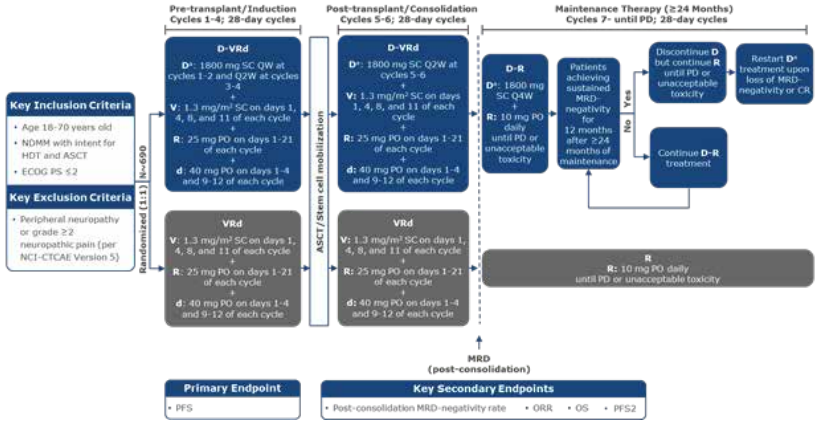
WINNER

Dr. Sumeet Mirgh

Asst Professor,
TMH, ACTREC ,
Mumbai

Q6.

Identify the trial with design below



A. PERSEUS B. ANDROMEDA C. GRIFFIN D. CEPHEUS

Q7.

Which one of the following is an incorrect statement based on the findings of FORTE trial ?

A. Rates of 1-year sustained minimal residual disease negativity were similar in patients with zero HRCA and one HRCA
B. Carfilzomib plus lenalidomide maintenance reduced the risk of progression or death versus lenalidomide alone in patients with high-risk and standard-risk disease myeloma
C. PFS with ASCT in patients with standard-risk disease was similar compared with KRd12 without transplant
D. Patients with 1-year sustained minimal residual disease negativity had a similar progression-free survival regardless of their cytogenetic status

Q8.

Which of these options is incorrectly matched cutoffs for HRCA positivity in the FORTE trial ?

A. Del 17 p : 10 % B. t(4;14) : 30 %
C. Del 1p32 : 10 % D. Gain 1q : 20 %

Q9.

As per the findings of MyXI trial, the highest PFS benefit from Len maintenance was seen in which of the following cytogenetic risk group?

A. Del 17 p B. 1 q amp
C. Del 1p D. t(4;14)

MYELOMA QUIZ

MYELOMA QUIZ

MAY 2023

WINNER

Dr. Rajat Pincha

Senior Resident,
Dept. of Clinical Hematology,
Tata Memorial Centre,
Kolkata

Q10.

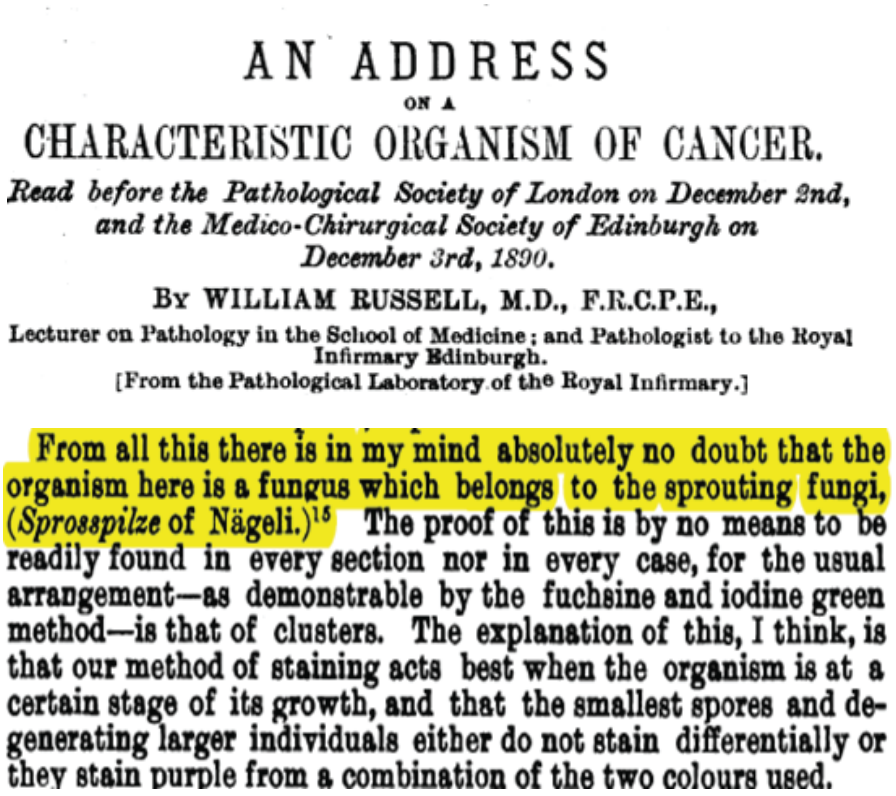
Which of the following statement(s) is correct as per the findings of Myeloma XI trial ?

A. Len maintenance had the biggest effect on PFS in patients with single hit followed by patients with no hit and those with double hit
B. OS was both numerically and statistically insignificant for Len maintenance in all genetic subgroups.
C. There is limited benefit of Len maintenance for patients with isolated gain(1q)
D. All the above statements are true

Q11.

First description of X in history ! X was described from following tissue sections :

- Syphilitic gumma
- TB spine
- Tumor of dura
- Tumor of lung alveolus
- Sarcoma
- Tumor of breast



AN ADDRESS
ON A
CHARACTERISTIC ORGANISM OF CANCER.

Read before the Pathological Society of London on December 2nd, and the Medico-Chirurgical Society of Edinburgh on December 3rd, 1890.

By WILLIAM RUSSELL, M.D., F.R.C.P.E.,

Lecturer on Pathology in the School of Medicine; and Pathologist to the Royal Infirmary Edinburgh.

[From the Pathological Laboratory of the Royal Infirmary.]

From all this there is in my mind absolutely no doubt that the organism here is a fungus which belongs to the sprouting fungi, (*Sprosspilze* of Nägeli.)[15] The proof of this is by no means to be readily found in every section nor in every case, for the usual arrangement—as demonstrable by the fuchsine and iodine green method—is that of clusters. The explanation of this, I think, is that our method of staining acts best when the organism is at a certain stage of its growth, and that the smallest spores and degenerating larger individuals either do not stain differentially or they stain purple from a combination of the two colours used.

A. Russell bodies B. Mott Cell C. Plasmacytoma D. Flame cells

Q12.

Which one of the following is an incorrect statement based on the findings of CARDAMON trial ?

A. An MRD-negative response after induction was not associated with significantly improved PFS; however, patients who were MRD negative after randomised treatment, had longer PFS than patients who were MRD positive
B. Carfilzomib related thromobotic microangiopathy was noticed during all three phases: induction, consolidation and maintenance
C. The 2-y PFS was 75% in the HSCT group and 68% in the KCd group and thereby met the primary end point of non-inferiority margin of 10 %
D. The most common treatment-related serious adverse events were infections

MYELOMA QUIZ

MYELOMA QUIZ

JUNE 2023

WINNER

Dr. Sumeet Mirgh

Asst Professor, TMH, ACTREC , Mumbai

Q13.

Which of these options is incorrect with regards to trial design of CARDAMON trial ?

A. Carfilzomib dose (56mg/m2) and schedule was same in both induction and consolidation phases
B. N Oral cyclophosphamide was administered at a flat dose of 500mg to all patients irrespective of BSA
C. Cyclophosphamide mobilisation was not allowed during stem cell harvest
D. Dexamethasone dose was reduced from weekly 40mg dose during induction to 20mg per week during consolidation

Q14.

Which of the following is an incorrect statement wrt the study results of Noemí etal?

A. MS using the EXENT system could identify Ig D and IgE myelomas also
B. The concordance between EXENT&FLC-MS and IFE was 82% post-induction, 84% post-consolidation
C. IFE was able to discriminate 2 subgroups of patients with significantly different median PFS post - induction and post-ASCT but not post-consolidation
D. Both statement A & B are incorrect

Q15.

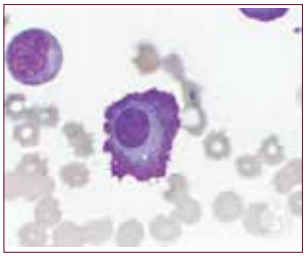
Which of the following statement is incorrect wrt LC MALDI MS use in MM as per the IMWG recommendations?

A. Intact LC MALDI-TOF can be used in lieu of immunofixation in the clinical assessment of patients
B. IMWG endorses the use of MS to aid in distinguishing therapeutic antibodies from endogenous M-proteins
C. IMWG endorses the use of MS for cross-comparisons of CR rates in trials done in different time periods
D. All the above statements are true

Q16.

Identify the incorrect statement with respect to the image shown!

A. This is a plasma cell with vermillion-staining glycogen-rich overstuffed fibrils
B. These cells are highly associated with IgA myelomas
C. These cells could represent reactive or clonal plasma cells
D. All are correct statements



Q17.

Prespecified analyses in the updated POLLUX trial demonstrated that an OS benefit was maintained with D-Rd versus Rd in all subgroups except :

A. Myeloma with high-risk cytogenetic abnormalities
B. ISS Stage III
C. MM patients with one, two, or three prior lines of therapy
D. None of the above

Q18.

In POLLUX trial ; samples size to assess the primary outcome was estimated to be 560 (280 in each arm). By what margin was DRd arm assumed to reduce the risk of the disease progression or death compared to Rd arm (PFS : 18m) in RRMM when this sample size was calculated ?

A. 30 % B. 50 % C. 40 % D. 20 %

Q19.

Which of these options is incorrect with regards to the findings of the trial by Pasvolsky et al studying the impact of clonal plasma cells (CPC) in the autograft on the outcomes of HRMM ?

A. The CPC + group was less likely to achieve MRD-negative CR post-transplant
B. Both the presence and degree of CPC in the autograft were highly predictive of inferior PFS and OS
C. Within the CPC + group, hematological responses prior to auto HCT predicted OS
D. When the analysis was restricted to CPC + patients who had achieved ≥VGPR or MRD-negative ≥VGPR after induction, presence of CPC in the autograft did not predicted worse outcomes

MYELOMA QUIZ

MYELOMA QUIZ

JULY 2023

WINNER

Dr. Saswata Saha

Ad-hoc Assistant Professor Dept. of Medical Oncology Tata Memorial Centre Mumbai

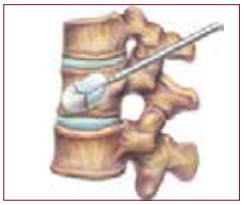
Q20.

Which of these options is incorrect with regards to the design of the trial by Pasvolsky et al studying the impact of clonal plasma cells (CPC) in the autograft on the outcomes of HRMM ?

A. High-risk cytogenetic abnormalities was defined by the presence of del17p/TP53 deletion, t(4;14)/IGH::FGFR3, t(14;16)/IGH::MAF, and 1q21/CKS1B gain or amplification on FISH
B. Evaluation for CPC by 6-color next-generation flow cytometry (NGF) was performed on the collected apheresis products, with a sensitivity of 0.001–0.003% on all samples analyzed in the study
C. MRD status in bone marrow samples was assessed using 8-color NGF. The sensitivity of our assay is 1/10−5 cells (0.001%)
D. All the above statements are true

Q21.

What intervention is being done in this myeloma patient?



A. Kyphoplasty
B. Vertebroplasty
C. Brachytherapy
D. Spinal fixation

Q22.

Which one of the following was not an inclusion criteria in the CARTITUDE4 trial ?

A. Progressive disease as per IMWG 2016 criteria
B. Subject must have undergone at least one complete cycle of treatment for each line of therapy, unless PD was the best response to the line of therapy
C. For subjects with > 1 prior line of therapy, there is no requirement to be lenalidomide refractory to the most recent line of prior therapy
D. Subjects with only 1 prior line of therapy must have progressed within 24 months of a stem cell transplant, or if not transplanted, then within 48 months of starting initial therapy

Q23.

In the CARTITUDE 4 trial which of the following statement is incorrect with regards to sample size calculation and study design ?

A. It was assumed that that JNJ-68284528 can reduce the risk of PD or death by 35%, ie, hazard ratio of 0.65 %
B. The sample size catered for an estimated annual dropout rate of 5% and one interim analysis for efficacy at approximately 165 PFS events (66% of the total planned 250 PFS events)
C. The median PFS for the standard therapy arm was taken as 13 months
D. The final analysis of PFS will be performed after approximately 150 PFS events are observed

Q24.

Which of these options is incorrect with regards to the findings of the trial by Samur et al studying the impact of HDM on mutational burden at relapse in MM patients ?

A. At the time of relapse majority of the mutations observed following HDM were subclonal
B. The mutational burden was higher in patients who relapsed after achieving CR
C. Neither patients with high mutational load after HDM treatment nor patients who achieved CR had significantly different survival after PFS1
D. All are correct statements

MYELOMA QUIZ

MYELOMA QUIZ

AUGUST 2023

WINNER

Dr. Aditya J

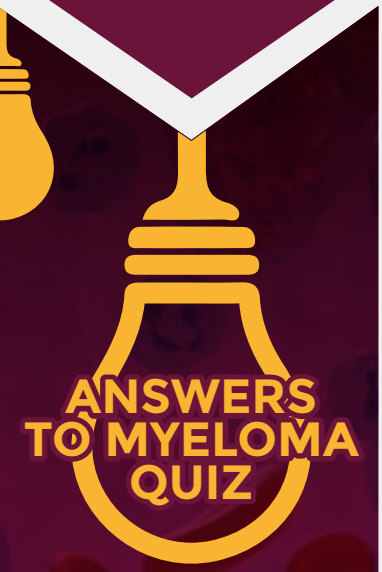
Asst Prof, Dept of Medical Oncology, Homi Bhabha Cancer Hospital & Research Centre, Mullanpur, New Chandigarh

Q25.

Which of these options is incorrect with regards to the findings of the trial by Samur et al studying the impact of HDM on mutational burden at relapse in MM patients ?

A. Translocations involving immunoglobulin heavy chain (t[4;14], t[6;14], t[11;14], t[14;16]) that were observed at diagnosis and maintained at relapse were discordant
B. Translocations involving the MYC region (involving immunoglobulin H [IgH], IgL, or IgK, superenhancers) were the most common translocation events in both study arms
C. Patients treated with HDM accumulated significantly more mutations within the regions between transcription start and transcription termination sites than those treated with RVD
D. Patients receiving HDM had significantly increased asymmetry favoring the transcribed strand for all SNV types

ANSWERS TO MYELOMA QUIZ



ANSWERS TO MYELOMA QUIZ : MARCH 2023 – SEPTEMBER 2023

Q1.

Which of these organisations/expert group on plasma cell dyscrasia use an ensign that is epicentered on the immune globulin structure ?

Answer : IKMG

The International Kidney and Monoclonal Gammopathy Reasearch Group was founded in Bath, UK in October 2010. IKMG was created to specifically bring together the worlds experts in kidney disease caused by monoclonal proteins. The multidisciplinary team is made up of Hematologists, Nephrologists, Nephropathologists, Immunologists and Scientists from around the world. Their mission is to improve the understanding and ultimately treatment strategies of these complex diseases through multidisciplinary collaborations.

Q2.

Which one of the following is an incorrect statement based on the findings of Friedrich etal study analysing the longitudinal profile of T cell repertoire in MM patients receiving BiTEs ?

Answer : Naive T cells require additional MHC class II signal and differentiate upon TCE activation

Findings in this trial demonstrate two modes of action of bispecific TCE treatment in multiple myeloma: the preferential expansion of specific transcriptionally defined T cell clones upon stimulation as well as differentiation and MHC class I-dependent priming of naive T cells.

Q3.

As per the study protocol by Friedrich etal what clone size threshold defined a large clonotype in TCE cohort ?

Answer : 1 %

Q4.

Which of these option is incorrectly matched positivity threshold and cytogenetic abnormality by FISH as per Schavgoulidze etal study of impact of del 1p32 in NDMM ?

Answer : Gain 1q : 50 %

Q5.

Which of the following statements is incorrect in the light of findings of Schavgoulidze etal study of impact of del 1p32 in NDMM ?

Answer : Melphalan based auto HCT upfront mitigates the adverse risk conferred by 1p32 loss

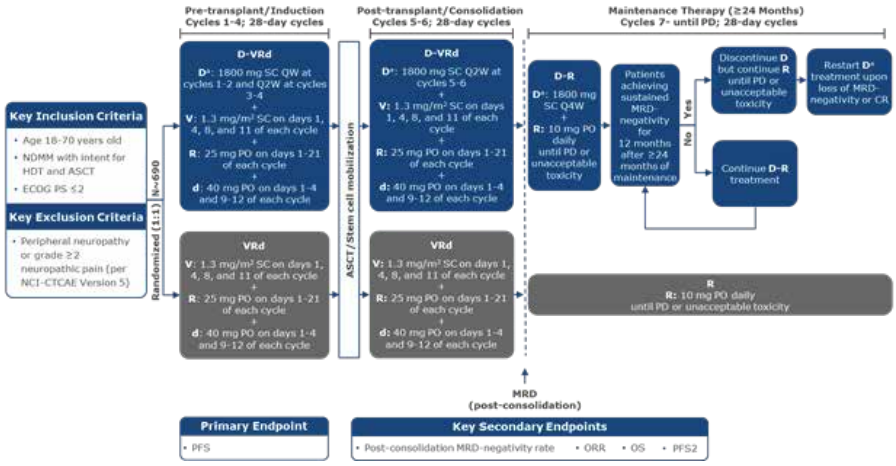
The risk of progression was 1.3 times higher among patients with del(1p32) (P = .0065), and the risk of death was 1.9 higher (P < .0001), after adjustment for age and type of treatment

ANSWERS TO MYELOMA QUIZ

ANSWERS TO MYELOMA QUIZ

Q6.

Identify the trial with design below



Answer : PERSEUS trial

Q7.

Which one of the following is an incorrect statement based on the findings of FORTE trial ?

Answer : PFS with ASCT in patients with standard-risk disease was similar compared with KRd12 without transplant

KRd plus ASCT consistently led to higher rates of 4-year progression-free survival and 1-year sustained minimal residual disease negativity across all cytogenetic risk subgroups compared with KRd12 and KCd plus ASCT

Q8.

Which of these options is incorrectly matched cutoffs for HRCA positivity in the FORTE trial ?

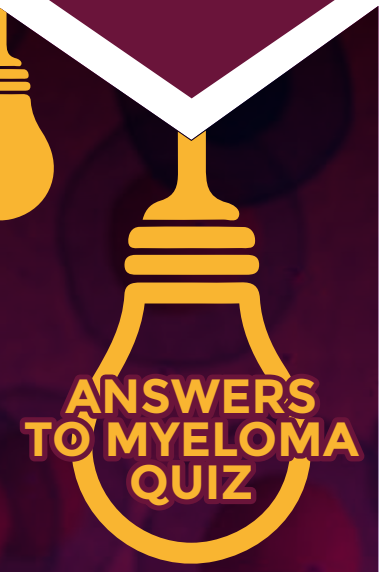
Answer : t(4;14) : 30 %

Q9.

As per the findings of MyXI trial, the highest PFS benefit from Len maintenance was seen in which of the following cytogenetic risk group?

Answer : Del 1p

ANSWERS TO MYELOMA QUIZ



Q10.

Which of the following statement(s) is correct as per the findings of Myeloma XI trial ?

Answer : All the above statements are true

Q11.

First description of X in history . What is X ?

Answer : Russell bodies

Q12.

Which one of the following is an incorrect statement based on the findings of CARDAMON trial?

Answer : The 2-y PFS was 75% in the HSCT group and 68% in the KCd group and thereby met the primary end point of non-inferiority margin of 10 %.

Trial results show that KCd consolidation did not meet the criteria for non-inferiority when compared with upfront transplantation. However, the non-inferiority margin was only exceeded by a small amount (confidence limit –11·1%, prespecified margin –10%), although this study was a phase 2 trial with 15% significance level

Q13.

Which of these options is incorrect with regards to trial design of CARDAMON trial ?

Answer : Cyclophosphamide mobilisation was not allowed during stem cell harvest

Q14.

Which of the following is an incorrect statement wrt the study results of Noemí etal?

Answer : MS using the EXENT system could identify Ig D and IgE myelomas also

The EXENT-iP500 liquid handler purified the immunoglobulins through paramagnetic beads coated with polyclonal sheep antibodies specific for human immunoglobulin G (IgG), IgA, or IgM heavy chains, and for total k and l light chains (EXENT-MS)

Q15.

Which of the following statement is incorrect wrt LC MALDI MS use in MM as per the IMWG recommendations ?

Answer : IMWG endorses the use of MS for cross-comparisons of CR rates in trials done in different time periods.

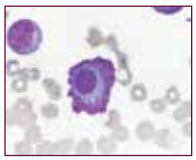
(Ref The International Myeloma Working Group (IMWG) Mass Spectrometry Committee report Murray et al. Blood Cancer Journal (2021) 11:24 https://doi.org/10.1038/s41408-021-00408-4)

ANSWERS TO MYELOMA QUIZ

ANSWERS TO MYELOMA QUIZ

Q16.

Identify the incorrect statement with respect to the image shown!



Answer : All the above statements are true

Q17.

Prespecified analyses in the updated POLLUX trial demonstrated that an OS benefit was maintained with D-Rd versus Rd in all subgroups except :

Answer : None of the above

Q18.

In POLLUX trial ; samples size to assess the primary outcome was estimated to be 560 (280 in each arm). By what margin was DRd arm assumed to reduce the risk of the disease progression or death compared to Rd arm (PFS : 18m) in RRMM when this sample size was calculated ?

Answer : 30 %

Q19.

Which of these options is incorrect with regards to the findings of the trial by Pasvolsky et al studying the impact of clonal plasma cells (CPC) in the autograft on the outcomes of HRMM ?

Answer : Within the CPC + group, hematological responses prior to auto HCT predicted OS

Within the CPC– and CPC+ groups, hematological responses prior to autoHCT and at day 100 after autoHCT mostly retained their statistical significance for both PFS and OS. However, within the CPC+group, hematological responses prior to autoHCT did not predict OS (p =0.60).

Q20.

Which of these options is incorrect with regards to the design of the trial by Pasvolsky et al studying the impact of clonal plasma cells (CPC) in the autograft on the outcomes of HRMM ?

Answer : Evaluation for CPC by 6-color next-generation flow cytometry (NGF) was performed on the collected apheresis products, with a sensitivity of 0.001–0.003% on all samples analyzed in the study.

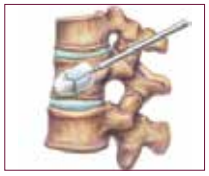
Evaluation for CPC by 6-color next-generation flow cytometry (NGF) was performed on the collected apheresis products, with a sensitivity of 0.001–0.003% depending on sample quality. Of note, 4-color flow cytometry was used before 2012, with a sensitivity of 0.05%

ANSWERS TO MYELOMA QUIZ

ANSWERS TO MYELOMA QUIZ

Q21.

Identify the incorrect statement with respect to the image shown!



Answer : Kyphoplasty

During vertebroplasty fluoroscopically we inject a cement mixture into the fractured bone through a hollow needle. During kyphoplasty, a balloon is first inserted into the fractured bone through the hollow needle to create a cavity or space

Q22.

Which one of the following was not an inclusion criteria in the CARTITUDE4 trial ?

Answer : Subjects with only 1 prior line of therapy must have progressed within 24 months of a stem cell transplant, or if not transplanted, then within 48 months of starting initial therapy

Q23.

In the CARTITUDE 4 trial which of the following statement is incorrect with regards to sample size calculation and study design ?

Answer : The final analysis of PFS will be performed after approximately 150 PFS events are observed

It was estimated that the enrollment of 400 patients and the occurrence of 250 events of disease progression or death would provide the trial with 90% power to detect a relative reduction of 35% in the risk of disease progression or death

Q24.

Which of these options is incorrect with regards to the findings of the trial by Samur et al studying the impact of HDM on mutational burden at relapse in MM patients ?

Answer : All are correct statements

Q25.

Which of these options is incorrect with regards to the findings of the trial by Samur et al studying the impact of HDM on mutational burden at relapse in MM patients ?

Answer : Translocations involving immunoglobulin heavy chain (t[4;14], t[6;14], t[11;14], t[14;16]) that were observed at diagnosis and maintained at relapse were discordant

Translocations involving immunoglobulin heavy chain (t[4;14], t[6;14], t[11;14], t[14;16]) that were observed at diagnosis and maintained at relapse were concordant.

Study:

Anaïs Schavgoulidze, Alexis Talbot, Aurore Perrot, Titouan Cazaubiel, Xavier Leleu, Salomon Manier, Laure Buisson, Sabrina Mahéo, Laura Do Souto Ferreira, Luka Pavageau, Cyrille Hulin, Jean-Pierre Marolleau, Laurent Voillat, Karim Belhadj, Marion Divoux, Borhane Slama, Sabine Brechignac, Margaret Macro, Anne-Marie Stoppa, Laurence Sanhes, Frédérique Orsini-Piocelle, Jean Fontan, Marie-Lorraine Chretien, Hélène Demarquette, Mohamad Mohty, Hervé Avet-Loiseau, Jill Corre; Biallelic deletion of 1p32 defines ultra-high-risk myeloma, but monoallelic del(1p32) remains a strong prognostic factor. Blood 2023; 141 (11): 1308–1315. doi: https://doi.org/10.1182/blood.2022017863

Authors validate del(1p32) as a high-risk marker in newly diagnosed myeloma. Importantly, the cut-off of cytogenetic abnormalities (CAs) was higher (30%)[1] than EMN recommendations (20%),[2] thereby possibly enriching a cohort with relatively high del1p burden. Moreover, unlike R-ISS,[3] t(14;16) was not included as a high-risk (HR) CA, thereby underestimating the HR-CA cohort. Significant missing data of two HR-CAs [t(14;16), t(14;20)] in majority (76%) of patients,[1] questions the value of del1p as the sole contributor of poor outcome. While ASCT patients had a median PFS of 2 years[1] (like Varma et al)[4], non-ASCT patients had inferior survival (PFS 18months) compared to standard triplet (VRd/KRd) regimen (PFS 29months)[5] (Table-1). This might be because majority (60%) of non-ASCT patients received a doublet. If all patients would have received lenalidomide maintenance post-ASCT, whether their PFS would have been longer (like Myeloma-XI)[6] remains debatable (Table-1). Going ahead, it would be interesting to see if disappearance of del1p before ASCT gives better survival as reported previously,[7] and if MRD negativity can abrogate the poor prognosis of del1p similar to other HR-CAs.[8]

References:

1. Schavgoulidze A, Talbot A, Perrot A, et al. Biallelic deletion of 1p32 defines ultra-high-risk myeloma, but monoallelic del(1p32) remains a strong prognostic factor. Blood. 2023;141(11): 1308-1315.

2. Ross FM, Avet-Loiseau H, Ameye G, et al. Report from the European Myeloma Network on interphase FISH in multiple myeloma and related disorders. Haematologica. 2012;97(8):1272-1277. doi:10.3324/haematol.2011.056176

3. Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. J Clin Oncol. 2015;33(26):2863-2869. doi:10.1200/JCO.2015.61.2267

4. Varma A, Sui D, Milton DR, et al. Outcome of Multiple Myeloma with Chromosome 1q Gain and 1p Deletion after Autologous Hematopoietic Stem Cell Transplantation: Propensity Score Matched Analysis. Biol Blood Marrow Transplant. 2020;26(4):665-671. doi:10.1016/j.bbmt.2019.12.726

5. Kapoor P, Schmidt T, Jacobus S, et al. OAB052: impact of chromosome 1 abnormalities on newly diagnosed multiple myeloma treated with proteasome inhibitor, immunomodulatory drug, and dexamethasone: analysis from the ENDURANCE ECOG-ACRIN E1A11 trial. Clin Lymphoma Myeloma Leuk. 2021;21:S33-S34.

JOURNAL SCAN COMMENTARIES

Eagle Eye Competition

BEST COMMENTARY WINNER

APRIL 2023

Dr. Sumeet Mirgh

Asst Professor, TMH, ACTREC , Mumbai

6. Panopoulou A, Cairns DA, Holroyd A, et al. Optimizing the value of lenalidomide maintenance by extended genetic profiling: an analysis of 556 patients in the Myeloma XI trial. Blood. 2023;141(14):1666-1674. doi:10.1182/blood.2022018339

7. Qazilbash MH, Saliba RM, Ahmed B, et al. Deletion of the short arm of chromosome 1 (del 1p) is a strong predictor of poor outcome in myeloma patients undergoing an autotransplant. Biol Blood Marrow Transplant. 2007;13(9):1066-1072. doi:10.1016/j.bbmt.2007.05.014

8. Corre J. Undetectable MRD can change the deal. Blood. 2021;137(1):5-6.

Table-1 – Comparison of present study with literature of del1p myeloma – both transplant and non-transplant patients

	Induction	Survival	Remarks
This study. Schavgoulidze et al. Blood 2023 (n=282) [1]	ASCT arm (n=134) – Triplet in 77% patients Non-ASCT arm (n=142) – Triplet in 31% patients	ASCT – Median PFS – 24 months Median OS – 68 months Non ASCT – Median PFS – 18 months Median OS – 48 months	Components of triplet not specified. Less than one-third patients (31%) in non-ASCT arm received a triplet.
Transplant patients			
Varma et al. BBMT 2020 (n=100) [4]	PI + IMiD (60%); VCd (19%)	Median PFS – 26 months, Median OS – Not reached (3-year OS 79%)	Both 1q and 1p were clubbed together
Panopoulou et al. Blood 2023 (n=20 in del1p cohort) [6]	Induction: CTd vs CRd vs KCRd; Post ASCT - Maintenance: Lenalidomide (+/- vorinostat) vs observation)	Median PFS - Lenalidomide maintenance – 57.6 months vs Observation – 7.5 months	Small cohort of del1p patients (n=20). 43% patients in Schavgoulidze et al study did not receive maintenance.
Non transplant patients			
Kapoor P et al. ENDURANCE trial. 2021 (Abstract only) (n=69) [5]	VRd or KRd	Median PFS – 29 months, 3-year OS – 74%	High risk CA [del17p, t(4:14), t(14:16), t(14;20), LDH>2xULN] not included. KRd was better than VRd in del1p cohort with respect to OS.

Study:

Panopoulou A, Cairns DA, Holroyd A et al. Optimizing the value of lenalidomide maintenance by extended genetic profiling: an analysis of 556 patients in the Myeloma XI trial. Blood. 2023 Apr 6;141(14):1666-1674. doi: 10.1182/blood.2022018339. PMID: 36564045; PMCID: PMC10113174

In theApril 2023 issue of Blood, Panopoulou et al.1provided clarity on the magnitude of benefit from Lenalidomide maintenance in post-transplant Multiple Myeloma patients based on baseline extended genetic profiling.

In this Myeloma XI subset analysis,3 groups of single-hit myelomas [del1p, t(4;14), del17p] had a significant PFS, PFS2 and OS benefit. Isolated gain(1q) derived no benefit, and double-hit myelomas only limited benefit.

However, there are few limitations in the study. 78% patients received no Proteasome Inhibitor (PI) based inductions, which resulted ininferior PFS of 57.3 months compared to 67.5 months in DETERMINATION trial2. Stage ISS-III in this cohort constituted only 22%, much less than Indian data of 70%3. Ideal comparison in high-risk myeloma currently could have been PI+Lenalidomide vs. Lenalidomide maintenance. Lenalidomide and Lenalidomide/Vorinostat were analyzed jointly and added value of Vorinostat remains unclear. Finally, the optimal duration of maintenance is not defined.

It would be worthy if further studies would evaluate finite duration of Lenalidomide maintenance, based on MRD and re-evaluate the role of maintenance in the era of quadruplet induction.

References:

1. Panopoulou A, Cairns DA, Holroyd A, et al. Optimizing the value of lenalidomide maintenance by extended genetic profiling: an analysis of 556 patients in the Myeloma XI trial. Blood. 2023;141(14): 1666-1674.
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JOURNAL SCAN COMMENTARIES

Eagle Eye Competition

BEST COMMENTARY WINNER

MAY 2023

Dr. Saswata Saha

Ad-hoc Assistant Professor Dept. of Medical Oncology Tata Memorial Centre Mumbai

Study:
Puig N, Contreras MT, et al, Mass spectrometry vs immunofixation for treatment monitoring in multiple myeloma. Blood Adv. 2022 Jun 14;6(11):3234-3239. doi: 10.1182/bloodadvances.2021006762. PMID: 35157768; PMCID: PMC9198943

Title: More is not always meaningful!!!

It is no doubt that MS is superior to IFE in terms of sensitivity, especially in patients treated with mAbs. Two practically relevant points need to be discussed here. First of all, Affordability and Availability are the two key mantras of any diagnostic test in a low middle income country like ours. Since we evaluate for treatment response at different time points, IFE stands economical than Mass Spectrometry. In terms of availability also, the former stands taller considering the technical expertise and difficulties with MS. Secondly, all myeloma patients are not just treated based on a single IFE report with biochemical relapse. Wait and watch approach can still be followed in a set of asymptomatic patients at least with standard risk1. Approximately 25% patients of biochemical relapse do not show symptomatic progression in 2 years2,3. In this scenario, meaningful clinical decision making by identifying a minuteM protein by MS stands questionable. Chasing behind deeper response by identifying a minute M protein by MS andchanging the treatment will exhaust the available drugs unnecessarily.

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1. Laubach J, Garderet L, Mahindra A, et al. Management of relapsed multiple myeloma: recommendations of the International Myeloma Working Group. Leukemia. 2016;30(5):1005-1017.
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3. Fernandez de Larrea C, Jim ´ enez R, Rosiñol L, et al. Pattern of relapse ´ and progression after autologous SCT as upfront treatment for multiple myeloma. Bone Marrow Transplant. 2014;49(2):223-227.

JOURNAL SCAN COMMENTARIES

Eagle Eye Competition

BEST COMMENTARY WINNER

JUNE 2023

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Study:
Journal Scan: Pasvolsky O et al; Impact of clonal plasma cells in autografts on outcomes in high-risk multiple myeloma patients. Blood Cancer J. 2023 May 3;13(1):68. doi: 10.1038/s41408-023-00842-6. PMID: 37137874; PMCID: PMC10156676

Title: Clonal Plasma Cells in autograft, 'a bee in the Bonnet'in outcomes of High-Risk Multiple Myeloma

In the May 2023 issue of Blood Cancer Journal, Pasvolsky et al.1 gave insight regarding the impact of CPC in autografts on outcomes in HRMM. In the study, presence of CPC showed lesser post-transplant MRD negative CR (11% vs. 42%; $p < 0.001$) similar to prospective study by Kostopoulos et al.2, inferior PFS (12.8 vs. 32.1 months) and OS (36.4 vs. 81.2 months).

However, being a retrospective study there is treatment heterogeneity, missing data, and patient selection bias. CPC + group had more chromosome 1 abnormalities and deletion of 17p13. The study is limited to HRMM and cannot be generalized. Flowcytometry technique used is mostly substandard (higher graft negativity with triplet induction, 78-89% vs. 40.5% in series by Sevalet al.3) and not standardized. Lesser percentage of patients in CPC + group received any form of maintenance therapy. Finally, the study does not mention outcome of quadruplet induction regimen. Assessment of clonal plasma cells in autograft in the current era of quadruplet induction with novel strategies for purging of CPC needs to be evaluated in future studies.

References:

1. Pasvolsky, O., Milton, D.R., Rauf, M. et al. Impact of clonal plasma cells in autografts on outcomes in high-risk multiple myeloma patients. Blood Cancer J. 13, 68 (2023).
2. Kostopoulos IV, Eleutherakis-Papaiakovou E, Rousakis P, Ntanasis-Stathopoulos I, Panteli C, Orologas-Stavrou N, Kanellias N, Malandrakis P, Liacos C-I, Papaioannou NE, et al. Aberrant Plasma Cell Contamination of Peripheral Blood Stem Cell Autografts, Assessed by Next-Generation Flow Cytometry, Is a Negative Predictor for Deep Response Post Autologous Transplantation in Multiple Myeloma; A Prospective Study in 199 Patients. Cancers. 2021.
3. Seval GC, Dalva K, Oz MD, Ozturk S, Soydan E, Gurman G, et al. Post-Induction Undetectable Minimal Residual Disease at 10-5 Sensitivity Level Within Marrow and/or Stem Cell Graft Overrides Cytogenetic High Risk. Blood (2021) 138(Supplement 1):2909

JOURNAL SCAN COMMENTARIES

Eagle Eye Competition

BEST COMMENTARY WINNER

JULY 2023

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Study:
Samur MK, Roncador M, Munshi NC et al. High-dose melphalan treatment significantly increases mutational burden at relapse in multiple myeloma. Blood. 2023 Apr 6;141(14):1724-1736. doi: 10.1182/blood.2022017094. PMID: 36603186; PMCID: PMC10273091.

Title: High Dose Melphalan treatement in Multiple Myeloma – Is today's blessing a curse for tomorrow?

IIn the April 2023 issue of Blood, Samuret al.1 compared patients with NDMM who received RVD +/- HDM-ASCT to look for mutational pattern. Using whole genome sequencing, the study showed majority of the mutational load following HDM was atthe sub clonal level. The findings were comparable to the findings by Maura et al.2HDM induced SNVs predominantly involve the transcribed strand. Mutational load was greater in patients achievingCR. The study also showed that despite increased mutational burden, thesurvival after first relapse was similar in patients achieving initial CR. This was explained by presence of significantly higher number of neoantigens in patientsrelapsing following HDM leading to higher immunogenicity.

However, this study has few limitations. First, it was conducted in a small subset of 68 patients from IFM 2009 study. Secondly, the mutagenic potential on normal cells and tumor microenvironment is not addressed. Finally, possible treatment strategies to overcome the mutational impact is not addressed. The study generate hypotheses regarding possible immunotherapeutic intervention post transplantation which needs future experimental validation.

References:

1. Mehmet Kemal Samur, Marco Roncador, Anil AktasSamur, et al. High-dose melphalan treatment significantly increases mutational burden at relapse in multiple myeloma. Blood 2023; 141 (14): 1724–1736.
2. Maura F, Weinhold N, Diamond B, et al. The mutagenic impact of melphalan in multiplemyeloma. Leukemia. 2021;35(8):2145-2150.

JOURNAL SCAN COMMENTARIES

Eagle Eye Competition

BEST COMMENTARY WINNER

AUGUST 2023

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