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PLENARY ABSTRACTS

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Results of the Phase III Randomized Iskia Trial: Isatuximab-Carfilzomib-Lenalidomide-Dexamethasone Vs Carfilzomib-Lenalidomide-Dexamethasone As Pre-Transplant Induction and Post-Transplant Consolidation in Newly Diagnosed Multiple Myeloma Patients

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Background. The current standard treatment for transplant-eligible (TE) patients (pts) with newly diagnosed multiple myeloma (NDMM) consists of quadruplet induction with proteasome inhibitors, immunomodulatory agents, dexamethasone and

anti-CD38 monoclonal antibody followed by high-dose melphalan and autologous stem-cell transplant (MEL200-ASCT), with subsequent consolidation. The phase III IsKia trial assessed efficacy and safety of isatuximab-carfilzomib-lenalidomide-dexamethasone (IsaKRd) as pre-ASCT induction and post-ASCT consolidation vs KRd.

Methods. TE NDMM pts aged <70 years were enrolled and randomized. IsaKRd pts received 4 28-day cycles of Isa: 10 mg/kg IV days 1, 8, 15, 22 cycle 1, followed by 10 mg/kg days 1, 15 cycles 2-4; K: 20 mg/m ^{2} IV day 1 cycle 1, followed by 56 mg/m ^{2} IV days 8, 15 cycle 1 and days 1, 8, 15 cycles 2-4; R: 25 mg PO daily days 1-21; d: 40 mg PO days 1, 8, 15, 22; MEL200-ASCT and 4 consolidation cycles with IsaKRd at the same schedule. KRd pts received 4 KRd induction cycles; MEL200-ASCT and 4 KRd consolidation cycles (K, R and d at the same schedule as in the IsaKRd arm). The primary endpoint was the rate of minimal residual disease (MRD) negativity by next-generation sequencing (NGS; 10 $^{-5}$) after consolidation in the intention-to-treat (ITT) population. MRD was tested in all pts who achieved at least a very good partial response (≥VGPR). Key secondary endpoints were the rate of NGS MRD negativity (10 $^{-5}$) after induction and PFS. MRD rates were evaluated in an ITT analysis (pts with missing MRD data or who achieved ≤PR were considered as MRD positive). The data cut-off for the analysis was May 22, 2023.

Results. 302 pts were enrolled and randomized (151 in both the IsaKRd and KRd arms). Pt characteristics were well balanced between the two arms: median age was 61 vs 60 years, respectively; 18% vs 19% of pts had high-risk (HiR) cytogenetic abnormalities (CA) [del(17p) and/or t(4;14) and/or t(14;16)]; 9% vs 8% had ≥2 HiR CA [double hit; including del(17p), t(4;14), t(14;16) and gain/amp(1q)]. In ITT analysis, the rates of MRD negativity at the 10 $^{-5}$ cut-off after consolidation (primary endpoint) were 77% vs 67% (OR 1.67; p=0.049) with IsaKRd vs KRd; the respective rates of MRD negativity at the 10 $^{-6}$ cut-off were 67% vs 48% (OR 2.29; p<0.001); consistent MRD results were detected by next-generation flow. ≥VGPR after consolidation was 94% in both arms; ≥CR 74% vs 72% and sCR 64% vs 67% in the IsaKRd vs KRd arms. The MRD negativity advantage, both at 10 $^{-5}$ and 10 $^{-6}$, was retained in all subgroups analyzed (*Figure*), with similar benefit in pts with standard-risk (SR) and HiR features. In particular, the 10 $^{-5}$ MRD negativity rates with IsaKRd were 76% in HiR and 77% in double-hit pts, comparable to the one in SR pts (79%). In the KRd arm, the 10 $^{-5}$ MRD negativity rates were 58% in HiR and 53% in double-hit pts, inferior to the one in SR pts (70%). The 10 $^{-6}$ MRD negativity rates with IsaKRd were 72% in HiR, 77% in double-hit pts and 67% in SR pts. The MRD negativity rate after induction (first key secondary endpoint) was also significantly higher with IsaKRd vs KRd (10 $^{-5}$: 45% vs 26%, OR 2.34, p<0.001; 10 $^{-6}$: 27% vs 14%, OR 2.36, p=0.004), with a consistent benefit in all subgroups. After induction, the MRD negativity rates in HiR and double-hit pts treated with IsaKRd were: 10 $^{-5}$, HiR 60%, double-hit 54%; 10 $^{-6}$, HiR 40%, double-hit 31%. The MRD negativity rates after ASCT were also significantly better with IsaKRd vs KRd (10 $^{-5}$: 64% vs 49%, OR 1.93, p=0.006; 10 $^{-6}$: 52% vs 27%, OR 3.01, p<0.001), with a consistent advantage in all subgroups. At the current follow-up (median, 20 months, IQR 18-23), there was no difference in PFS (95% at 1 year in both arms). 55% of pts had ≥1 hematologic adverse events (AEs) with IsaKRd vs 43% with KRd; main grade 3-4 hematologic AEs in IsaKRd vs KRd were neutropenia (37% vs 22%) and thrombocytopenia (15% vs 17%). 41% of pts had ≥1 non-hematologic AEs with IsaKRd vs 37% with KRd, including infections (16% vs 12%), gastrointestinal (7% vs 5%), vascular (2% vs 7%) and cardiac events (1% vs 4%). Discontinuation for toxicity was 6% in IsaKRd vs 5% in KRd arms; treatment-related deaths were 4 with IsaKRd (2 COVID, 1 pneumonia, 1 pulmonary embolism) and 1 with KRd (septic shock).

Conclusion. In TE NDMM pts, the addition of isatuximab to KRd induction and consolidation significantly increased MRD negativity rates in every treatment phase as compared to KRd, with no new safety concerns. This benefit was retained in HiR pts.

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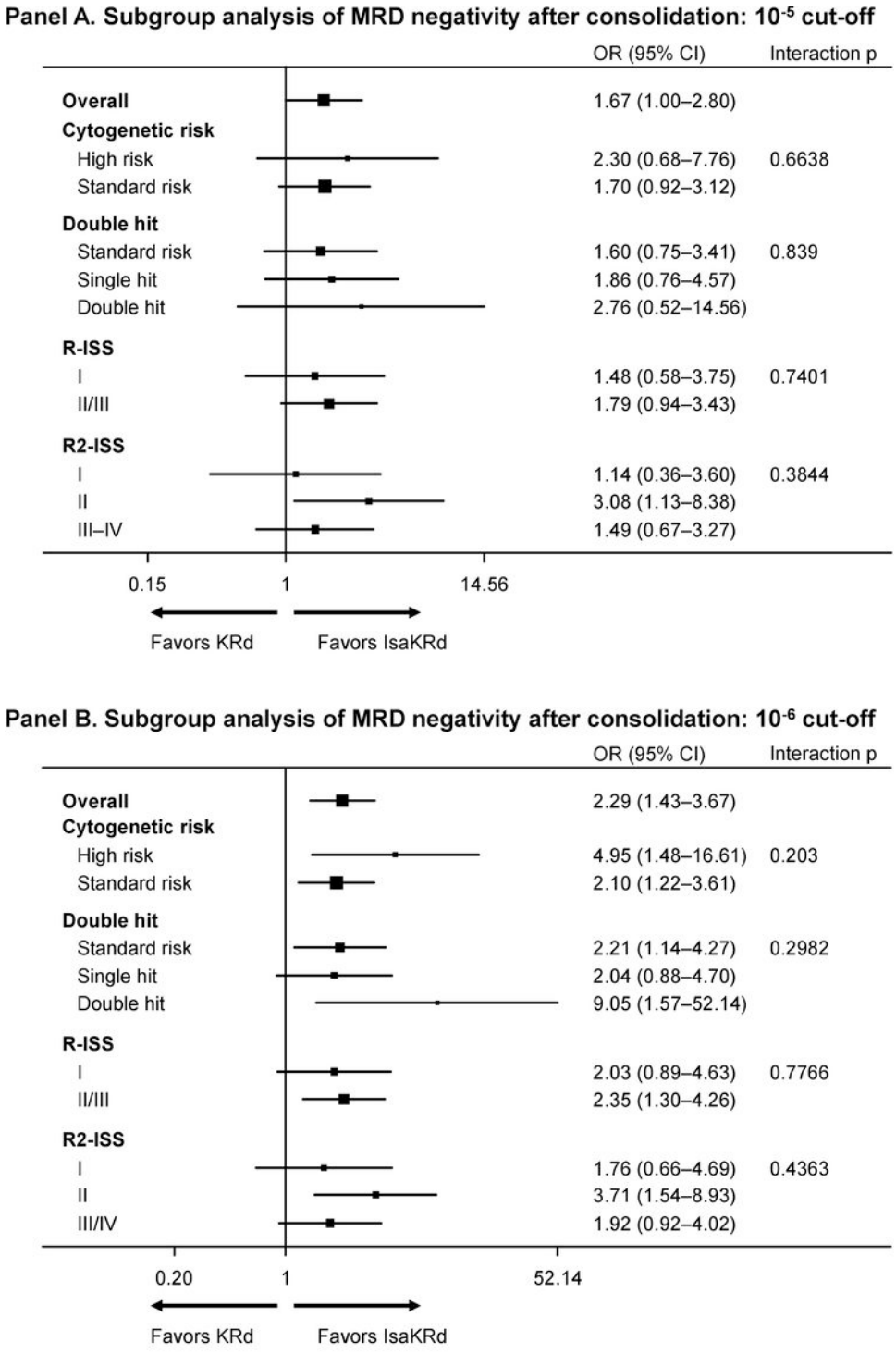
OffLabel Disclosure: This presentation includes information or discussion of the off-label use of a drug or drugs for the treatment of multiple myeloma: isatuximab, carfilzomib, lenalidomide, and dexamethasone.



Abbreviations. MRD, minimal residual disease; OR, odds ratio; CI, confidence interval; p, p-value; R-ISS, Revised International Staging System stage; R2-ISS, Second Revision of the International Staging System stage; K, carfilzomib; R, lenalidomide; d, dexamethasone; Isa, isatuximab.

Figure 1

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