



NEWSLETTER

Issue no-01 | Month-Jan | Year-2023

An Indian Myeloma Academic Group Publication (IMAGe)

JOURNAL CLUB

**AWARDS &
ACCOLADES**

QUIZ

**EAGLE EYE
COMPETITION**

**NATIONAL MYELOMA
REGISTRY**

**INDIAN
PUBLICATIONS**

FELLOWSHIPS

**UPCOMING
EVENTS**

WISHING YOU A
★ **HAPPY NEW YEAR** ★

“

*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 have led to fruition of this snippet on myeloma on new year eve.*

- 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.

**- Dr Joseph John,
Head - Newsletter Committee**

”



Dr. Aditya Jandial

Sr. Research
Associate,
Dept. of Clinical
Hematology and
Medical Oncology,
PGIMER,
Chandigarh



Richardson PG, Jacobus SJ, Weller EA, Hassoun H, Lonial S, Raje NS, Medvedova E, et al. Triplet Therapy, Transplantation, and Maintenance until Progression in Myeloma. *N Engl J Med.* 2022 Jul 14;387(2):132-147. doi: 10.1056/NEJMoa2204925. Epub 2022 Jun 5. PMID: 35660812.

Summary:

In the phase 3 DETERMINATION trial, newly diagnosed multiple myeloma (NDMM) patients (18 to 65 years old) from United States were randomized to receive lenalidomide, bortezomib, and dexamethasone (VRd alone, n= 357) or VRd plus autologous stem cell transplant (VRd plus ASCT, n= 365), followed by lenalidomide maintenance until progression in all patients. The trial met its primary endpoint – incorporation of ASCT to VRd improved PFS by almost 21 months versus VRd alone (67.5 vs 46.2 months; HR 1.53; P < .0001); however, there was no significant difference in 5-year OS between 2 arms. In the subgroup analysis, Black patients and ISS stage 3 patients derived lesser PFS benefit; however, high-risk NDMM patients showed remarkable improvement in PFS with ASCT. The proportion of MRD negative patients at start of maintenance therapy was higher in the ASCT arm (54.4% vs 39.8%). However, irrespective of the treatment received, the 5-year PFS was similar for patients who achieved MRD negative status. MRD positive patients in VRd plus ASCT arms achieved longer PFS than VRd alone. There was no new safety signal. VRd plus ASCT led to higher grade ≥ 3 hematologic adverse events and transient decline in quality of life during ASCT. Both arms demonstrated similar incidence of second primary malignancies (nearly 10%); however, the incidence of AML/MDS was higher in VRd plus ASCT arm (10 vs 0 cases).

Commentaries:

The results of DETERMINATION trial confirm the efficacy of ASCT in terms of PFS benefit when it is combined with initial antimyeloma therapy in eligible NDMM patients. It also reinforces the role of continuous maintenance with lenalidomide after ASCT. The major caveat of this trial is significantly lower rate of salvage ASCT (28%) in VRd alone arm, compared to 74% in IFM 2009 trial. The lack of OS difference seen in the trial was possibly due to effective subsequent (post-protocol) antimyeloma therapies received by patients in either arm. Conventionally, ASCT is considered a frontline treatment strategy in NDMM. However, this trial adds to the evidence that a flexible approach towards the timing of ASCT may be adopted in a select group of patients who are relatively young and have standard-risk disease. Nevertheless, ASCT is not an unlimited treatment option and attrition is known to occur at each relapse. These results also suggest that some patients who achieve MRD negativity after induction therapy may choose to defer or avoid ASCT without compromising on PFS and OS, particularly in settings where they have access to effective subsequent therapies (bispecific antibodies and CAR-T cell therapy). However, before adopting such approach, more work is required to refine the contemporary MRD assessment strategies. Lastly, frontline treatment with ASCT is a cost-effective strategy in LMICs. Given the fact that economic constraints and limited access to new therapies strongly influence the treatment decisions, ASCT shall continue to be the standard of care for NDMM patients in LMICs.

Video Link

<https://www.youtube.com/watch?v=DTNFR7dshl8>



**Dr. Sachin
Puntar**

Professor, Adult
Hematolymphoid
Unit, Dept. of
Medical Oncology,
ACTREC, Tata
Memorial Centre

Larocca A, Bonello F, Gaidano G, D'Agostino M, Offidani M, Cascavilla N, Capra A, et al. Dose/schedule-adjusted Rd-R vs continuous Rd for elderly, intermediate-fit patients with newly diagnosed multiple myeloma. *Blood*. 2021 Jun 3;137(22):3027-3036. doi: 10.1182/blood.2020009507.

Summary:

Lenalidomide with dexamethasone is one of the standard treatments for elderly patients with multiple myeloma. The “FIRST” randomized trial has previously shown that continuous lenalidomide – dexamethasone (Rd) was better than a fixed duration Rd. However, the “FIRST” trial did not have maintenance therapy in any of the arms. Therefore, it remained unanswered whether changing to maintenance lenalidomide after an initial induction would result in similar outcomes (but reduced toxicity) compared to continuous Rd. With this background, this multicentre randomized trial was conducted at 33 Italian centres to compare 9 cycles of Rd followed by R maintenance (10 mg/day, no steroids) versus continuous Rd. The trial included newly diagnosed multiple myeloma with age 65-80 years and intermediate fitness (i.e. IMWG fitness score of 1). The primary objective was to compare event free survival (with event being defined as grade IV hematological adverse event, grade III or IV non-hematological adverse event, progression, death irrespective of the cause, discontinuation of lenalidomide or occurrence of 2nd primary neoplasm). Secondary objectives were to compare PFS, OS, best response rates, and toxicities. A total of 210 patients were randomized; 11 did not meet inclusion and exclusion criteria leaving 199 eligible patients. Of these, 101 were in the Rd-R arm and 98 in continuous Rd arm. The median follow up was 37 months. The median EFS was significantly better in the Rd-R (10.4 vs 6.9 months, HR 0.70, 95% CI for HR 0.51 – 0.95, $p = 0.02$). The PFS (median 20.2 vs 18.3 months, $p = 0.16$) and OS (3-year OS 74% vs 63%, $p = 0.06$) were similar. Although not statistically significant, the grade III or more severe non-hematological adverse events were 10 percentage points lesser in the Rd-R arm and there were fewer therapy related deaths. This study concludes that in intermediate fit elderly myeloma patients, changing to maintenance lenalidomide after 9 cycles of induction is associated with similar disease related outcomes with lesser toxicity.

Commentaries:

This Italian randomized trial is the first such trial to compare continuous duration Rd to induction Rd (9 cycles) followed by maintenance lenalidomide. The authors conclusively show that reducing the lenalidomide dose and omitting steroids after 9 cycles of induction therapy does not compromise the treatment efficacy (in fact, the PFS and OS are slightly better) but reduces the toxicities. Thereby, the Rd-R arm had a statistically significantly better EFS (the event was defined well to capture both the efficacy and toxicities). The major strengths of the study are a simple study design with very clinically relevant endpoints. Although there are no translational elements in this study, this study is potentially practice changing and gives extremely relevant clinical findings. From the broader perspective of clinical practice (not just in myeloma), this trial conveys that “subtraction (of therapy) may lead to addition (of life)” which may be especially important in elderly patients (particularly when cure is not the aim). And from the broader perspective of clinical research, this highlights that simple well-powered study designs can give relevant results and that it is not necessary to have a translational element always. I would end by saying that more such studies are essential in several other settings in myeloma (and elsewhere too) to optimize treatment efficacy, and minimize toxicities.

Video Link

<https://www.youtube.com/watch?v=huHOPiHTVrk>





**Dr. Akshay
Lahoti**

Clinical Associate
Dept. of
Hematology and
Bone Marrow
Transplant,
Tata Medical
Center, Kolkata

Kumar SK, Jacobus SJ, Cohen AD, Weiss M, Callander N, Singh AK, et al. Carfilzomib or bortezomib in combination with lenalidomide and dexamethasone for patients with newly diagnosed multiple myeloma without intention for immediate autologous stem-cell transplantation (ENDURANCE): a multicentre, open-label, phase 3, randomized, controlled trial. *Lancet Oncol.* 2020 Oct;21(10):1317-1330. doi: 10.1016/S1470-2045(20)30452-6.

Summary:

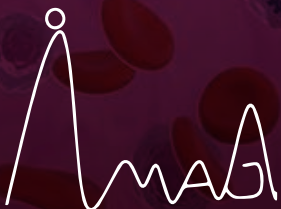
Randomized Phase III Trial popularly known as ENDURANCE trial directly compares two 3-drug combinations for initial treatment of NDMM standard or intermediate risk patients who are ineligible for ASCT or did not intend to have early ASCT. 1087 patients were randomly assigned to induction therapy with VRd or KRd. PFS, OS and overall response rates were also comparable between the regimens. Although VGPR or better response rate were better with KRd, but this did not translate into PFS benefit. Dose reduction as well as discontinuation rates were more with VRd whereas Grade 3-5 serious adverse events and mortality was seen more in KRd arm. The QoL compliance rate by the end of induction was 97%, no difference was observed between the arms. Given the efficacy, safety, convenience, and cost, VRd remains the standard of care for NDMM patients considered for treatment with a PI-IMiD-based triplet, as well as the backbone to build quadruplet regimen. Study results have major implications for our clinical practice. Equal efficacy of the 2 regimens provides evidence for KRd being an option for induction in patients presenting with neuropathy or not tolerating Bortezomib.

Commentaries:

This randomized trial is the first such Phase III trial to compare VRd vs KRd. The authors conclusively show that KRd is not superior to VRd in terms of PFS, OS as well as ORR. In fact, Grade 3-5 SAE and mortality rates were more with KRd. The major strengths of the study are a simple study design, have major implications for our clinical practice. VRd is a well-tolerated, out-patient regimen with manageable toxicity for NDMM. Equal efficacy of the 2 regimens provides evidence for KRd being an option for induction in patients presenting with neuropathy or not tolerating Bortezomib. From the broader perspective of clinical practice (not just in myeloma), this trial conveys and highlights the need to wait for randomized trial results before moving into clinical practice based on data from single-arm or Phase II studies.

Video Link

<https://www.youtube.com/watch?v=mYAix3s4nm4>



Awards and Accolades

For the period from June - Dec 2022



Brig. Tathagata Chatterjee (Retd.), Senior Professor Hematology and Pathology and Head IHBT ESIC Medical College and Hospital, Faridabad was awarded with the Dr JG Parekh Oration award on 04th November 2022 at the ISHBT National Hematology Conference held at Kolkata for his work in Multiple Myeloma.



Dr. Rashmi Yawalkar from Amrita Hospital, Kochi received the ASH 2022 abstract achievement award for her abstract titled "Bortezomib maintenance appears feasible, safe and effective in newly diagnosed Multiple Myeloma in a resource limited setting – a retrospective analysis from South India" at the 64th ASH Annual Meeting and Exposition held at New Orleans, Louisiana from 10 – 13 December 2022.



Mr. Atul Basnal, a PhD Student at Department of Laboratory Oncology, IRCH, AIIMS, New Delhi was awarded IMS Young Investigator Award for exemplary abstract titled "Deep coverage targeted next generation sequencing approach to determine somatic mutational spectrum of recurrently mutated genes in newly diagnosed multiple myeloma in a large Indian cohort" at the 19th International Myeloma Society annual meeting held at Los Angeles, California in August 2022



Ms. Harshini Sriram, a Ph.D. student at the Hematopathology Laboratory, ACTREC, Tata Memorial Centre, Mumbai was an ASH Abstract Achievement Award recipient for her abstract titled "Serum microRNA signature predicting poor therapeutic response to bortezomib-based therapy and clinical outcome in newly diagnosed multiple myeloma: A result of miRNA profiling by deep sequencing" at the 64th ASH Annual Meeting and Exposition held at New Orleans, Louisiana from 10 – 13 December 2022



Col (Dr.) Y Uday, Professor (Med & Hemat), Armed Forces Medical College, Pune, won the Overseas Contribution Award (Oral Presentation) for his paper titled "Indian Multicentre Phase II Randomized Study Comparing Post Stem Cell Transplantation Consolidation/ Maintenance Regimens for Newly Diagnosed Multiple Myeloma Patients (IMPOSE-Bortecon) Study Number: 4905/2017" at the ICBMT 2022 and 27th annual congress of KSBMT, held at Busan, Korea in September 2022.

"Know our celebrated experts"

AWARDS
&
ACCOLADES

"In case of any other awardees in the field of Plasma Cell Dyscrasias during the last 6 months - please contact the editorial team at secretary@imagesociety.co.in"

IMAG

MYELOMA QUIZ

MYELOMA QUIZ

SEP 2022

WINNER

Dr. Pankaj Patil

Q1.

The National List of Essential Medicines (NLEM) was first compiled in 1996 and it was revised thrice earlier in 2003, 2011, and 2015. 384 drugs find place in the new list released on 14 Sep 22. Which of these myeloma drugs was added to the newly compiled list?

- A. Lenalidomide
- B. Pomalidomide
- C. Bortezomib
- D. Carflizomib

Q2.

In the MajesTEC-1 trial ; Ph1 -2 trial about Teclistamab in R/R Multiple Myeloma which of the following was not an exclusion criteria?

- A. Prior treatment with any therapy that is targeted to BCMA or any other CD3-redirecting drug
- B. Autologous stem cell transplant ≤ 24 weeks before the first dose of study drug
- C. Plasma cell leukemia
- D. Myeloma with CNS involvement

Q3.

Which of the following statement is incorrect with respect to Teclistamab induced cytokine release syndrome (CRS) as per the MajesTEC-1 trial results ?

- A. Any grade CRS occurred in 72%
- B. Most CRS events occurred after step-up and cycle 1 doses
- C. Two patients discontinued teclistamab due to CRS
- D. For CRS treatment ; Tocilizumab was used in 36% cases; steroids in 8% and single vasopressor was administered in < 1 %

Q4.

In the DETERMINATION trial which of the following was not considered a time point for bone marrow aspiration for response assessment and correlative analysis ?

- A. D + 100 of ASCT (RVd+ASCT arm)
- B. Day 1 of RVd cycle 4 (RVd+ASCT arm)
- C. Prior to lenalidomide maintenance
- D. Annually during maintenance in consenting subjects only

Q5.

Originally the DETERMINATION trial study was planned to be conducted together with the IFM 2009 study with a planned population size of 1000. However a landmark research finding X led to protocol revision twice and the sample size was reduced to 720. What was X ?

- A. Favourable PFS hazards ratio with indefinite lenalidomide maintenance
- B. PFS benefit of early autologous HSCT
- C. PFS benefit of triplet over doublet induction
- D. Deep and sustained MRD negativity with high dose melphalan based autologous HSCT

MYELOMA QUIZ

MYELOMA QUIZ

OCT 2022

WINNER



Dr. Tintu MV

Sr. Resident,
Medical Oncology,
Madras Medical
College



Q6.

The European Myeloma Network, within the HARMONY project have recently proposed a second revision (R2-ISS) of the current Revised International Staging System (R ISS). Which of the following was not considered a variable for risk stratification as per R2-ISS ?

- A. t(4;14)(p16;q32)
- B. t(14;16)(q32;q23)
- C. LDH
- D. 1q +

Q7.

In the MCARH109 trial ; 10/17 patients relapsed post CART during the follow up period. What percentage of patients continued to show persistent GPRC5D expression on myeloma cells at relapse?

- A. None
- B. 40 %
- C. 90 %
- D. < 10 %

Q8.

In the MCARH109 trial , the primary end point was to identify the the maximum tolerated dose. What was the maximum dose level planned by investigators that could never be reached due to dose limiting toxicities encountered in the trial ?

- A. 450 million total CAR+ cells
- B. 900 million total CAR+ cells
- C. 600 million total CAR+ cells
- D. 800 million total CAR+ cells

Q9.

In the Larocca trial, a novel primary end point@EFS was defined by the investigators to study efficacy & feasibility of dose /schedule adjusted Rd- R in NDMM. Which of these parameters contributed maximum to the EFS benefit in the study arm ?

- A. Discontinuation rates of lenalidomide
- B. Incidence of grade 4 hematological adverse event
- C. Incidence of \geq grade 3 non - hematological adverse event
- D. Rate of progressive disease

Q10.

In the Larocca trial, patients could be enrolled regardless of abnormal baseline laboratory values unlike most previous trials. Which of the following parameters was not considered an exclusion criteria?

- A. Creatinine clearance < 30 mL/min
- B. ANC < 1000/ μ l
- C. Platelet count < 80000 / μ l
- D. None of the above

MYELOMA QUIZ

MYELOMA QUIZ

NOV 2022

WINNER



Dr. Malini Garg

Asst. Professor,
BMT Unit, HBCH,
Varanasi

MAG

Q11.

The ENDURANCE trial compared the combination of the drugs bortezomib, lenalidomide, and dexamethasone (VRd) against Carfilzomib, lenalidomide, and dexamethasone (KRd) when treating patients with newly diagnosed multiple myeloma. Which of the following is not true regarding the results from the trial?

- A. KRd improved PFS compared with VRd
- B. A significantly higher rate of cardiopulmonary and renal toxicity was observed with KRd
- C. Neuropathy rates were higher with VRd
- D. VRd remains the standard triplet induction regimen in standard- and intermediate-risk newly diagnosed multiple myeloma and a suitable backbone for four-drug combinations

Q12.

The IKEMA study was a randomized open label multicenter study assessing the clinical benefit of isatuximab combined with carfilzomib and dexamethasone vs carfilzomib with dexamethasone in R/R Multiple Myeloma. Which of these is the incorrect statement as per data from the trial?

- A. More patients in Isa-Kd vs Kd reached MRD-negative status
- B. At least twice reached CR with MRD negativity status
- C. MRD negativity with Isa-Kd can be reached independently of bad prognosis such as renal impairment, ISS Stage III, ≥ 3 prior lines of therapy, and in patients with gain(1q21)
- D. Reaching MRD-negative status was not associated with longer PFS in Isa-Kd arm.

Q13.

Trispecific antibodies are being evaluated in Phase I/II trials in myeloma led by Ichnos Sciences. The trispecific antibody targets two areas found on multiple myeloma cells (BCMA and CD38) and joins that with the CD3 T cells. The company's proprietary platform is called BEAT® 2.0 technology. Which of these statements is the incorrect statement with regards to the initial research work on the drug?

- A. The main limitation of the drug is that the risk of keratopathy
- B. The presence of the CD28 also increased the ability of T-cells to kill different types of myeloma cells 'even at the lowest dosage level
- C. The CD 38 protein on the surface of the myeloma cell provides a mechanism for the tsAb to latch onto the myeloma cell
- D. The CD3 protein 'is part of the T-cell receptor (TCR), which recognizes abnormal cells by binding molecules called antigens

Q14.

A drug used in the treatment of relapsed/refractory multiple myeloma (RRMM) is in the process of being pulled off the US market by its manufacturer. The drug is belantamab mafodotin-blmf, an antibody drug conjugate that targets B-cell maturation antigen (BCMA). What is the reason for its withdrawal?

- A. High rates of CRS
- B. Keratopathy
- C. High Incidence of \geq grade 3/4 non - hematological adverse event
- D. Phase III trials did not meet its primary end point of PFS benefit

Q15.

What is the colour of cancer ribbon for multiple myeloma?

- A. Lilac
- B. Black
- C. Burgundy
- D. Green

Study:

Moreau P, Garfall AL, van de Donk NWCJ, Nahi H, San-Miguel JF, Oriol A, Nooka AK, et al. Teclistamab in Relapsed or Refractory Multiple Myeloma. N Engl J Med. 2022 Aug 11;387(6):495- 505. doi: 10.1056/NEJMoa2203478. Epub 2022 Jun 5. PMID: 35661166.

Title:

All That Glitters Is Not Gold: The Majestic MajesTEC-1 of Multiple Myeloma

In this pharma-driven (Janssen R & D) study, Teclistamab resulted in 63% ORR, 26.7% MRD negativity. The study had high rates of mortality from disease progression (41.2%) and attrition (6m-40%). Most reported deaths are attributed/aggravated by Teclistamab. Poor external validity and universalization with 81% whites and only 1.8% Asians. There is a dismal representation of the elderly (>75y -14.5%) and EMD (<20%). Selection bias as study population being good PS (ECOG-0/1) and low risk (ISS III-12%). The primary endpoint based on PR doesn't support the investigators' claim for deep response and an outcome-based endpoint would've been preferable. The authors talk of triple class exposure which shouldn't be misinterpreted with triple refractory (76.8%). With alternative therapies for triple exposure and no head-to-head comparison, the study is premature to draw conclusions. A high percentage of grade 3/4 adverse events (94.5%) and infections (35.8%) adds significantly to costs/mortality in the Indian scenario. Nevertheless, with existing logistic challenges (limited production capabilities/ long manufacturing times) in CAR-T, safer BCMA may prove useful in managing RRMM.

01 | Dec | 2022

**JOURNAL
SCAN
COMMENTARIES**

**Eagle Eye
Competition**

**BEST
COMMENTARY
WINNER**



Dr. Harikrishnan P

Sr. Resident,
Dept. of Internal
Medicine, AFMC
Pune

MAG

Study:

Mailankody S, Devlin SM, Landa J, Nath K, Diamonte C, Carstens EJ, Russo D, et al. GPRC5D Targeted CAR T Cells for Myeloma. N Engl J Med. 2022 Sep 29;387(13):1196-1206. doi: 10.1056/NEJMoa2209900.

Title:

GPRC5D Targeted CAR-T in Multiple Myeloma (MM): A New Ray of Hope

In this pharma-driven (Juno Therapeutics) Phase-I dose-escalation study, GPRC5D targeted CAR-T (MCARH109) resulted in 50% MRD negativity in the dose ranges of 25 – 150 x 10⁶ cells. Major strengths are the inclusion of non-secretory myeloma, plasma cell leukemia, and prior BCMA-directed therapies, who weren't eligible for ongoing BCMA-directed CAR-T trials. The study's achievement of secondary objectives is debatable. Despite 50% MRD-negativity, it's premature to consider it efficacious, being a Phase-I non-randomized single-center study, with no head-to-head comparison with existing CAR-T therapies, limited elderly representation (Median-60y), and only 20m follow-up. At progression, 67% and 33% had no/decreased GPCR5D expression respectively, indicating antigen downregulation/ escape over time needing further trials. Expression of either BCMA/ GPCR5D in malignant clones rather than co-expression may add to the cost of workup and treatment outcomes with MCARH109. The cost-benefit ratio of MCARH109 is questionable in resource-limited settings like India considering logistic challenges and adverse events (CRS requiring Tocilizumab in 60% of study subjects). Considering MM incurable to date and dismal prognosis of RRMM, MCARH109 may evolve as a promising therapeutic approach.

**JOURNAL
SCAN
COMMENTARIES**

**Eagle Eye
Competition**

**BEST
COMMENTARY
WINNER**



Dr. Nazneen S

Divisional Medical
Officer,
Consultant
Physician and
MOIC ICU at
Divisional Railway
Hospital,
Ponmalai, Tiruchy,
Tamil Nadu

Study:

Sperling AS, Guerra VA, Kennedy JA, et al. Lenalidomide promotes the development of TP53-mutated therapy-related myeloid neoplasms. *Blood*. 2022;140(16):1753-1763. doi:10.1182/blood.2021014956

Title:

Lenalidomide promotes the development of TP53-mutated therapy-related myeloid neoplasms

Sperling et al, developed a proof-of-concept that lenalidomide (and not pomalidomide/iberdomide) leads to TP53-mutated myeloid neoplasms. It would be intriguing to see whether such differential effects on CK1 α are due to the extra oxygen atom of pomalidomide/iberdomide. But, as majority of pomalidomide patients had received lenalidomide before, it is likely that the effect of lenalidomide is not long-lasting. In-vitro data showed dose dependent effects of lenalidomide on TP53, however, its validity in clinical practice is unknown. This is important because lower doses of lenalidomide are used in Indian patients due to tolerance issues. Importantly, patients with prior auto-HSCT were only 17%. Literature (Table 1) has shown that second haematological malignancies are higher in transplanted patients although causality (melphalan versus lenalidomide) cannot be teased out. Like myeloma cells, whether high-dose melphalan increases mutation burden in non-myeloma cell compartment (stem cells, myeloid cells) too, remains unanswered. Higher incidence of haematological malignancies coupled with encouraging MRD-directed de-escalation strategy probably means that we will soon witness an era of finite maintenance.

**JOURNAL
SCAN
COMMENTARIES**

**Eagle Eye
Competition**

**BEST
COMMENTARY
WINNER**



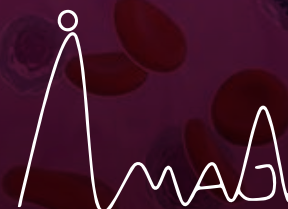
Dr. Sumeet Mirgh

Assistant
Professor, Tata
Memorial Centre
ACTREC Mumbai

A white handwritten signature of Dr. Sumeet Mirgh, featuring a stylized 'M' and 'A'.

Table1 – Data of incidence of second malignancies with lenalidomide maintenance in transplant versus non-transplant settings

	Treatment arms	Maintenance and duration	Median follow-up	Incidence of malignancies in two arms
DETERMINATION trial	RVd + ASCT vs RVd alone- RVd consolidation- R maintenance	R maintenance (<i>till disease progression</i>)	76 months	SPM - 10.7% (ASCT) vs 10.4% (non-ASCT); AML/MDS - 2.7% (ASCT) vs 0% (non-ASCT); 5-year cumulative incidence of second primary haematological cancers (CI-SPHC) 3.5% vs 1.6%
IFM 2009 study	RVd + ASCT vs RVd alone - RVd consolidation - R maintenance	R maintenance - 1 year	44 months	5-year CI-SPHC 1.4% (ASCT) vs 0.6% (ASCT)
UK NCRI Myeloma XI study	Induction:CTD vs CRD (vs KCRD), pre-transplant consolidation: <VGPR – VCD vs none, ≥VGPR - ASCT – Maintenance: Lenalidomide (+/- vorinostat) or active observation)	Lenalidomide (+/- vorinostat) (<i>till disease progression</i>) or active observation	68 months	7-year cumulative incidence of SPM - 10.8%; Haematological: 2.8% t (ASCT) vs 1.4% (non-ASCT) 2022 update - Higher in double exposed (R in induction+maintenance) than other groups ⁵
MAIA study (non-transplant)	Dara-Rd vs Rd until progression	Dara-Rd vs Rd (<i>till disease progression</i>)	28 months	SPM - 3.3% vs 3.6%; Haematological - 0.5% vs 0.5%



List of Institutions and No. of Registrations

The National Myeloma Registry, as part of the IMAGE group, forms the backbone of research in collecting and collating the data prospectively on patients of Multiple Myeloma and other plasma cell dyscrasias across the subcontinent. The platform provides an opportunity for the doctors to follow up with the patients, acts as an EMR, and research database with real-time information regarding the patients. At the same time, the patient mobile application component of the Hybrid application helps improve their compliance through reminders, graphs of their investigations, answers to their routine questions, reminders regarding the investigations, hospital appointments, and drug dosing, and lastly, acts as a patient diary. The various centers registered with the number of patients enrolled by each center respectively are depicted below. The salient features of statistical analysis as on 01st Jan 2023 are depicted in the pictorial form below as a ready reckoner. For those institutes who want to join hands with IMAGE can write to us at secretary@imagesociety.co.in

We sincerely hope that more centres get added and share their data so that a comprehensive National Myeloma Registry can be maintained to add value to the research. Those who haven't joined yet are requested to come forward and join at <https://care4myeloma.in/welcome>



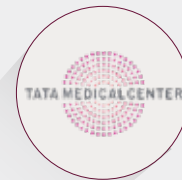
PGIMER, Chandigarh

1150



Army Hospital (Research & Referral)

711



TMC Kolkata

637



Rajiv Gandhi Cancer Institute

265



SGPGI

144



CH(SC) & AFMC

132



NIMS, Hyderabad

113



CMC Ludhiana

87



JIPMER

62



Apollo Amrishi

23

For other institutes who are a part of the registry, please click on <https://care4myeloma.in/welcome>

Registry
Analysis



REGISTRY

IMAGE

Registry Analysis

Total Number Registered **3427**

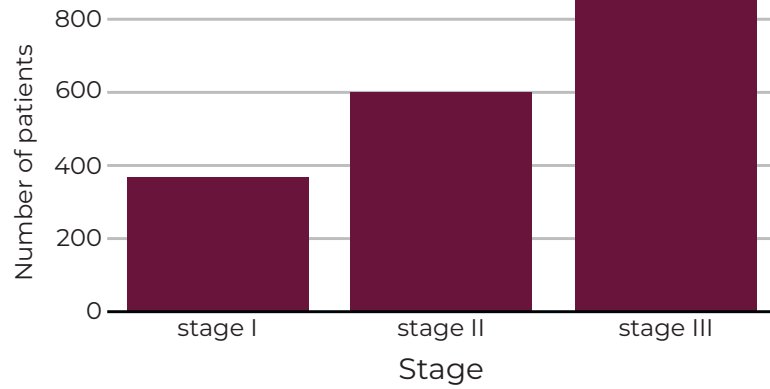
No. of Deaths Till Date **492**

Registry Link

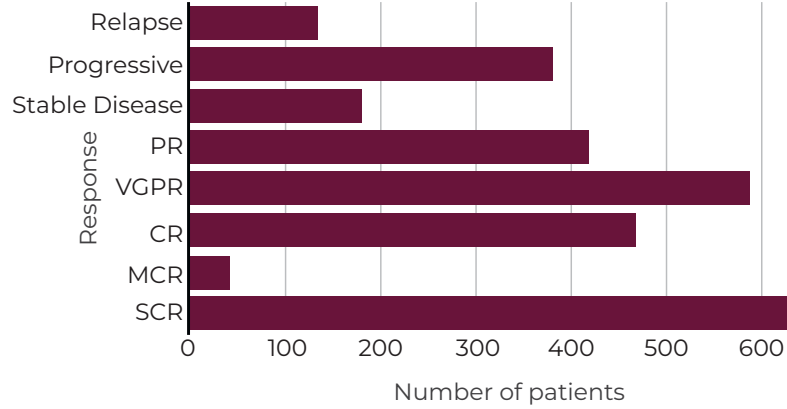
<https://care4myeloma.in/welcome>



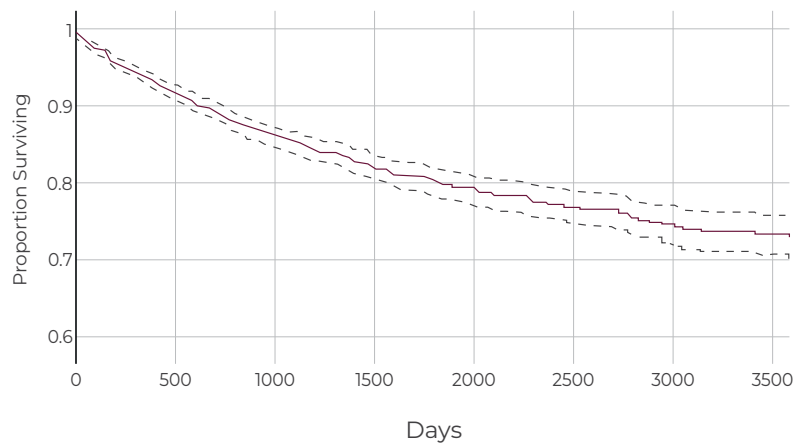
ISS Stage



Distribution of Responses



Overall Survival



Article - Punatar S, Katti K, Rajamanickam D, et al. Role of Curcumin in Reducing Toxicities Associated With Mucosal Injury Following Melphalan-Based Conditioning in Autologous Transplant Setting. *Cell Transplant.* 2022;31:9636897221086969. doi:10.1177/09636897221086969

Prelude:

Autologous stem cell transplant is the standard of care for all transplant-eligible newly diagnosed multiple myeloma, and even relapsed myeloma. The incidence of World Health Organization (WHO) grades I-IV oral mucositis with certain myeloablative conditioning regimens is approximately 90%, up to three-quarters of them manifesting with severe mucositis (WHO grade III/IV). The standard conditioning regimen for autologous HSCT for multiple myeloma is melphalan 200 mg/m². However, melphalan at this dose often leads to significant mucositis with its associated issues of pain, impaired nutrition, opioid use and even use of total parenteral nutrition. Several strategies (cryotherapy, palifermin, laser therapy) have been attempted to reduce the mucositis associated with high dose melphalan. However, cryotherapy has its own limitations – viz only local effects limited to the oral cavity (leaving gastro-intestinal mucositis as it is), and variable duration in studies with small sample sizes. Moreover, as used in some studies, prolonged cryotherapy for more than 6 h becomes uncomfortable for patients. Proinflammatory cytokines (IL-1, IL-6, IL-8, IL-17, TNF- α , TGF- β , IFN- γ) play a central role in pathogenesis of mucositis. NF- κ B modifies the genetic expression of these cytokines and therefore, NF- κ B inhibition could be beneficial in the reduction of mucosal injury. Curcumin, a polyphenol derivative with low toxicity profile used for its anti-inflammatory actions, inhibits various inflammatory cytokines through inhibition of NF- κ B.

Summary:

The investigators used curcumin (a commonly used Indian spice) lozenges in a single centre prospective study (at a dose of 4 g twice daily – from day-3 till day +28 along with standard supportive care) to assess the impact of these lozenges on the acute post-transplant complications. They compared 30 patients who received curcumin with 10 controls who received standard supportive care. They found a reduced incidence of grade 3-4 toxicities with curcumin - mucositis (43% vs 60%), diarrhoea (33% vs 70%), vomiting (3% vs 40%); and reduced used of opioids (33% vs 50%) and total parenteral nutrition (47% vs 90%). Through a detailed cytokine analysis of serum and saliva at specified time points, the authors demonstrated that beneficial effects of curcumin are likely mediated through modulation of interleukin-8. This study provides a strong proof of concept that curcumin lozenges comprising of solid lipid curcumin particles abrogate the GI-toxicities of high-dose melphalan. However, this was a pilot study and a confirmatory randomized trial would be warranted to confirm these findings. As stated by the authors, such a randomized trial is ongoing at their centre.

“Original
research
publications
from India”

Publications
from Indian
Faculty from
Sep 22 - Nov 22



MAG

Article - Kumar L, Sahoo RK, Kumar S, et al. Autologous stem cell transplant for multiple myeloma: Impact of melphalan dose on the transplant outcome [published online ahead of print, 2022 Nov 23]. *Leuk Lymphoma*. 2022;1-10. doi:10.1080/10428194.2022.2148214

Prelude:

High dose melphalan (HDM) (200 mg/m²) conditioning is used in multiple myeloma (MM) patients undergoing hematopoietic stem cell transplant (HSCT). In our patient population, it is associated with 60% incidence of grade 3-4 oral mucositis, increased risk of life-threatening infections, increased use of total parenteral nutrition (TPN), antibiotics and prolonged hospital stay. Though the mortality in this setting has decreased to less than 2%, life threatening infections due to multidrug resistant organisms is an important consideration in patient management, especially in low-middle income countries. Intermediate dose melphalan (IDM) (140 mg/m²) is associated with a lesser transplant related morbidity and mortality in patients more than 65 years of age and in those with renal dysfunction, and results in similar response rate (RR), event free survival (EFS) and overall survival (OS). Multiple retrospective and observational studies have proposed that 140mg/m² melphalan can be a safer yet equally efficacious alternative dosing strategy. A randomised trial compared Melphalan 200mg/m² with Melphalan 140mg/m² + 8 Gy TBI, and showed that former was less toxic and at least as effective as the latter.

Summary:

Kumar et al, evaluated impact of melphalan dose on transplant outcomes in MM. In their 24-year retrospective period (1995-2019), 459 consecutive transplant patients were analysed. Their primary end-point was OS. 85% (n=390) patients received Melphalan 200mg/m² (Mel-200) and 15% (n=69) received Melphalan ≤150mg/m² (Mel-150). As expected, patients in Mel-150 had adverse baseline clinical and laboratory parameters, notably, patients with GFR <40ml/min [50% (Mel-150) vs 19% (Mel-200)] and ISS-III [62% (Mel-150) vs 31% (Mel-200)]. Post-ASCT response rates (CR+VGPR) were significantly better in Mel-200 cohort [72% (Mel-150) vs 84% (Mel-200); p<0.024]. Importantly, at a median follow-up of 88-months, there was no difference in median OS (100 months vs 102 months; p=0.817), median PFS (60 months vs 53 months; p=0.746), and 2-year relapse rates (32.4% vs 30.9%; p=0.745). Moreover, there was no difference in frequency of grade 3-4 mucositis (p=0.823). This study re-iterates the need of a randomised study for comparing Melphalan vs 200mg/m² with Melphalan 140mg/m², especially in the era of effective induction regimens.



MAG

Article – Shekhawat AS, Singh B, Malhotra P, et al. Imaging CXCR4 receptors expression for staging multiple myeloma by using 68Ga-Pentixafor PET/CT: comparison with 18F-FDG PET/CT. *Br J Radiol.* 2022;95(1136):20211272. doi:10.1259/bjr.20211272

Prelude:

Chemokine receptor-4 (CXCR-4) is a member of the G-protein-coupled chemokine receptor family. Its natural ligand is CXCL12/SDF-1. SDF-1 binding to CXCR-4 activates downstream signalling pathways (MAPK, PI3K). CXCR-4 is popular, as its inhibitor Plerixafor is used in stem-cell mobilization. Pathological CXCR-4 overexpression has been reported in various types of solid cancers and in hematopoietic malignancies viz. leukaemia and lymphoproliferative disorders. CXCR-4 mediated interaction holds cancer (re-) initiating cells within a protective tumour microenvironment which seems to be responsible for resistance to pharmacological treatment, and for relapse, at-least in blood cancers. Studies on both cultured and patients' primary MM cells showed a strong correlation between CXCR-4/SDF-1 activation and MM-related bone disease. Besides the different cell types constituting the BM niche, primary MM cells themselves secrete SDF-1, which results in autocrine stimulation of plasma cell proliferation. Therefore, the CXCR4/SDF-1 axis represents a highly relevant molecular target in MM and other cancers due to its important role in pathogenesis and its potential involvement as a mediator of resistance to treatment. Moreover, this represents a novel tool for sensitive, and non-invasive in vivo quantification of CXCR-4 which will help in selecting patients for CXCR4-directed treatment.

Summary:

34 newly-diagnosed MM patients between January, 2018 – June, 2019 underwent both 18F-FDG PET/CT and 68Ga-Pentixafor PET/CT imaging within a week. 68Ga-Pentixafor was synthesized in-house in PGIMER, Chandigarh. PET findings of both the tracers were compared and used to stage the patients as I-a, I-b, II & III using the Durie Salmon Plus Staging System. As per this staging system, the stage I-a patients demonstrated no lesion, stage I-b patients had <5 lesions or mild diffuse BM uptake, stage II patients had 5-20 lesions or moderately diffuse BM uptake, and stage III patients had >20 lesions or severe marrow uptake respectively. Overall, in comparison to 18FDG PET-CT, 68Ga-Pentixafor changed the disease stage in 14/34 (41%) patients. Four patients were upstaged from stage I-a to I-b, 2 patients from stage I-a to III, one patient from stage I-b to II, 3 patients from stage I-b to III and three patients from stage II to stage-III respectively. On the other hand, in all the stage-III patients, the disease stage remained the same, except one patient in whom the disease stage was downstaged from III to II. Disease extent was defined by avidity i.e., SUVmax of lesions. With respect to SUVmax, 68Ga-Pentixafor showed higher disease extent (higher SUV) in two-third cases (n=23;68%), and similar SUV in one-fourth (n=9;25%) of them. Moreover, on co-relating imaging with BM findings, only 68Ga-Pentixafor TBRmax (SUVmax of each lesion divided by SUVmax of the mediastinal blood pool) correlated significantly ($p=0.421;0.013$) with BM plasma cell percentage. Thus, they observed that 68Ga-Pentixafor proved superior or equal to 18F-FDG for the detection of MM lesions in 94% patients, however, 18F-FDG was superior in only 6% patients. To conclude, rather than replacing 18FDG PET-CT, it appears that dual 68Ga-Pentixafor/18FDG PET-CT imaging may help in determining the tumour heterogeneity in MM..

“Original
research
publications
from India”

Publications
from Indian
Faculty from
Sep 22 - Nov 22



“Original research publications from India” Publications from Indian Faculty from Sep - Nov 2022

- Punatar S, Katti K, Rajamanickam D, et al. Role of Curcumin in Reducing Toxicities Associated With Mucosal Injury Following Melphalan-Based Conditioning in Autologous Transplant Setting. *Cell Transplant*. 2022;31:9636897221086969. doi:10.1177/09636897221086969
- Kumar L, Sahoo RK, Kumar S, et al. Autologous stem cell transplant for multiple myeloma: Impact of melphalan dose on the transplant outcome [published online ahead of print, 2022 Nov 23]. *Leuk Lymphoma*. 2022;1-10. doi:10.1080/10428194.2022.2148214
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“Original research publications from India” Publications from Indian Faculty from Sep - Nov 2022

- Vashist A, Gupta N, Nafees S, Sharma A. Habb-e-Asgandh Suppresses Cell Proliferation and Induces Apoptosis through Mitochondria Dysfunction in Multiple Myeloma Cells (RPM18226). *Asian Pac J Cancer Prev.* 2022;23(11):3629-3639. Published 2022 Nov 1. doi:10.31557/APJCP.2022.23.11.3629
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- Bhuyan B, Padhi S, Das PK, Biswal S. Hypercalcemia (C), renal dysfunction (R), anemia (A), and lytic bone lesion (B) (CRAB) as presenting features in non myelomatous malignancies: A case report and review of the literature. *Int J Lab Hematol.* 2022;44(5):e198-e203. doi:10.1111/ijlh.13847
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ASH 2022 abstracts in Plasma Cell Dyscrasias from India

- Rudra Prasad Dutta, Rohit Kumar, Prashant R. Tembhare, et al. Targeting Transcriptional Kinase of CDK7 Halts Proliferation of Multiple Myeloma Cells By Modulating the Function of Canonical NF- κ B Pathway and Cell Cycle Regulatory Proteins. *Blood* 2022; 140 (Supplement 1): 7058–7059. doi: <https://doi.org/10.1182/blood-2022-168357>
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- Fen Saj, Prasanth Ganesan, Smita Kayal, et al. Pomalidomide, Bortezomib, and Dexamethasone Combination Chemotherapy for Newly Diagnosed Multiple Myeloma: Pomace Phase II Study. *Blood* 2022; 140 (Supplement 1): 12612. doi: <https://doi.org/10.1182/blood-2022-165013>
- Sandeep Abhijit Pattnaik, Hisham Ahamed, et al. Light Chain(AL) Cardiac Amyloidosis: A Real World Data on Therapy and Outcomes. *Blood* 2022; 140 (Supplement 1): 12578–12580. doi: <https://doi.org/10.1182/blood-2022-169597>
- Abhishek Singh, Anusha Chidharla, Nidhi Jain, et al. IgD Multiple Myeloma, Does It Still Have a Poor Prognosis?. *Blood* 2022; 140 (Supplement 1): 12520. doi: <https://doi.org/10.1182/blood-2022-170630>
- Abstract – 469. Prashant R. Tembhare, Harshini Sriram, Twinkle Khanka, et al. Circulating Clonal Plasma Cells at Diagnosis and Peripheral Blood Measurable Residual Disease Assessment Provide Powerful Prognostication Biomarkers in Newly-Diagnosed Multiple Myeloma Patients Treated without Autologous Transplant.

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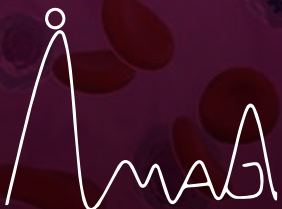
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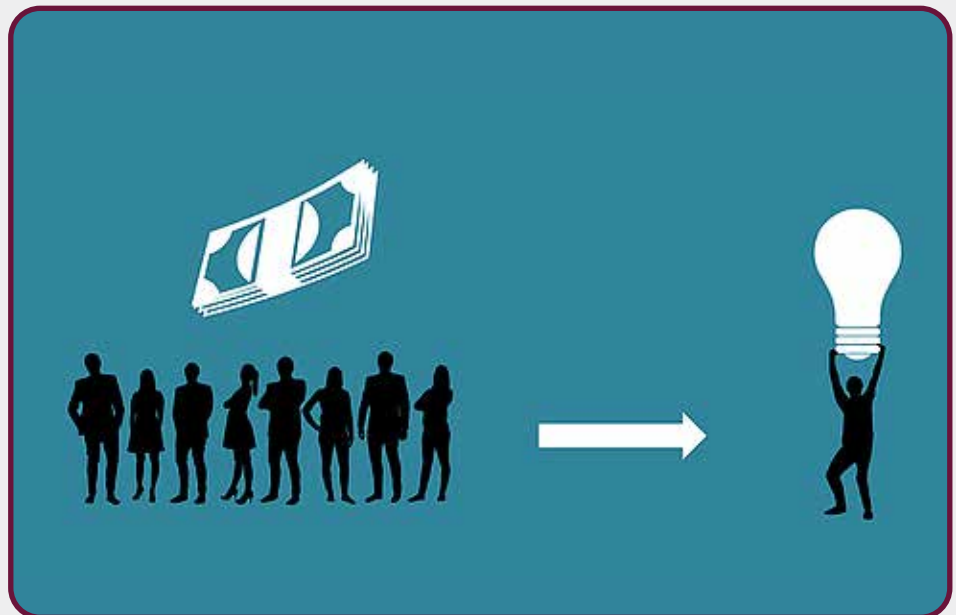


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Annual Conference of
Mumbai Hematology Group (MHG)

January 26th to January 29th 2023, Mumbai.

[Registration Link](https://in.eregnow.com/ticketing/register/ash-mhg2023)

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4TH IMMUNE EFFECTOR CELL THERAPIES IN MULTIPLE MYELOMA WORKSHOP

March 24 - 25, 2023

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[Registration Link](https://www.myelomasociety.org/events/20th-ims-annual-meeting/)

<https://www.myelomasociety.org/events/20th-ims-annual-meeting/>

20th Annual Meeting and Exposition

SEPTEMBER 27-30, 2023

Megaron Athens Concert Hall | Athens, Greece

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