Highlights in Multiple myeloma

Final analysis of the MASTER trial: MRD-driven Daratumumab-KRd therapy in newly diagnosed MM patients

Dr. Costa presented the final analysis of the phase 2 MASTER trial (1). This study evaluated the efficacy and safety of a quadruplet Daratumumab-KRd induction followed by autologous stem cell transplant and further consolidation with Daratumumab-KRd blocks guided by MRD negativity. It is worth noting that MASTER was deliberately enriched for high-risk MM patients, with 37 % of patients with one high-risk (HR) genetic abnormality and 20 % with at least 2 adverse genetic features. In patients with two successive MRD-negative evaluations (defined as MRDsure status) active treatment was discontinued. The primary endpoint was the rate of MRD negativity, defined as 10^{-5} by NGS on bone marrow samples. Disease control of the observation cohort after reaching MRDsure was a key secondary endpoint. With a median follow-up period of 42.2 months, 123 participants were enrolled. The transition towards MRD sure status was accomplished in 71 % of the overall population, in 82 % of HR and 63 % of ultra-HR patients. Overall, 73 % of MRDsure patients remained treatment-free. The risk of disease progression was low in standard and HR patients (9 %), but significantly higher among the ultra-HR patients (47 %).

MRD negativity was highly prognostic at any given timepoint, but patients who reached MRD negativity later on still benefited from a longer PFS. The 36-month PFS rate was 88 %, 79 % and 50 % for patients with 0, 1, or 2+ high-risk features. In the ultra-HR cohort, a significant percentage of progression events occurred during the first induction phase.

Clinical significance

This is the first formal evaluation of an MRD-driven approach as a viable, tailored substitute for protracted maintenance therapy. In view of the overall costs of the expanding treatment options of multiple myeloma, such a research question is overdue. This treatment strategy resulted in a substantial prevalence of MRD negativity, even in the high-risk MM population. Still, there remains an unmet need for ultra-HR patients, where novel therapies may constitute a superior option.

KarMMa-3 Sub-analysis: Idecabtagene vicleucel (Ide-cel) versus standard regimens for high-risk myeloma

The phase 3 KarMMa-3 trial compared the efficacy in patients with triple-class exposed disease between Ide-cel and current standard regimens after 2 to 4 lines of therapy. The experimental arm met its primary endpoint, showing an improved median PFS of 13.3 vs. 4.4 months (HR: 0.49; 95 % CI: 0.38–0.65; $p < 0.001$), along with superior disease control rates (2).

Dr. Patel presented a post-hoc sub-analysis focusing on the high-risk population of KarMMa-3, which accounted for 85 % of the whole study population (3). Patients considered as high-risk presented with triple-class refractory status, extramedullary disease, adverse cytogenetic abnormalities, bone marrow infiltration greater than 50 % and advanced R-ISS stage.

With a median follow-up of 18 months in the intention-to-treat population, the efficacy advantage for Ide-cel as compared to standard therapy was preserved in the various high-risk subgroups: in the HR cytogenetics cohort, the median PFS was 11.9 vs. 4.2 months (HR: 0.61; 95 % CI: 0.41–0.90); in the EMD cohort, the PFS was 7.2 vs. 2.0 months (HR: 0.40; 95 % CI: 0.25–0.65); for the triple-class refractory patients the PFS resulted in 11.2 vs. 3.5 months (HR 0.46; 95 % CI: 0.34–0.62) and finally in high tumor burden patients 11 vs. 4.9 months (HR: 0.60; 95 % CI: 0.37–0.97). The R-ISS stage 3 subgroup showed only a trend towards benefit, possibly due to its small numbers. Overall response rates and in particular CRs were also improved, and responses were deeper with Ide-cel versus standard regimens.

Clinical significance

This sub-analysis showed that the benefit of Ide-cel was maintained across HR patients. Advancing CAR-T cellular therapy onto earlier lines could prove beneficial as T-cell fitness is likely better preserved.

Nevertheless, these data also hinted at a reduced efficacy of Ide-cel in high tumor burden scenarios, highlighting the need for future clinical trials to focus on more effective or different bridging strategies.

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References:

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2. Rodriguez-Otero P et al.: Ide-cel or Standard Regimens in Relapsed and Refractory Multiple Myeloma. N Engl J Med. 2023;388(11):1002-1014. doi: 10.1056/NEJMoa2213614.
3. Patel K et al.: Idecabtagene vicleucel (Ide-cel) vs standard regimens in patients with triple-class-exposed (TCE) relapsed and refractory multiple myeloma (RRMM): a KarMMa-3 analysis in high-risk subgroups. EHA 2023, Abstract S195.