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Survival Analysis of Newly Diagnosed Transplant-Eligible Multiple Myeloma Patients in the Randomized Forte Trial

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Background: Proteasome inhibitor (PI)-based induction/consolidation proved to be effective in newly diagnosed multiple myeloma (NDMM) patients (pts) eligible for melphalan 200 mg/m^2 plus autologous stem-cell transplantation (MEL200-ASCT). High response rates have been reported with carfilzomib (K) plus lenalidomide-dexamethasone (KRd) or cyclophosphamide-dexamethasone (KCd). Lenalidomide (R) alone is a standard of care for post-ASCT maintenance; K maintenance showed promising results in phase I/II studies, but no data on KR maintenance vs R are available.

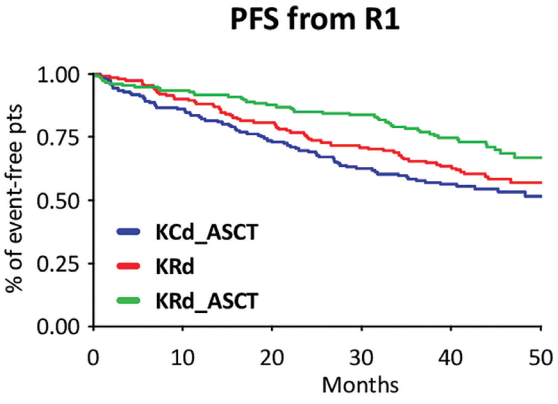
Aims: The aims of this analysis were to evaluate the progression-free survival (PFS) of KRd induction-ASCT-KRd consolidation (KRd_ASCT) vs 12 cycles of KRd (KRd12) vs KCd induction-ASCT-KCd consolidation (KCd_ASCT) and the PFS of KR vs R maintenance. Secondary aims were efficacy in different subgroups of pts and safety of the maintenance phase.

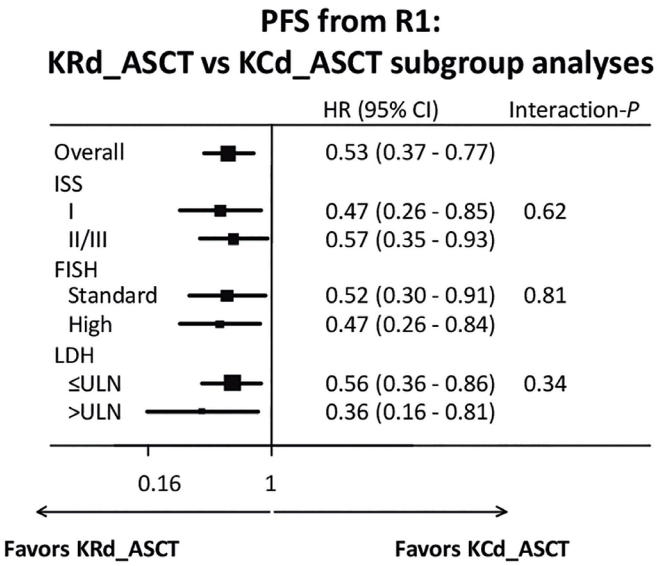
Methods: NDMM pts ≤65 years were randomized [R1: 1:1:1, stratification International Staging System (ISS) and age] to: *KRd_ASCT:* 4 28-day cycles with KRd induction (K 20/36 mg/m^2 IV days 1,2,8,9,15,16; R 25 mg days 1-21; dexamethasone [d] 20 mg days 1,2,8,9,15,16) followed by MEL200-ASCT and 4 KRd consolidation cycles; *KRd12:* 12 KRd cycles; KCd_ASCT: 4 28-day induction cycles with KCd (K 20/36 mg/m^2 IV days 1,2,8,9,15,16; cyclophosphamide 300 mg/m^2 days 1,8,15; d 20 mg days 1,2,8,9,15,16) followed by MEL200-ASCT and 4 KCd consolidation cycles. Thereafter, pts were randomized (R2) to maintenance with KR (K 36 mg/m^2 days 1,2,15,16, subsequently amended to 70 mg/m^2 days 1,15 for up to 2 years; plus R 10 mg days 1-21 every 28 days until progression) or R alone (10 mg days 1-21 every 28 days until progression). Centralized minimal residual disease (MRD) evaluation (8-color second-generation flow cytometry, sensitivity 10^{-5}) was performed in pts achieving ≥very good partial response before maintenance and every 6 months (m) during maintenance. Data cut-off was June 30, 2020.

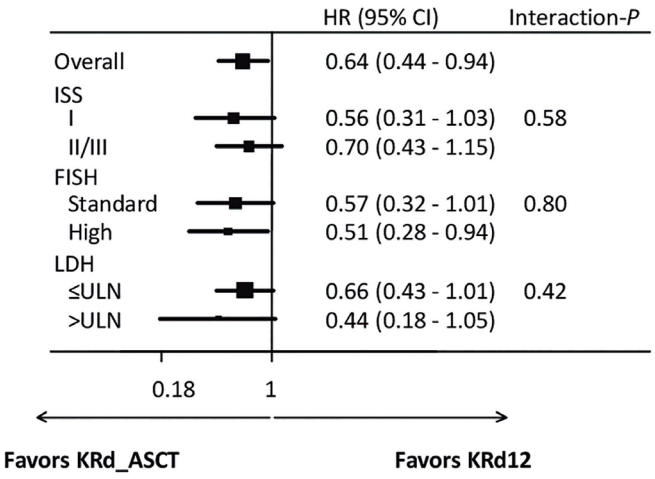
Results: 474 NDMM pts were randomized (KRd_ASCT, n=158; KRd12, n=157; KCd_ASCT, n=159) and analyzed. Pt characteristics were well balanced. Intention-to-treat (ITT) data of pre-maintenance MRD (KRd_ASCT, 62%; KRd12 56%, KCd_ASCT 43%) and safety of the induction/consolidation phases in the 3 arms were already reported (F. Gay et al. ASH 2018; S. Oliva et al. ASH 2019). After a median follow-up from R1 of 45 m, median PFS was not reached with KRd_ASCT, 57 m with KRd12 and 53 m with KCd_ASCT (KRd_ASCT vs KCd_ASCT: HR 0.53, *P*<0.001; KRd_ASCT vs KRd12: HR 0.64, *P*=0.023; KRd12 vs KCd_ASCT: HR 0.82, *P*=0.262). The benefit of KRd_ASCT vs both KCd_ASCT and KRd12 was observed in most subgroups (Figure). 3-year overall survival (OS) was 90% with KRd_ASCT and KRd12 vs 83% with KCd. 356 pts (KR, n=178; R, n=178) were randomized to maintenance; pt characteristics, pre-maintenance response (≥complete response [CR]: KR 62% vs R 59%; stringent CR: KR 50% vs R 48%) including MRD negativity (KR 65% vs R 66%) in the 2 groups were well balanced. After a median follow-up from R2 of 31 m and a median duration of maintenance of 27 m in both arms, 46% of MRD-positive pts at randomization turned negative in KR vs 32% in R (*P*=0.04). By ITT analysis, 3-year PFS from R2 was 75% with KR vs 66% with R (HR 0.63; *P*=0.026). The benefit of KR vs R was observed in most subgroups (Figure). 3-year OS was 90% in both arms.

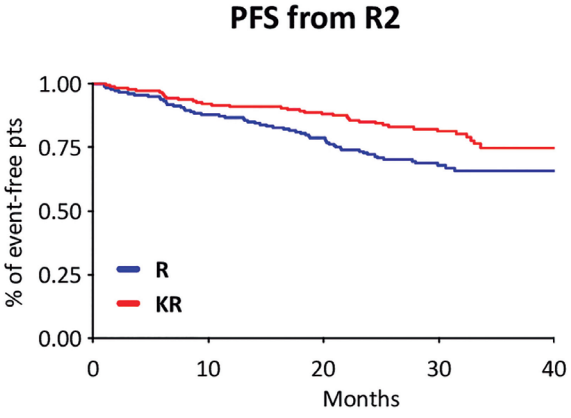
During maintenance, a similar proportion of pts experienced ≥1 grade (G)3-4 hematologic adverse events (AEs)/serious AEs (SAEs) in the 2 arms (KR 22% vs R 23%); the most frequent were neutropenia (KR 18% vs R 21%) and thrombocytopenia (KR 3% vs R 3%). Rate of ≥1 G3-4 non-hematologic AEs/SAEs was higher with KR (27%) compared with R (15%), *P*=0.012; the most frequent were infections (KR 4% vs R 7%); all other events were reported in ≤5% of pts and included: gastrointestinal (KR 5% vs R 2%), cardiac (KR 4% vs R 1%), hypertension (KR 3% vs R 0%), and thrombotic microangiopathy (3% vs 0%). 4 pts developed a second primary malignancy in KR (breast 1 pt; thyroid 1 pt; myelodysplastic syndrome 1 pt; non-melanoma skin cancer 1pt) vs 1 pt in R (acute lymphoblastic leukemia). Dose reductions of R were reported in 23% of KR and 29% of R pts; dose reductions of K were reported in 20% of pts. The rate of discontinuation due to AEs was similar in the 2 arms (KR 10% vs R 9%).

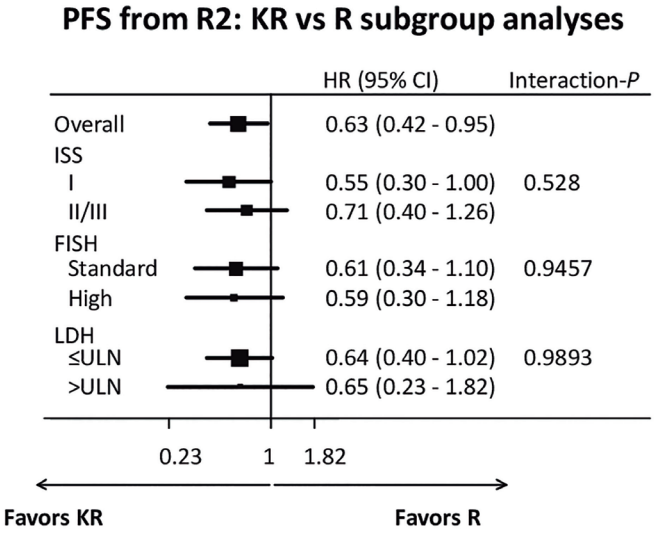
Conclusions: Treatment with KRd_ASCT significantly improved PFS compared with both KRd12 and KCd_ASCT. Maintenance with KR also improved PFS vs R.











Abbreviations. PFS, progression-free survival; R1, first randomization (induction treatment); R2, second randomization (maintenance treatment); pts, patients; K, carfilzomib; C, cyclophosphamide; R, lenalidomide; d, dexamethasone; KRd12, 12 cycles of KRd; ASCT, autologous stem-cell transplantation; HR, hazard ratio; CI, confidence interval; *P*, p-value; ISS, International Staging System stage; FISH, fluorescence *in situ* hybridization; LDH, lactate dehydrogenase; ULN, upper limit of normal.

Disclosures:

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OffLabel Disclosure: The presentation includes discussion of off-label use of a drug or drugs for the treatment of multiple myeloma (including carfilzomib, cyclophosphamide, lenalidomide and dexamethasone).

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