# Isatuximab plus lenalidomide and dexamethasone with weekly bortezomib versus isatuximab plus lenalidomide and dexamethasone in newly diagnosed transplant ineligible Multiple Myeloma. The BENEFIT (IFM 2020-05) study

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# Background

- IMROZ study sought to determine the added value of CD38 targeting immunotherapy using twice weekly VRd SOC[1], however, Dara-Rd has also become a new SOC in various countries including France[2–4]
- It was shown that in NDMM Ti patients, including in the context of the combination of bortezomib plus lenalidomide and dexamethasone, a weekly schedule demonstrated less peripheral neuropathy and has been adopted in clinical practice[5–7]
- To further enhance the safety profile of treatments for Ti patients, a fixed duration of dexamethasone was evaluated and proved beneficial in various studies[5,8]
- MRD negativity rate has become an important endpoint in MM (ODAC approval in April 24)[9]
- To improve current standard of care, we evaluated the added value of weekly bortezomib (V) to Isatuximab plus lenalidomide and dexamethasone (Isa-VRd versus Isa-Rd). We report the results of the primary endpoint analysis of BENEFIT/IFM2020-05 (NCT04751877), the first academic French Phase 3 study investigating the efficacy and safety of Isa-VRd vs Isa-Rd in Ti patients with NDMM

d, dexamethasone; Dara, daratumumab; Isa, isatuximab; NDMM, newly diagnosed multiple myeloma; ODAC, Oncologic Drugs Advisory Committee; R, lenalidomide; SOC, Standard of care; Ti, transplant ineligible; V, bortezomib.

1. ClinicalTrials.gov; NCT03319667; 2. Facon T, et al. *N Engl J Med* 2019;380:2104–15; 3. Dimopoulos MA, et al. *Ann Oncol* 2021;32:309–22; 4. Rajkumar SV, Kumar S. *Blood Cancer J* 2020;10:94; 5. O'Donnell EK, et al. *Br J Haematol* 2018;182:222–30; 6. Mateos MV, et al. *Haematologica* 2014;99:1114–22; 7. Hoff F, et al. *Blood Cancer J* 2024;14:52; 8. Durie BGM, et al. *Lancet* 2017;289:519–27; 9. U.S. Food & Drug Administration. Last updated April 17, 2024. Accessed April 22, 2024. https://www.fda.gov/advisory-committees/advisory-committee-calendar/april-12-2024-meeting-oncologic-drugs-advisory-committee-meeting-announcement-04122024.

# Key highlights

- BENEFIT is the first academic Phase 3 study of an anti-CD38 mAb in combination with VRd in patients with Ti NDMM
- It is also the first Phase 3 study to readout with MRD as a primary endpoint in Ti NDMM

- In this presentation we will show that Isa-VRd led to:
  - A statistically significant improvement in MRD at 12 and 18 months
  - Deep response rates, including MRD at $10^{-6}$
  - Statistically significant improvement in MRD- CR rate
  - A safety profile consistent with that of each agent

- This study shows for the first time Isa-Rd results in NDMM Ti patients

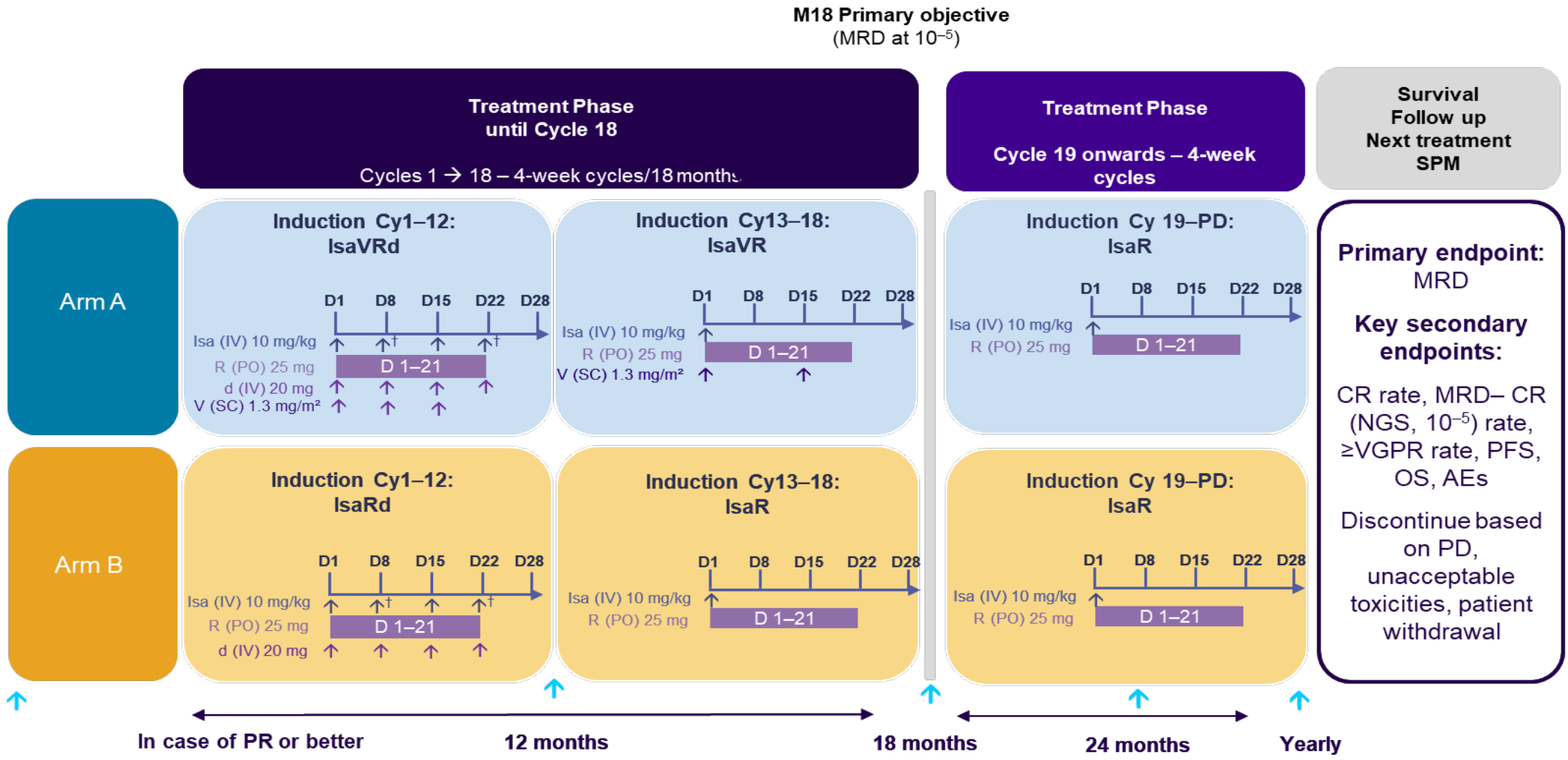
CR, complete response; d, dexamethasone; Isa, isatuximab; mAb, monoclonal antibody; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; R, lenalidomide; Ti, transplant ineligible; V, bortezomib.

# Study design: Isa-VRd vs Isa-Rd in Ti NDMM

**N=270**

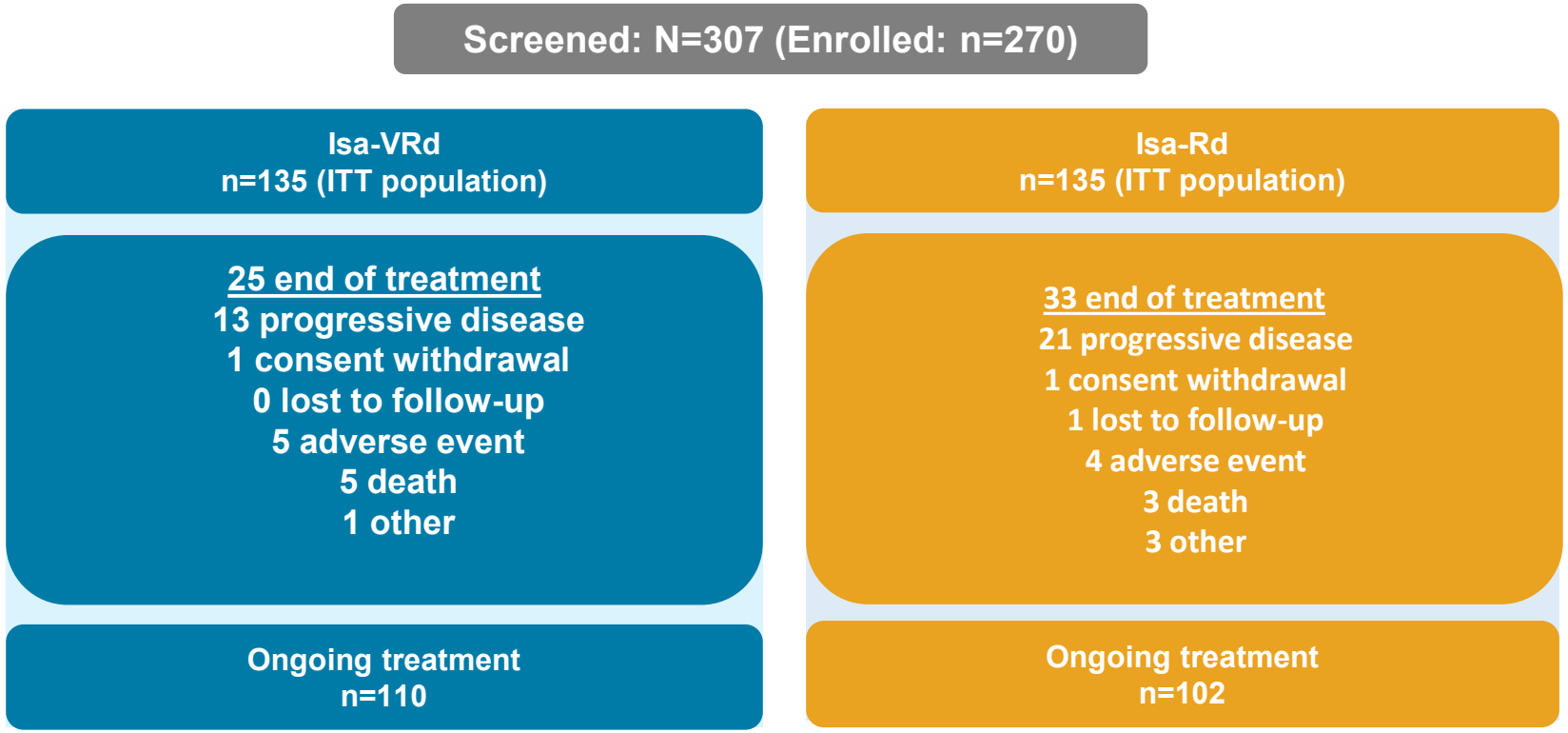
- **Randomization1:1**
- **Stratified by:**

- Age: <75 and ≥ 75yrs
- Cytogenetic result by FISH (Modified Perrot score)
- Center




†Cycle 1 only. CR, complete response; Cy, cycle; d, dexamethasone; D, day; Isa, isatuximab; M, month; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; NGS, next generation sequencing; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; R, lenalidomide; SPM, second primary malignancy; Ti, transplant-ineligible; V, bortezomib; VGPR, very good partial response.

# Patient disposition




**A higher percentage of patients are still on treatment in the Isa-VRd arm**

d, dexamethasone; Isa, isatuximab; ITT, intent-to-treat; R, lenalidomide; V, bortezomib.

# Baseline characteristics

| ITT population | Isa-VRd (n=135) | Isa-Rd (n=135) |
|---|---|---|
| **Age, median (range), years** | 73.2 (71–76) | 73.6 (71–76) |
| **Age by category, years, n (%)** | | |
| <70 | 28 (21) | 25 (19) |
| [70–75] | 65 (48) | 62 (46) |
| ≥75 | 42 (31) | 48 (36) |
| **ECOG PS, n (%)** | | |
| 0 or 1 | 125 (93) | 119 (88) |
| >1 | 10 (7) | 16 (12) |
| **eGFR <60 mL/min/1.73 m² (MDRD), n (%)** | 19 (14) | 28 (21) |

| ITT population | Isa-VRd (n=135) | Isa-Rd (n=135) |
|---|---|---|
| **ISS stage at baseline** | | |
| Stage I + II | 114 (84) | 108 (80) |
| Stage III | 21 (16) | 27 (20) |
| **R-ISS stage at baseline, n (%)** | | |
| Stage I | 32 (24) | 35 (26) |
| Stage II | 92 (68) | 89 (66) |
| Stage III | 11 (8) | 11 (8) |

**Patient characteristics were balanced in both arms**

*Cytogenetic risk was assessed according to Perrot et al. for study analysis.[1]
d, dexamethasone; ECOG PS, Eastern Cooperative Oncology Group Performance Scale; eGFR, estimated glomerular filtration rate; Isa, isatuximab; ITT, intent-to-treat; MDRD, modification of diet in renal disease; R, lenalidomide; R-ISS, Revised International Staging System; V, bortezomib.
1. Perrot A, et al. *J Clin Oncol* 2019;37:1657–65.

# Baseline characteristics

| ITT population | Isa-VRd (n=135) | Isa-Rd (n=135) |
|---|---|---|
| **Deletion 17p** | | |
| **Deletion 17p sup 20%** | 9 (6) | 10 (8) |
| **Deletion 17p sup 50%** | 5 (4) | 8 (6) |
| **TP53 mutation** | 5 (4) | 6 (5) |
| **t(11;14)+** | 31 (23) | 26 (20) |
| **t(4;14)+** | 11 (8) | 10 (8) |
| **High-risk** | 5 (4) | 2 (2) |
| **Non high-risk** | 6 (4) | 8 (6) |
| **t(14;16)+** | 3 (2) | 5 (4) |
| **t(14;20)+** | 1 (1) | 1 (1) |
| **Gain/amplification 1q** | 32 (24) | 35 (27) |
| **Del(1p32)** | 11 (8) | 13 (10) |
| **Del(1p32)$^{del/wt}$** | 11 (8) | 12 (9) |
| **Del(1p32)$^{del/del}$** | 0 | 1 (1) |

| ITT population | Isa-VRd (n=135) | Isa-Rd (n=135) |
|---|---|---|
| **Cytogenetic risk at baseline – no. (%)$^{+}$** | | |
| **Standard** | 76 (60) | 68 (53) |
| **Intermediate** | 41 (32) | 48 (37) |
| **High** | 10 (8) | 13 (10) |
| **IMS HR definition – no. (%)*** | | |
| **High** | 24 (18) | 33 (24) |
| **Non-high** | 111 (82) | 102 (76) |
| **Deletion 17p** | 8 (6%) | 10 (7%) |
| **TP53 mutation** | 5 (4%) | 6 (4%) |
| **Del(1p32)$^{del/del}$** | 0 | 1 (1%) |
| **t(4;14) or t(14;16) or t(14;20) +gain/amp 1q or del(1p32)$^{del/wt}$** | 10 (7%) | 14 (10%) |
| **Gain/amp 1q +del(1p32)$^{del/wt}$** | 5 (4%) | 6 (4%) |

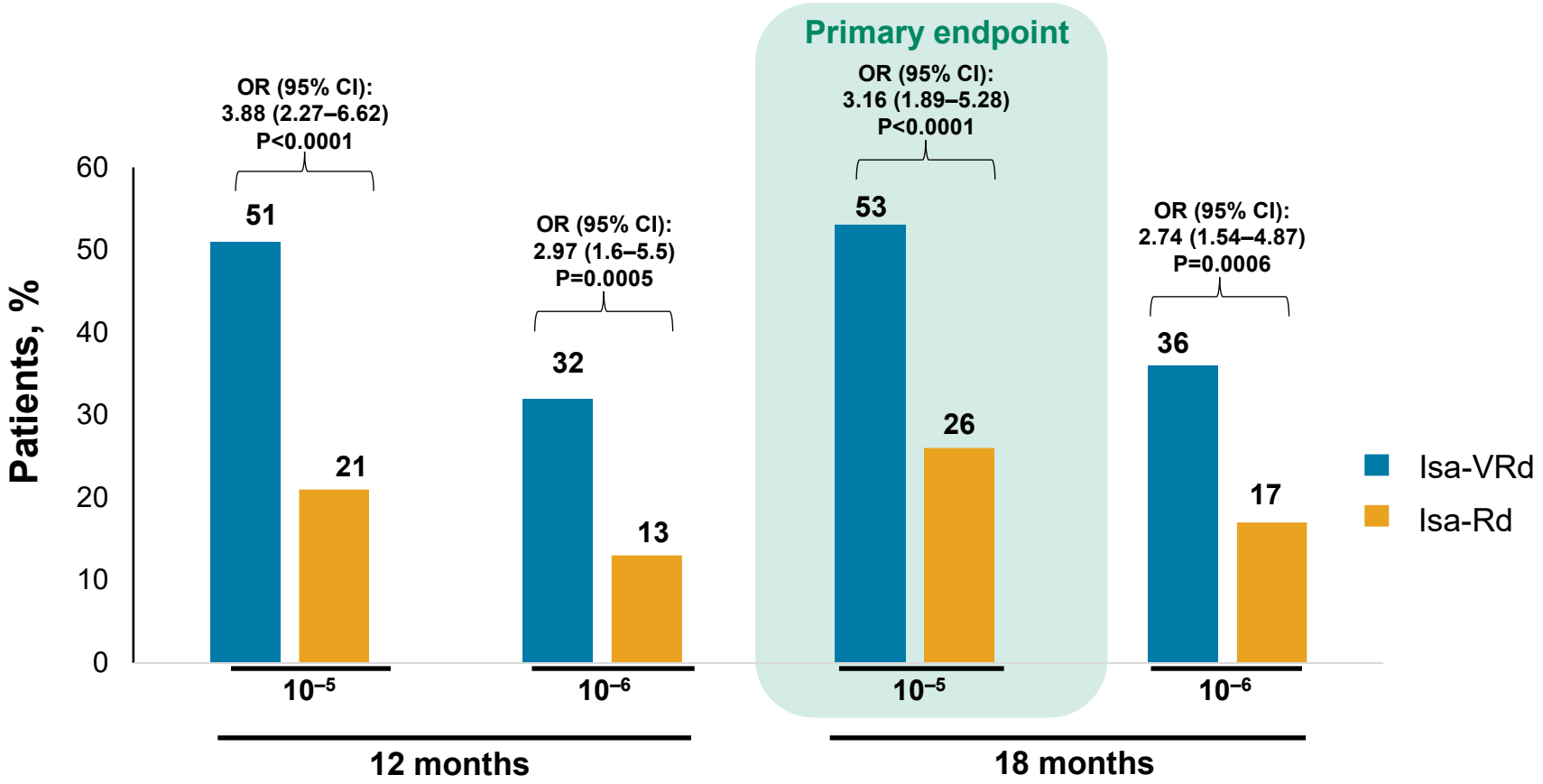
**Patient HR characteristics were balanced in both arms**

+Cytogenetic risk was assessed according to Perrot et al. for study analysis[28]. Bone marrow samples were obtained at diagnosis and shipped overnight to a central laboratory. Upon receipt, plasma cells (PCs) were isolated using CD138+ MAC-Sorting (Miltenyi Biotec, Paris, France). Post-sorting purity was checked by cytologic analysis of a spin from positive fraction, and only samples with ≥ 70% PCs after sorting were kept for the analysis. The mean purity was 94%. PCs were analyzed by NGS using NextSeq 500 (Illumina). For each positive del(17p) assessed by NGS, an additional FISH analysis was performed to assess the percentage of positive plasma cells. NGS sequencing was performed using a panel of specific probes targeting regions of interest, as previously described[29,30].

*IMS HR definition was assessed according to xxxxxxx for study analysis ref.

FISH, fluorescence *in situ* hybridization; HR, High-risk; ISS, International Staging System; ITT, intention-to-treat; no., number; R-ISS, Revised International Staging System; yr, years.

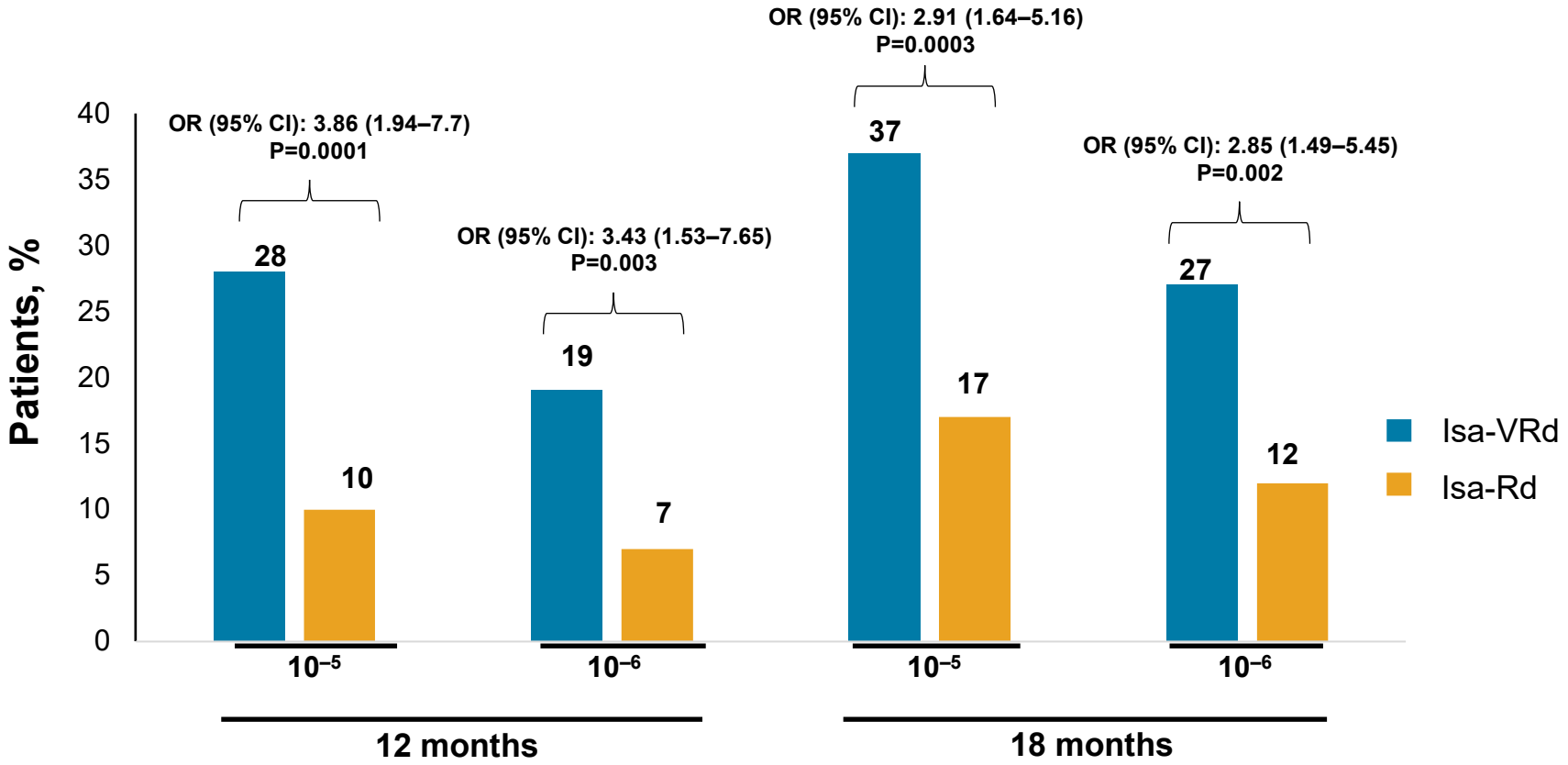
# Primary endpoint: MRD–* rate at 18 months – ITT population




**Isa-VRd resulted in deep response rates, with a significant improvement in the MRD at 12 and 18 months, and at $10^{-5}$ and $10^{-6}$ in the ITT population**

*MRD was assessed on the basis of IMWG recommendations.[1]
CI, confidence interval; Isa, isatuximab; ITT, intent-to-treat; MRD–, minimal residual disease negativity; NGS, next generation sequencing; OR, odd ratio; R, lenalidomide; V, bortezomib.
1. Kumar S, et al. *Lancet Oncol* 2016;17:e328–e346.

# MRD–*-CR rate at 18 months - ITT population

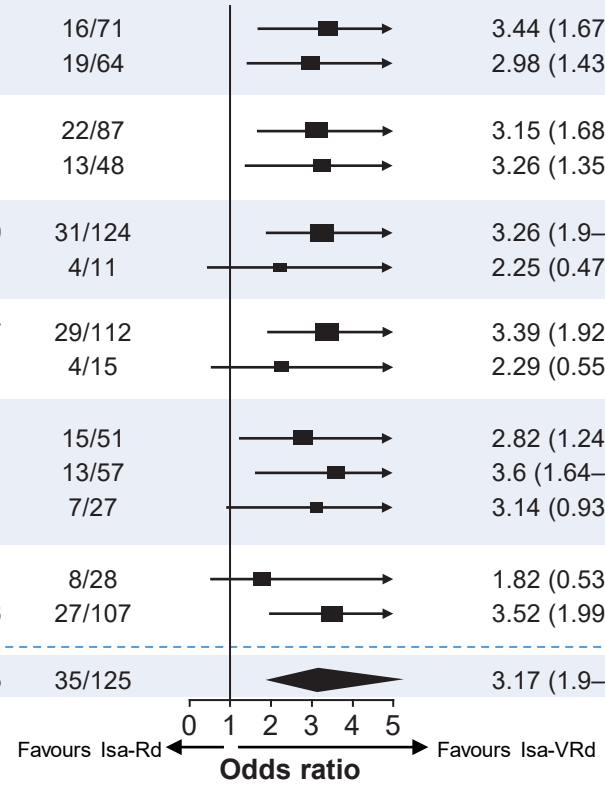



**Isa-VRd resulted in a significant improvement in the MRD– CR rate at 12 and 18 months, and at $10^{-5}$ and $10^{-6}$ in the ITT population**

*MRD was assessed on the basis of IMWG recommendations.[1]
CI, confidence interval; CR, complete response; Isa, isatuximab; ITT, intent-to-treat; MRD–, minimal residual disease negativity; NGS, next generation sequencing; OR, odd ratio; R, lenalidomide; V, bortezomib.
1. Kumar S, et al. *Lancet Oncol* 2016;17:e328–e346.

# MRD subgroup analyses

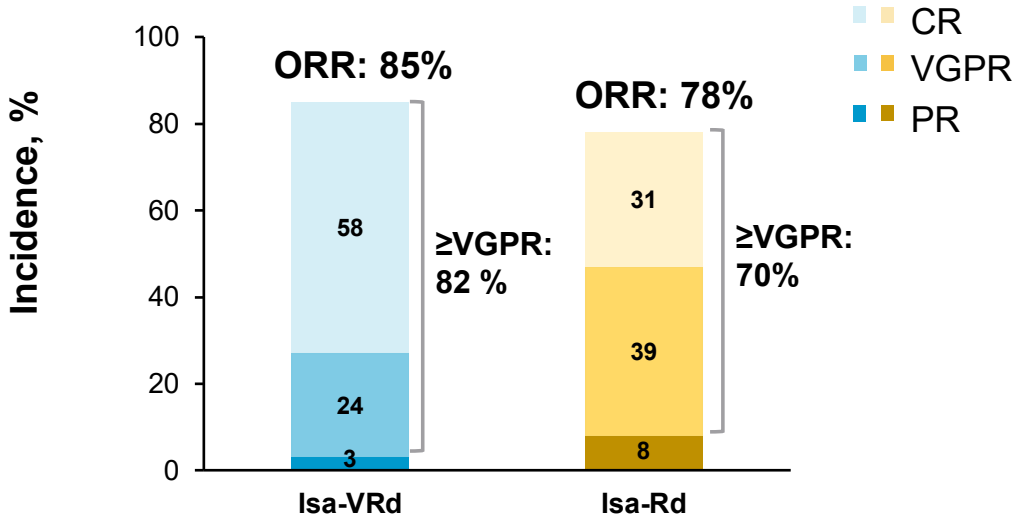
| Subset | | Isa-VRd Events/Pts | Isa-Rd Events/Pts | OR (95% CI) | P-value for interaction |
|---|---|---|---|---|---|
| **Sex** | Male | 37/74 | 16/71 | 3.44 (1.67–7.06) | **0.79** |
| | Female | 34/61 | 19/64 | 2.98 (1.43–6.23) | |
| **Age** | ≤ 75 yr | 48/93 | 22/87 | 3.15 (1.68–5.93) | **0.95** |
| | > 75 yr | 23/42 | 13/48 | 3.26 (1.35–7.86) | |
| **Cytogenetic profile (LP FISH)** | LP HR- | 62/119 | 31/124 | 3.26 (1.9–5.62) | **0.66** |
| | LP HR+ | 9/16 | 4/11 | 2.25 (0.47–10.88) | |
| **Cytogenetic profile (NGS)** | Standard risk | 58/107 | 29/112 | 3.39 (1.92–5.98) | **0.62** |
| | High risk | 10/22 | 4/15 | 2.29 (0.55–9.47) | |
| **ISS** | I | 27/50 | 15/51 | 2.82 (1.24–6.4) | **0.91** |
| | II | 33/64 | 13/57 | 3.6 (1.64–7.93) | |
| | III | 11/21 | 7/27 | 3.14 (0.93–10.58) | |
| **eGFR (MRDR Formula)** | <60 | 8/19 | 8/28 | 1.82 (0.53–6.19) | **0.34** |
| | ≥60 | 63/116 | 27/107 | 3.52 (1.99–6.22) | |
| | All patients | 71/135 | 35/125 | 3.17 (1.9–5.29) | |



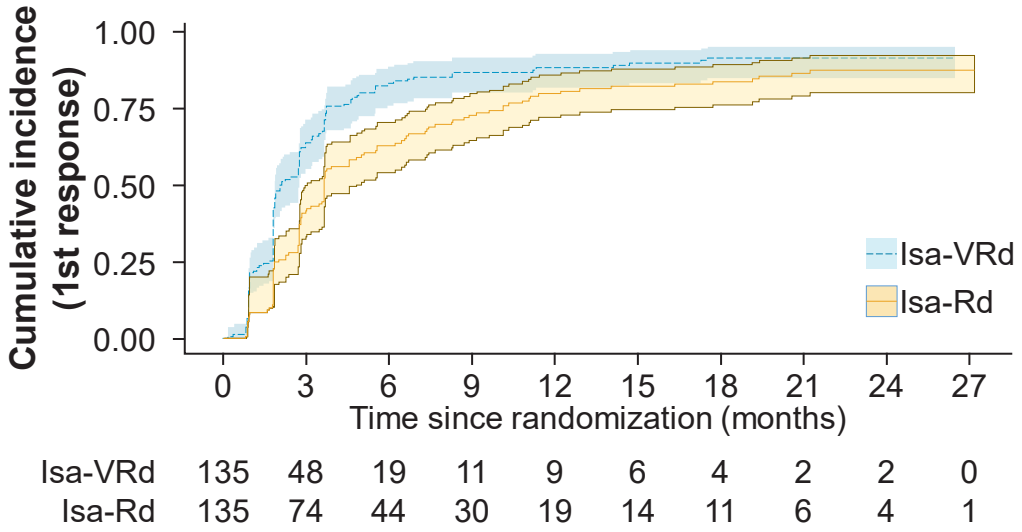

**A consistent MRD benefit was observed with Isa-VRd vs Isa-Rd across most subgroups, including difficult-to-treat populations with negative prognostic factors**

CI, confidence interval; d, dexamethasone; eGFR, estimated glomerular filtration rate; FISH, fluorescent in situ hybridation; Isa, isatuximab; ISS, international staging system; MRD, minimal residual disease; MDRD, modification of diet in renal disease; NGS, next generation sequencing; OR, odd ratio; R, lenalidomide; V, bortezomib.

# Depth of response* at 18 months and the first occurrence of a CR - ITT Population




**≥CR rate 58% vs. 31%, OR (95% CI): 2.97 (2–5), p<0.0001**



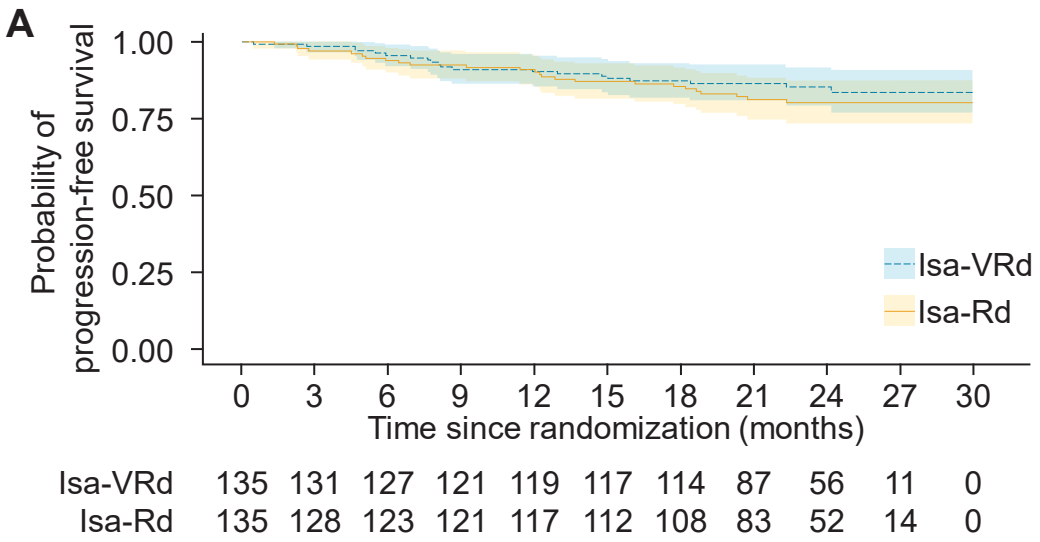

**≥VGPR†**
**HR: 1.65 (95% CI, 1.27 to 2.14, p=0.0002)**

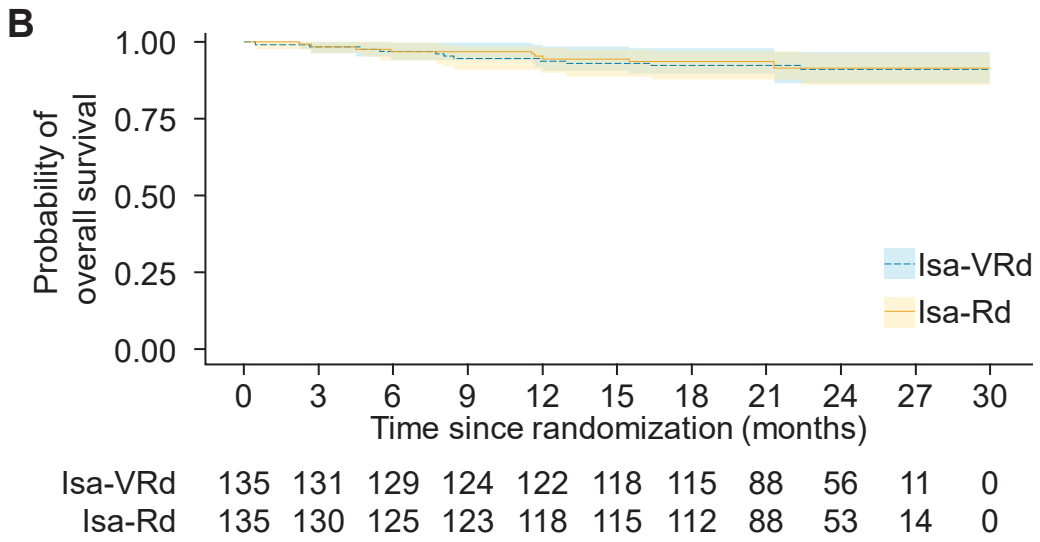
**VGPR, median (95% CI)**
Isa-VRd: 2.1 (95%CI, 1.9–2.9) months
Isa-Rd: 3.7 (95%CI, 3–4.9) months

**Isa-VRd resulted in deep response rates, particularly ≥CR rate at 18 months, and a shorter time to the first occurrence of a confirmed response ≥VGPR in the ITT population**

*Response was assessed on the basis of IMWG recommendations[1]; †Distribution of time to ≥VGPR were compared between arm using a Cox cause specific proportional Hazard model to account for competing risk of death or progressive disease with treatment as explanatory variable and adjusting for randomization stratification factors. CI, confidence interval; CR, complete response; d, dexamethasone; HR, hazard ratio; Isa, isatuximab; ITT, intent-to-treat; ORR, overall response rate; PR, partial response; R, lenalidomide; V, bortezomib; VGPR, very good partial response

# Survival analysis-IRC assessment in ITT population




**Estimated 24 months PFS**
85.2% (95%CI 79.2–91.7) for Isa-VRd
80.0% (95% CI 73.3–87.4) for Isa-Rd

**Estimated 24 months OS**
91.1% (95%CI 86.1–96.4) for Isa-VRd
91.5% (95%CI 86.5–96.8) for Isa-Rd

**At a median follow-up of 23.5 months, survival is still immature**

d, dexamethasone; Isa, isatuximab; IRC, independent review committee; ITT, intent-to-treat; CI, confidence interval; OS, overall survival; PFS, progression-free survival; R, lenalidomide; V, bortezomib.

# Exposure to study treatments (Safety population*)

| Exposure parameter | Isa-VRd (n=135) | Isa-Rd (n=135) |
|---|---|---|
| **Isatuximab** | | |
| **Duration of treatment, months** | 15.9 [15.6–16.3] | 15.8 [15.6–16.1] |
| **Relative dose intensity†, %** | 96.1 [90.9–99.9] | 95.8 [91–99] |
| **Bortezomib** | | |
| **Duration of treatment, months** | 15.7 [13.4;16.3] | - |
| **Relative dose intensity†, %** | 91.6 [81.8;95.6] | - |
| **Lenalidomide** | | |
| **Duration of treatment, months** | 15.9 [15.6–16.3] | 15.8 [15.6–16.1] |
| **Relative dose intensity†, %** | 91.7 [72.5–99.5] | 91 [74.3–99] |
| **Dexamethasone** | | |
| **Duration of treatment, months** | 10.2 [10.1–10.6] | 10.2 [10.1–10.6] |
| **Relative dose intensity†, %** | 95.8 [71.9–100] | 97.9 [75.5–100] |

**Similar relative dose intensity of Isatuximab, lenalidomide, and dexamethasone in both arms**

*The safety population included all patients who received at least one dose of study treatment; †Dose intensity was defined as the ratio of total administered dose to total planned dose. d, dexamethasone; Isa, isatuximab; R, lenalidomide; V, bortezomib.

# Safety summary (safety population*)

| TEAE overview, n (%) | Isa-VRd (n=135) | Isa-Rd (n=135) |
|---|---|---|
| **Any TEAE** | 134 (99) | 128 (95) |
| **Grade ≥3 TEAEs** | 93 (69) | 91 (67) |
| **Serious TEAEs** | 46 (34) | 47 (35) |
| **Any TEAE leading to definitive treatment discontinuation** | | |
| Isatuximab | 3 (2) | 4 (3) |
| Lenalidomide | 14 (10) | 13 (10) |
| Dexamethasone | 14 (10) | 7 (5) |
| Bortezomib | 14 (10) | 0 |
| **Event rate per patient-year†** | | |
| Any TEAE | 12.53 | 5.57 |
| Grade ≥3 TEAEs | 0.96 | 0.88 |
| Serious TEAEs | 0.26 | 0.28 |
| Any TEAE leading to definitive treatment discontinuation (all treatments) | 0.01 | 0.01 |

**Isa-VRd was well tolerated, and the safety profile remains consistent with the known safety profiles of each agent**

*The safety population included all patients who received at least one dose of study treatment; †Calculated as number of patients with an event divided by total patient-years. d, dexamethasone; Isa, isatuximab; R, lenalidomide TEAE, treatment-emergent adverse event; V, bortezomib

# Safety summary (Safety population*)

| Event, no. of patients (%) | Isa-VRd (n=135) | | Isa-Rd (n=135) | |
|---|---|---|---|---|
| | Any Grade | ≥Grade 3 | Any Grade | ≥Grade 3 |
| **Hematologic adverse events** | | | | |
| Neutropenia | 77 (57) | 53 (40) | 82 (61) | 61 (45) |
| Lymphopenia | 53 (39) | 44 (33) | 38 (28) | 33 (24) |
| Anemia | 30 (22) | 13 (10) | 27 (20) | 7 (5) |
| Thrombocytopenia | 37 (27) | 16 (12) | 19 (14) | 8 (5) |
| **Event, no. of patients (%)** | **Any Grade** | **≥Grade 2** | **Any Grade** | **≥Grade 2** |
| **Nonhematologic adverse events** | | | | |
| Diarrhea | 66 (49) | 39 (29) | 65 (48) | 30 (22) |
| Constipation | 52 (39) | 30 (22) | 41 (30) | 19 (14) |
| Rash | 21 (16) | 12 (9) | 16 (12) | 9 (7) |
| Asthenia | 41 (30) | 24 (18) | 48 (36) | 18 (14) |
| Peripheral Oedema | 48 (36) | 18 (14) | 27 (20) | 10 (7) |
| Muscle spasms | 27 (20) | 7 (5) | 28 (21) | 9 (7) |
| Psychiatric disorders | 33 (24) | 22 (16) | 32 (24) | 17 (13) |
| Vascular disorders | 36 (27) | 21 (15) | 34 (25) | 23 (17) |

| Event, no. of patients (%) | Isa-VRd (n=135) | | Isa-Rd (n=135) | |
|---|---|---|---|---|
| | Any Grade | ≥Grade 2 | Any Grade | ≥Grade 2 |
| **Nonhematologic adverse events (cont'd)** | | | | |
| Eye disorders | 20 (15) | 10 (7) | 19 (14) | 12 (8) |
| SPMs | 6 (4) | 6 (4) | 6 (4) | 6 (4) |
| Infections and infestations | | | | |
| Infection of other types | 61 (45) | 48 (36) | 48 (36) | 35 (28) |
| Infection of the respiratory system | 65 (48) | 47 (35) | 64 (47) | 54 (40) |
| Covid-19 | 55 (41) | 34 (24) | 59 (44) | 31 (23) |
| Nervous system disorders | | | | |
| Peripheral neuropathy | 70 (52) | 37 (27)† | 38 (28) | 13 (10)‡ |
| Other | 38 (28) | 19 (14) | 41 (30) | 17 (13) |

**Isa-VRd was well tolerated, and the safety profile remains consistent with the known safety profiles of each agent**

*The safety population included all patients who received at least one dose of study treatment; †Four patients had a Grade 3 event in Isa-VRd arm; ‡One patient had a Grade 3 event in the Isa-Rd.
d, dexamethasone; Isa, isatuximab; R, lenalidomide; SPM, second primary malignancies; V, bortezomib.

# Conclusions

- BENEFIT is the first academic Phase 3 study of an anti-CD38 mAb in combination with VRd in patients with Ti NDMM
- Isa-VRd resulted in deep response rates vs. Isa-Rd at 18 months, with a statistically significant improvement in the MRD– (NGS, $10^{-5}$) rate (53% vs 26%; P<0.0001)
- Isa-VRd resulted in deep response rates vs. Isa-Rd already at 12 months, including even more stringent $10^{-6}$ threshold MRD– rate vs Isa-Rd at 12 (32% vs 13%) and 18 months (36% vs 23%)
- A consistent MRD benefit was observed with Isa-VRd vs Isa-Rd across most subgroups, including difficult-to-treat patient populations with negative prognostic factors
- Isa-VRd was well tolerated, and the safety profile remains consistent with that of each agent
- Isa-Rd MRD– data are, as expected, comparable to previously reported data with anti-CD38 Rd regimens[2]
- The study provides evidence that a weekly bortezomib regimen in Isa-VRd can be a very effective and feasible option in NDMM Ti
- **The improved efficacy of Isa-VRd vs Isa-Rd, combined with a consistent safety profile, provides an important treatment option for frontline disease control, supporting Isa-VRd as a new SOC for patients with Ti NDMM**

d, dexamethasone; CR, complete response; Isa, isatuximab; mAb, monoclonal antibody; MM, multiple myeloma; MRD–, minimal residual disease negativity; NDMM, newly diagnosed multiple myeloma; NGS, next generation sequencing; R, lenalidomide; SOC, Standard of care; Ti, transplant ineligible; V, bortezomib.
U.S. Food & Drug Administration. Last updated April 17, 2024. Accessed April 22, 2024. https://www.fda.gov/advisory-committees/advisory-committee-calendar/april-12-2024-meeting-oncologic-drugs-advisory-committee-meeting-announcement-04122024; 2. San-Miguel, et al. Blood 2022;139:492–501.

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