# QUAD PRO QUO: DECIPHERING THE ROLE OF ANTI-CD38 QUADRUPLETS IN NEWLY DIAGNOSED MULTIPLE MYELOMA (NDMM)

## Introduction

Disease outcomes in multiple myeloma (MM) have improved with the development of multi-drug combinations and in transplant eligible (Te) patients, autologous stem cell transplantation (ASCT).[1] In patients with newly diagnosed MM (NDMM), recommended triplet induction combinations consist of a proteasome inhibitor such as bortezomib (V) or carfilzomib (K), and an immunomodulatory drug (IMiD) such as lenalidomide (R) or cyclophosphamide (C), in combination with dexamethasone (d).[2,3]

VRd is commonly used as a frontline treatment for NDMM,[2,3] and the potential role of KRd as the backbone of therapy is currently less well-established. Additionally, with the availability of the anti-CD38 monoclonal antibodies (mAbs), daratumumab (D) and isatuximab (Isa) for MM,[4,5] there is a need to re-assess the optimal treatment approach for patients with NDMM. This is particularly important as selecting an optimal treatment regimen for patients with NDMM is key for maximising clinical outcomes.[6] This article presents highlights from a sponsored symposium at the European Hematology Association (EHA) 2023 Congress considering the role of KRd- anti-CD38 mAb quadruplets in NDMM.

## Partnering KRd with anti-CD38 mAbs

The potential to improve responses in Te patients with NDMM by adding anti-CD38 mAbs to triplet therapy has been demonstrated in the Phase III CASSIOPEIA (DVTd vs VTd), Phase III GMMG-HD7 (Isa-RVd vs RVd), and Phase II GRIFFIN (DVRd vs VRd) trials. In CASSIOPEIA (45 months follow-up) median progression-free survival (mPFS) was longer with DVTd versus VTd (not reached [NR] vs 51.5 months; hazard ratio [HR]: 0.58; P<0.0001) and DVRd versus VRd in GRIFFIN (50 months follow-up) (NR vs NR; HR: 0.45; P=0.0324); mPFS data are not mature for GMMG-HD7.[7-11] Additionally, in all three trials, patients treated with these quadruplets showed an increased depth of response including minimal residual disease negativity (MRD–) ($10^{-5}$ by multiparametric flow cytometry [MFC]) status or next generation sequencing [NGS]), and a complete response or better (≥CR) or very good partial response or better (≥VGPR) with quadruplet vs triplet regimens.[9-11]

touch™ ONCOLOGY

**Table 1.** Summary of the studies investigating KRd with anti-CD38 mAbs in NDMM

| Studies | Patient population | Treatment arm(s) | Key results (to date) |
|---|---|---|---|
| FORTE (Phase II)[12] | Te (n=474) | • KRd induc. → ASCT → KRd conso. → KR or R maint.<br>• KCd induc. → ASCT → KCd conso. → KR or R maint.<br>• KRd induc. and conso. → KR or R maint. | • **Median (IQR) follow-up (from 1st randomization):** 51 (46, 55) months<br>KRd-ASCT versus KCd-ASCT<br>• **mPFS:** NR vs 53 months; HR: 0.54 (95% CI: 0.38; 0.78); P=0.0008<br>• **MRD− (MFC 10−5)**: 47% vs 25%; OR: 2.72; P<0.0001<br>• **Non-hematologic AEs**: 92% vs 57%<br>• **Discontinuation due to toxicity:** 4% vs 3%<br>KRd-ASCT versus KRd<br>• **mPFS**: NR vs 55 months; HR: 0.61 (95% CI: 0.43, 0.88); p=0.0084<br>• **MRD− (MFC 10−5)**: 47% vs 35%; OR: 1.69 (95% CI: 1.07, 2.66); p=0.024 |
| ENDURANCE (Phase III)[13] | Te, no immediate intent for transplant (n=1087) | • KRd induc. → R maint.<br>• VRd induc. → R maint. | • **Median (IQR) follow-up**: 9 (5–23) months<br>KRd vs VRd<br>• **mPFS**: 34.6 vs 34.4 months; HR: 1.04 (95% CI: 0.83, 1.31); P=0.74<br>• **Grade ≥3 non-hematologic toxicities**: 48% vs 41%<br>• **Treatment discontinuation due to AEs**: 10% vs 17% |
| Real-world retrospective study[14] | Te and Ti (n=389) | • KRd<br>• VRd | • **Median (95% CI) follow-up**: 59 (55, 63)<br>KRd vs VRd<br>• **5-year PFS**: 67% vs 56%; P=0.027<br>• **5-year OS**: 90% vs 80%; P=0.053<br>• **Discontinuation due to AEs**: 7% vs 10% |
| GMMG-CONCEPT (Phase II)[21] | Te (N=127) and Ti (N=26), high-risk[a] | • Te: Isa-KRd induc.→ ASCT → Isa-KRd conso. → Isa-KR maint.<br>• Ti: Isa-KRd induc. and conso. → Isa-KR maint. | Te patients<br>• **Post-consolidation MRD− ($10^{-5}$ by NGF)**: 68% (P=0.0004)<br>• **≥CR after induction**: 49%<br>• **≥CR at end of consolidation**: 73%<br>Ti patients<br>• **Post-consolidation MRD− ($10^{-5}$ by NGF)**: 54% (P=0.012)<br>• **≥CR after induction**: 38%<br>• **≥CR at end of consolidation**: 58%<br>Te and Ti patients<br>• **Safety**: profile consistent with known toxicities of the individual agents |
| IFM 2018-04 (Phase II)[20] | Te high-risk (N=50)[b] | • DKRd induc. → ASCT → DKRd conso. → ASCT → DR maint. | • **Median follow-up**: 19 months<br>• **≥VGPR post-induction**: 91%<br>• **MRD− rate post-induction**: 62%<br>• **18 month PFS**: 92%<br>• **Safety**: no new signals observed |
| ADVANCE (Phase II)[22] | Te (n=TBC) | • DKRd induc.<br>• KRd induc.<br>• VRd induc.<br>• Optional ASCT in MRD+ patients and subsequent R maint. | No results reported as of EHA 2023 |
| SKylaRk (Phase II)[23] | Te (N=50) | • Upfront transplant: Isa-KRd induc. → ASCT → Isa-KRd conso.<br>• Deferred transplant: Isa-KRd induc.<br><br>Maintenance:<br>• High-risk: Isa-KR<br>• Standard risk: R | • **Median follow-up**: 15 months<br>Upfront transplant<br>• **≥CR rate (4 cycles)**: 38%<br>• **≥CR rate (8 cycles)**: 67%<br>• **MRD− rate (4 cycles):** 43%<br>• **MRD− rate (8 cycles)**: 74%<br>All patients<br>• **15.4 month PFS rate**: 89%<br>• **Safety**: Isa-KRd was well-tolerated and consistent with previous reports of similar regimens |

*Continued*

touch™ ONCOLOGY

**Table 1.** Continued

| Studies | Patient population | Treatment arm(s) | Key results (to date) |
|---|---|---|---|
| IsKia/EMN24 (Phase III)[26] | Te (n=TBC) | • Isa-KRd vs KRd induc. → ASCT → Isa-KRd vs KRd conso. → Isa-KRd vs KRd de-intensification → optional R maint. | No results reported as of EHA 2023 |
| MIDAS (Phase III)[26] | Te (n=TBC) | • Isa-KRd induc.<br>Subsequent:<br>• MRD− patients: Isa-KRd or ASCT + Isa-KRd conso. → R maint.<br>• MRD+ patients: ASCT + Isa-KRd conso. or tandem ASCT → Isa + iber maint. | No results reported as of EHA 2023 |
| MASTER (Phase II)[27,28] | Te (N=123) | • DKRd induc. → ASCT → DKRd conso. → R maint.<br>• MRD-SURE (treatment-free observation if 2nd consecutive MRD− assessment) | • **Median follow-up**: 34 months<br>• **MRD− consolidation (10−5 by NGS)**: 81%<br>• **Entered treatment-free observation (2 consecutive MRD− assessments**: 71%<br>• **≥VGPR (induction cycle 2)**: 63%<br>• **≥VGPR (consolidation)**: 98%<br>• **Safety**: quadruplet therapy with DKRd was well-tolerated |
| MANHATTAN (Phase II)[29] | Te or Ti (N=41) | • DKRd induc. → SoC | After ≤8 cycles<br>• **Median follow-up**: 11 months<br>• **MRD− (10−5 by MFC)**: 71%<br>• **≥VGPR**: 95%<br>• **1-year PFS**: 98%<br>• **Safety**: No added toxic effects |

*[a]ISS II or III plus ≥1 of: del17p, t[4;14], t[14;16] or 1q21 [≥4 copies]; [b]≥1 of: del17p, t[4;14] or t[14;16].*
*AE, adverse events; ASCT, autologous stem cell transplantation; C, cyclophosphamide; CI, confidence interval; Conso., consolidation; CR, complete response; D, daratumumab; d, dexamethasone; EHA, European Hematology Association; K, carfilzomib; Iber, iberdomide; IMiD, immunomodulatory; Induc., Induction; IQR, interquartile range; Isa, isatuximab; ISS, International Staging System; Maint, maintenance; MFC, multiparametric flow cytometry; mPFS, median progression-free survival; MRD−, minimal residual disease negativity; NDMM, newly diagnosed multiple myeloma; NGF, next generation flow cytometry; NR, not reached; PRF, progression-free survival; R, lenalidomide; SoC, standard of care; Te, transplant eligible; Ti, transplant ineligible; V, bortezomib; VGPR, very good partial response or better.*

Current evidence for the use of KRd as frontline therapy is supported by the FORTE and ENDURANCE trials, and a real-world study (**Table**). The Phase II FORTE study assessed KRd or KCd for 4 induction and consolidation cycles, both with post-induction ASCT or 12 KRd induction and consolidation cycles without ASCT, all followed by 1:1 randomization to KR or R maintenance in Te NDMM.[12] Although still in progress (51 months of follow-up from 1st randomization), the study has demonstrated promising mPFS results with KRd-ASCT versus KCd-ASCT (NR vs 53 months; HR: 0.54 [95% CI: 0.38; 0.78]; P=0.0008) and versus KRd 12 cycles (55 months). One-year sustained MRD− (MFC $10^{-5}$) results were also improved with KRd-ASCT (47%) versus KCd-ASCT (25%; odds ratio [OR]: 2.72; P<0.0001) and versus KRd 12 cycles (35%; OR: 1.69; P=0.024).[12] Although, non-hematologic adverse events (AEs) were more frequent with KRd than KCd (92% vs 57%), the rate of discontinuation due to toxicity after induction was similar (4% vs 3%).[12]

The Phase III ENDURANCE study assessed 12 cycles of VRd versus 9 cycles of KRd followed by subsequent randomization to R maintenance for 2 years or until progressive disease in patients with NDMM with no immediate intent for transplant.[13] The results for the primary endpoint, PFS from 1st randomization indicated similar efficacy of KRd and VRd (34.6 vs 34.4 months; HR: 1.04 [95% CI: 0.83, 1.31]; P=0.74). In terms of safety, although there were more Grade ≥3 non-hematologic toxicities with KRd versus VRd (48% vs 41%), more patients discontinued treatment due to AEs with VRd versus KRd arm (17% vs 10%).[13]

A real-world, single-centre, retrospective study assessed patients treated with frontline VRd or KRd between 2015 and 2022.[14] The results indicated improved 5-year PFS with KRd vs VRd (67% vs 56%; P=0.027), but with no difference in 5-year overall survival (OS) (90% vs 80%; P=0.053). Additionally, discontinuation rates due to AEs were lower with KRd than VRd (7% vs 10%).[14]

Ongoing questions for quadruplets include optimal dosing for carfilzomib and the choice of proteasome inhibitor (K vs V) in different patient populations. There are currently various carfilzomib dosing schedules approved in relapsed/refractory (RR) MM and being explored for induction and consolidation in NDMM.[15,16] A post-hoc analysis of the ENDEAVOR, ARROW, and CHAMPION-1 studies found no difference in PFS and safety profile with weekly and twice weekly dosing of carfilzomib.[17] In terms of selecting appropriate patients, the safety profiles of carfilzomib and bortezomib need to be taken into consideration, with carfilzomib associated with more frequent cardiac toxicities, and bortezomib with peripheral neuropathy.[13,14]

## KRd-anti-CD38 mAb combinations in high-risk NDMM

Previous evidence has indicated that KRd versus Rd improves outcomes in high-risk patients with RRMM. A sub-analysis of the randomized, open-label, Phase III ASPIRE trial found that in patients with 1–3 prior lines of therapy, KRd versus Rd significantly extended mPFS in both high-risk (23.1 vs 13.9 months; HR: 0.70 [95% CI: 0.43; 1.16]; P=0.0829) and standard-risk (29.6 vs 19.5 months; HR: 0.66 [95% CI: 0.48; 0.90]; P=0.0039) patients.[18] However the incidence of Grade ≥3 treatment-emergent AEs was higher with KRd versus Rd (89% vs 78%) in high-risk patients.[18] Additionally, in a sub-analysis of the FORTE trial, KRd improved both PFS and OS in patients with high-risk (1) and ultra-high risk (≥2) cytogenetics versus standard-risk patients at 4 years from first randomization.[19] Additionally, real-world patients with NDMM receiving KRd in the US are significantly (P=0.021) more likely to have high-risk cytogenetics than patients receiving VRd (46% versus 34%), suggesting that KRd is a relevant treatment for high-risk patients.[14]

Evidence for the benefit of adding anti-CD38 mAbs to KRd in patients with high-risk NDMM comes from the GMMG-CONCEPT and IFM 2018-04 trials (**Table**).[20,21] The Phase II GMMG-CONCEPT trial assessed Isa-KRd as induction and consolidation in both Te and transplant ineligible (Ti) patients.[21] Isa-KRd was given for 6 induction cycles followed by ASCT in Te patients versus 8 Isa-KRd induction cycles in Ti patients, both followed by 4 cycles of Isa-KRd consolidation and 2 years of Isa-KR maintenance in a high-risk NDMM population (International Staging System [ISS] II or III plus ≥1 of: del17p, t[4;14], t[14;16] or 1q21 [≥4 copies]).[21] The study met its primary endpoint of post-consolidation MRD– ($10^{-5}$ by next generation flow cytometry [NGF]) rate of 68% in the 93 Te patients (P=0.0004) and 54% in the 24 Ti patients (P=0.012). Isa-KRd also resulted in responses which deepened over time, from a ≥CR of 49% (Te) and 38% (Ti) after induction to 73% (Te) and 58% (Ti) at the end of consolidation. Finally, Isa-KRd was well-tolerated, with an overall safety profile consistent with the known toxicities of the individual agents.[21]

In the Phase II IFM 2018-04 study, 50 high-risk (≥1 of: del17p, t[4;14] or t[14;16]) Te NDMM patients received 6 DKRd induction cycles, followed by ASCT, 4 DKRd consolidation cycles, a second ASCT then DR maintenance for 2 years.[20] Patients achieved deep responses with DKRd induction, including ≥VGPR of 91%, a high MRD– rate (62%) in evaluable patients (n=48), and an 18-month PFS of 92%. Furthermore, DKRd induction had a favorable safety profile, with no new safety signals observed.[20]

## Anti-CD38-KRd quadruplets beyond the high-risk setting

Beyond the high-risk setting, several studies are investigating anti-CD38-KRd combinations in patient with NDMM irrespective of cytogenetic status. The ongoing Phase II ADVANCE trial is investigating DKRd versus KRd versus VRd, with optional ASCT in MRD+ patients following induction, in all-risk Te NDMM, and may shed further light on the efficacy of KRd and VRd in Te NDMM patients irrespective of risk status.[22]

The combination of Isa-KRd is being investigated in all-risk patients in three trials (Phase II SKylaRk, and Phase III IsKia/EMN24 and MIDAS) (**Table**). The Phase II SKylaRk trial of all-risk Te NDMM patients assessed Isa-KRd as a 4-cycle induction, followed by ASCT and 2 consolidation cycles in patients with upfront transplant, or Isa-KRd 8-cycle induction in patients with deferred transplant, both followed by Isa-KR or R maintenance in high- and standard-risk patients, respectively.[23] Isa-KRd induced deep responses in all patients including the 46% with high-risk cytogenetics; the ≥CR rate was 38% after 4 cycles (primary endpoint) in patients with upfront transplant and 67% after cycle 8 in transplant-deferred patients, the MRD- rate was 43% at cycle 4 and 74% at cycle 8. Additionally, a 15.4 months PFS rate of 89% was observed for all patients (mPFS NR). Furthermore, Isa-KRd was well-tolerated, with a safety profile consistent with reports of similar regimens.[23]

touch™ ONCOLOGY

The Phase III IsKia/EMN24 trial assessed Isa-KRd induction and post-ASCT consolidation, followed by de-intensification (light consolidation) versus KRd in Te NDMM. The primary endpoint is the MRD– rate ($10^{-5}$ by NGS) post-ASCT consolidation.[24] Since the EHA 2023 Congress, the Phase III IsKia/EMN24 trial data has been presented (not shown here).[25] The Phase III MIDAS trial assessed 6 cycles of Isa-KRd induction, followed by 1:1 randomization to Isa-KRd or ASCT + Isa-KRd consolidation followed by R maintenance in MRD– patients, and ASCT + Isa-KRd consolidation or tandem ASCT followed by isa + iberdomide maintenance in MRD+ patients. The primary endpoint is the change in rate of MRD– (10–6 by NGS) from post-induction baseline to end of consolidation, and 1, 2, or 3 years post-induction.[26]

Data supporting the combination of DKRd was provided at the time by two Phase II trials (MASTER and MANHATTAN) (**Table**). The MASTER study included a population enriched for high-risk cytogenetic abnormalities (57%) and assessed DKRd- induction, followed by ASCT, DKRd consolidation, and R maintenance in Te patients. Patients with two consecutive MRD– assessments entered into treatment-free observation and MRD surveillance (MRD-SURE).[27,28] After a median follow-up of 34.1 months, 81% of patients were MRD– ($10^{-5}$ by NGS) and 71% of patients entered treatment-free observation after two consecutive MRD– assessments. The responses deepened over time, with the proportion of patients with ≥VGPR increasing from 63% at post-induction cycle 2 to 98% at consolidation. Furthermore, quadruplet therapy with DKRd was well-tolerated.[27,28]

The Phase II MANHATTAN study assessed 8 cycles of DKRd induction followed by standard of care therapy. After ≤8 cycles of DKRd induction, 71% of patients met the primary endpoint of MRD– ($10^{-5}$ by MFC), 95% had a ≥VGPR and the 1-year PFS rate was 98%. Furthermore, there were no added major clinical toxic effects with the addition of daratumumab to KRd.[29]

Finally, studies have shown that the addition of anti-CD38 mAbs to KRd does not impact the feasibility of stem cell collection in NDMM, with similar stem cell yields in the GMMG-CONCEPT, IFM 2018-04, MASTER and MANHATTAN trials.[20,29–31]

## Summary

Anti-CD38 mAb-based quadruplets have replaced triplets as the standard of care for the treatment of Te NDMM. KRd has shown good efficacy, similar to VRd in patients with all-risk NDMM. However, further research into the optimal dosing of carfilzomib, and the choice of PI (K vs V) in different patient populations is required. In high-risk patients, KRd in combination with anti-CD38 mAbs has demonstrated efficacy with tolerable safety. Finally, several studies have demonstrated the efficacy of anti-CD38-KRd combinations.

**Acknowledgments:** Medical writing support was provided by Alex Lowe for Touch Medical Communications and funded by Sanofi.

**Sponsored by:** This promotional activity has been sponsored by Sanofi, who provided financial support and has had input into the detailed project scope and content. This activity is provided by Touch Medical Communications (TMC) for touchONCOLOGY.

**MAT-GLB-2302932**

**Date of preparation:** April 2024

touch™ ONCOLOGY

## References


1. Cavo M, Tacchetti P, Zamagni E. Front-line treatment of multiple myeloma. *Hemasphere* 2019; 3(Suppl): 127-30.
2. Dimopoulos MA, Moreau P, Terpos E, et al. Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up(†). *Ann Oncol* 2021; 32(3): 309-22.
3. National Comprehensive Cancer Network. Multiple Myeloma Version 1.2024 Avaliable at: https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf (accessed October 2023).
4. Food and Drug Administration. Highlights of Prescribing Information, DARZALEX. Avaliable at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761036s041lbl.pdf (accessed October 2023).
5. Food and Drug Administration. Highlights of Prescribing Information, SARCLISA. Avaliable at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761113s003lbl.pdf (accessed October 2023).
6. Fonseca R, Usmani SZ, Mehra M, et al. Frontline treatment patterns and attrition rates by subsequent lines of therapy in patients with newly diagnosed multiple myeloma. *BMC Cancer* 2020; 20(1): 1087.
7. Clinicaltrials.gov. Study Comparing Daratumumab, Lenalidomide, Bortezomib, and Dexamethasone (D-RVd) Versus Lenalidomide, Bortezomib, and Dexamethasone (RVd) in Subjects With Newly Diagnosed Multiple Myeloma. Avaliable at: https://clinicaltrials.gov/ct2/show/NCT02874742 (accessed October 2023).
8. Moreau P, Hulin C, Perrot A, et al. Daratumumab maintenance or observation after treatment with bortezomib, thalidomide, and dexamethasone daratumumab and autologous stem cell transplant in patients with newly diagnosed multiple myeloma: CASSIOPEIA Part 2. Presented at the European Hematology Association Viritual Meeting, 9-17 June 2021.
9. Moreau P, Attal M, Hulin C, et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study. *Lancet* 2019; 394(10192): 29-38.
10. Goldschmidt H, Mai EK, Bertsch U, et al. Addition of isatuximab to lenalidomide, bortezomib, and dexamethasone as induction therapy for newly diagnosed, transplantation-eligible patients with multiple myeloma (GMMG-HD7): part 1 of an open-label, multicentre, randomised, active-controlled, phase 3 trial. *Lancet Haematol* 2022; 9(11): e810-e21.
11. Sborov D, Laubach J, Kaufman JL. Daratumumab (DARA) + Lenalidomide, Bortezomib, and Dexamethasone (RVd) in Patients With Transplant-eligible Newly Diagnosed Multiple Myeloma (NDMM): Final Analysis of GRIFFIN. Presented at the 19th International Myeloma Society Annual Meeting, August 25-27, 2022. Los Angeles, CA, USA.
12. Gay F, Musto P, Rota-Scalabrini D, et al. Carfilzomib with cyclophosphamide and dexamethasone or lenalidomide and dexamethasone plus autologous transplantation or carfilzomib plus lenalidomide and dexamethasone, followed by maintenance with carfilzomib plus lenalidomide or lenalidomide alone for patients with newly diagnosed multiple myeloma (FORTE): a randomised, open-label, phase 2 trial. *Lancet Oncol* 2021; 22(12): 1705-20.
13. Kumar SK, Jacobus SJ, Cohen AD, 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, randomised, controlled trial. *Lancet Oncol* 2020; 21(10): 1317-30.
14. Tan CR, Derkach A, Nemirovsky D, et al. Bortezomib, lenalidomide and dexamethasone (VRd) vs carfilzomib, lenalidomide and dexamethasone (KRd) as induction therapy in newly diagnosed multiple myeloma. *Blood Cancer Journal* 2023; 13(1): 112.
15. Food and Drug Administration. Highlights of Prescribing Information, KYPROLIS. Avaliable at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/202714s025lbl.pdf (accessed October 2023).
16. European Medicines Agency. Summary of Product characteristics, Kyprolis. Avaliable at: https://www.ema.europa.eu/en/documents/product-information/kyprolis-epar-product-information_en.pdf (accessed October 2023).
17. Moreau P, Stewart KA, Dimopoulos M, et al. Once-weekly (70 mg/m(2) ) vs twice-weekly (56 mg/m(2) ) dosing of carfilzomib in patients with relapsed or refractory multiple myeloma: A post hoc analysis of the ENDEAVOR, A.R.R.O.W., and CHAMPION-1 trials. *Cancer Med* 2020; 9(9): 2989-96.
18. Avet-Loiseau H, Fonseca R, Siegel D, et al. Carfilzomib significantly improves the progression-free survival of high-risk patients in multiple myeloma. *Blood* 2016; 128(9): 1174-80.
19. Mina R, Musto P, Rota-Scalabrini D, et al. Carfilzomib induction, consolidation, and maintenance with or without autologous stem-cell transplantation in patients with newly diagnosed multiple myeloma: pre-planned cytogenetic subgroup analysis of the randomised, phase 2 FORTE trial. *Lancet Oncol* 2023; 24(1): 64-76.
20. Touzeau C, Perrot A, Hulin C, et al. Daratumumab carfilzomib lenalidomide and dexamethasone as induction therapy in high-risk, transplant-eligible patients with newly diagnosed myeloma: Results of the phase 2 study IFM 2018-04. Presented at the American Society of Clinical Oncology Annual Meeting, June 2-8, 2022. Chicago, IL, USA.
21. Weisel K, Besemer B, Haenel M, et al. Isatuximab, Carfilzomib, Lenalidomide, and Dexamethasone (Isa-KRd) in Patients with High-Risk Newly Diagnosed Multiple Myeloma: Planned Interim Analysis of the GMMG-Concept Trial. Presented at the 64th ASH Annual Meeting and Exposition, December 10-13, 2022. New Orleans, LA, USA.
22. Clinicaltrials.gov. A Study of Daratumumab, Carfilzomib, Lenalidomide, and Dexamethasone in Patients With Newly-Diagnosed Multiple Myeloma (ADVANCE). Avaliable at: https://clinicaltrials.gov/study/NCT04268498 (accessed October 2023).
23. O'Donnell EK, Mo CC, Nadeem O, et al. A Phase II Study of Once Weekly Carfilzomib, Lenalidomide, Dexamethasone, and Isatuximab in Newly Diagnosed, Transplant-Eligible Multiple Myeloma (The SKylaRk Trial). Presented at the American Society of Hematology Annual Meeting, December 10-13, 2022. New Orleans, LA, USA.
24. Clinicaltrials.gov. Isa-KRd vs KRd in Newly Diagnosed Multiple Myeloma Patients Eligible for Autologous Stem Cell Transplantation (IsKia TRIAL) (IsKia). Avaliable at: https://clinicaltrials.gov/study/NCT04483739 (accessed October 2023).
25. Gay F, Roeloffzen W, Dimopoulos MA, et al. 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. *Blood* 2023; 142(Supplement 1): 4.
26. Clinicaltrials.gov. MInimal Residual Disease Adapted Strategy (MIDAS). Avaliable at: https://clinicaltrials.gov/study/NCT04934475 (accessed October 2023).
27. Costa LJ, Chhabra S, Medvedova E, et al. Daratumumab, Carfilzomib, Lenalidomide, and Dexamethasone With Minimal Residual Disease Response-Adapted Therapy in Newly Diagnosed Multiple Myeloma. *J Clin Oncol* 2022; 40(25): 2901-12.
28. Costa LJ, Chhabra S, Medvedova E, et al. Outcomes of MRD-Adapted Treatment Modulation in Patients with Newly Diagnosed Multiple Myeloma Receiving Daratumumab, Carfilzomib, Lenalidomide and Dexamethasone (Dara-KRd) and Autologous Transplantation: Extended Follow up of the Master Trial. Presented at the American Society of Hematology Annual Meeting, December 10-13, 2022. New Orleans, LA, USA; 2022.
29. Landgren O, Hultcrantz M, Diamond B, et al. Safety and Effectiveness of Weekly Carfilzomib, Lenalidomide, Dexamethasone, and Daratumumab Combination Therapy for Patients With Newly Diagnosed Multiple Myeloma: The MANHATTAN Nonrandomized Clinical Trial. *JAMA Oncol* 2021; 7(6): 862-8.
30. Asemissen AM, Scheid C, Leypoldt L, et al. Mobilization of autologous stem cells under induction therapy with Isatuximab, Carfilzomib, Lenalidomide, Dexamethasone (Isa-KRd) in high risk myeloma patients: First results of the GMMG-CONCEPT trial. *Oncol Res Treat* 2020; 43(S4). 94-6.
31. Chhabra S, Callander N, Watts NL, et al. Stem Cell Mobilization Yields with Daratumumab- and Lenalidomide-Containing Quadruplet Induction Therapy in Newly Diagnosed Multiple Myeloma: Findings from the MASTER and GRIFFIN Trials. *Transplant Cell Ther* 2023; 29(3): 174.e1-.e10.


touch™ ONCOLOGY