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https://reachmd.com/programs/cme/clinical-evidence-for-anti-cd38based-frontline-regimens-in-transplant-ineligible-patients-with-multiple-myeloma/60962/

Released: 08/24/2026
Valid until: 08/24/2027
Time needed to complete: 38m

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Clinical Evidence for Anti-CD38–Based Frontline Regimens in Transplant-Ineligible Patients With Multiple Myeloma

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Dr. Usmani:
Welcome to this educational activity with GLC. I'm Dr. Saad Usmani. Today, I'll be reviewing pivotal data on anti-CD38-based frontline regimens in transplant-ineligible patients with multiple myeloma.

Let's start with the phase 3 MAIA study, which looked at the combination of daratumumab with LenDex, comparing it to LenDex in transplant-ineligible newly diagnosed multiple myeloma patients. This trial enrolled 737 patients in a 1:1 randomization, and treatment was until disease progression or intolerance.

The primary endpoint for this trial was progression-free survival, with key secondary endpoints revolving around response, CR or better, VGPR or better rates, MRD negativity, overall response rate, overall survival, and safety were also looked at. And let's review the data here.

So this was the first clinical trial that actually demonstrated over 90% response rates in the transplant-ineligible patient population. Very high VGPR and CR rates compared to the historic controls in previous trials, as well as the standard-of-care arm. These were statistically significant, and the depth of response continued to get better with a longer follow-up, and the clinical trial read out favorably for the primary endpoint of progression-free survival. So the initial data that was shown at the 5-year mark demonstrated that the median PFS had not been reached on DRd initially, and then with subsequent follow-up, it was around 62 months compared to 34 months. And if we look at the overall survival at the 5-year mark, it had been reached for Rd at around 64 months. At that time, it had not been reached in the MAIA study.

Now, the next phase of clinical trials was looking at the quadruplet induction, so adding anti-CD38s to the VRd as part of induction therapy, and then adding daratumumab to Rd during the maintenance phase. So this CEPHEUS clinical trial looked at the transplant-ineligible or deferred patient population. The standard-of-care arm was the SWOG S0777 clinical trial-like design, so VRd as induction for eight cycles, followed by Rd as maintenance on a continuous schedule, and daratumumab was added on the experimental arm in both those phases.

Overall MRD-negative CR rate was the primary endpoint, with key secondary endpoints being PFS, sustained MRD-negative CR rates beyond 12 months, and of course overall survival.

If we look at the MRD negativity overall rate at 10^{-5} as well as 10^{-6} thresholds, they were significantly higher for the experimental arm, which was the D-VRd arm, 61 versus 40-odd percent. If we look at sustained MRD negativity beyond 12 months, that was superior in the quadruplet arm, as was the sustained MRD-negative CR rate beyond 24 months in favor of D-VRd for both the 10^{-5} and 10^{-6} threshold.

Now, if we look at the PFS for the intent-to-treat population, it was favorable for the D-VRd arm, and with subsequent follow-up of 76 months, which was just reported, focusing on the transplant-ineligible patient population, the median PFS had still not been reached for the D-VRd arm, and for the VRd arm it was 50.2 months. So speaking to the efficacy that translated from the depth of response accomplished with those regimens.

Now, the IMROZ clinical trial looked at a different anti-CD38, isatuximab. Very similar kind of design to the CEPHEUS, where a quadruplet induction was followed by a three-drug maintenance strategy. This clinical trial looked at PFS as the primary endpoint, which was met in favor of the quadruplet. So the same principle, very similar kind of PFS curves as you saw with the CEPHEUS clinical trial. And more importantly, the message about depth of response is the same. So overall response rates were higher in the Isa-VRd arm. Depth of response was significantly better, and that really came from the MRD-negative rate and sustained MRD negativity that was seen.

So, if we were to summarize all of these clinical trials, picking the right strategy for myeloma patients at initial diagnosis is very important. Anti-CD38-based quadruplets, Dara-RVd as well as Isa-RVd, provide better depth of response. They translate into better PFS for fit and intermediate-fit patients.

I think DRd still is a very acceptable standard of care for the older frail myeloma patients who are transplant ineligible. I think supportive care measures is very important, and future therapies such as bispecifics and biomarker-driven small molecules will be incorporated for this patient population, making the outcomes for these patients even better in the future.

Well, my time is up. I hope you found this brief overview useful. Thank you for listening.

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