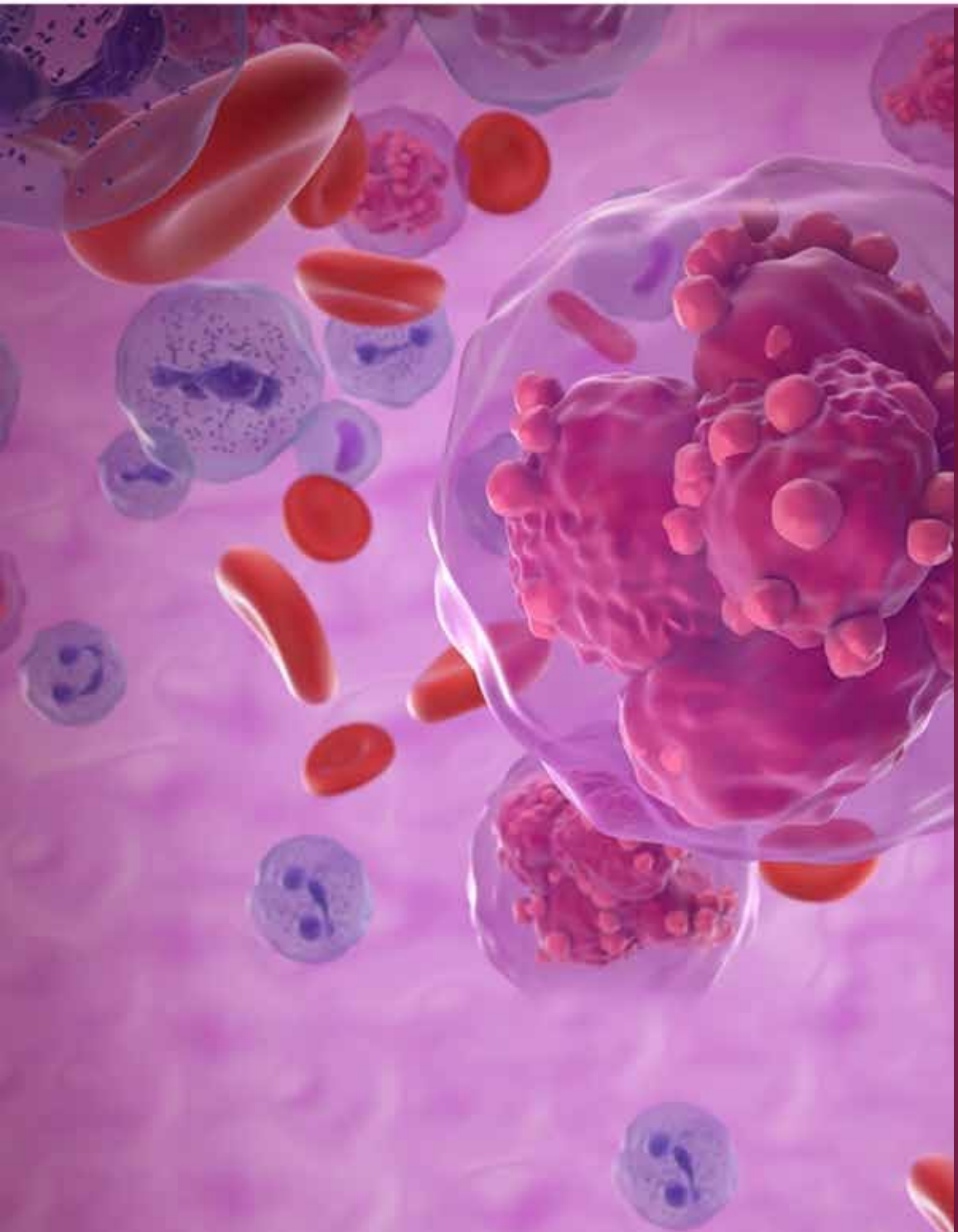
NEWSLETTER

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

An Indian Myeloma Academic Groupe Publication (IMAGe)



WISHING YOU A

★ HAPPY NEW YEAR ★

"Inshorts- Through expert's lens" Journal Club

Dr. Aditya Jandial
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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

"Inshorts- Through expert's lens" Journal Club

Dr. Sachin Puntar
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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 that 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=huH0PlHTVrk

"Inshorts- Through expert's lens" Journal Club

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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

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