# ASH 2024 Newly Diagnosed MM

Najib Dally


המרכז הרפואי זיו
المركز الطبي زيف
ZIV MEDICAL CENTER
מסונף לפקולטה לרפואה בגליל ע"ש עזריאלי

# Important takeaways from the ASH 2024 meeting I

- MRD-driven approaches
- Efficacy of quadruplet regimens
- Maintenance therapy, doublet combinations
- Therapies for specific populations
- Refinement of diagnostic criteria

# Important takeaways from the ASH 2024 meeting I

- MRD-driven approaches
- Efficacy of quadruplet regimens
- Maintenance therapy, doublet combinations
- Therapies for specific populations
- Refinement of diagnostic criteria

# Important takeaways from the ASH 2024 meeting II

- **MRD-driven approaches:** Studies like:

- 1.QUAD (Optimal MRD-Based Endpoint in the Setting of Upfront Quadruplets (QUADs) to Support Response-Adapted Treatment Cessation in NDMM
- 2.Cepheus (Phase 3 Randomized Study of (DARA) + Bortezomib, Lenalidomide and Dexamethasone (VRd) Versus Alone in Patients with Transplant-Ineligible NDMM or for Whom Transplant Is Not Planned As Initial Therapy: Analysis of MRD

Highlight MRD as a **robust endpoint** for treatment decision-making, with implications for therapy cessation and outcomes in transplant-ineligible patients

# Important takeaways from the ASH 2024 meeting III

- **Efficacy of quadruplet regimens:** Trials exploring quadruplet regimens, including bimedicines and anti-CD38 antibody-based therapies, demonstrate enhanced efficacy in NDMM and transplant-eligible patients, including improved progression-free survival

.

- **Maintenance therapy, doublet combinations:** In maintenance settings, combinations like an anti-CD38 mAb with lenalidomide or bispecific antibodies and Lenalidomide (EMN30/MajesTEC-4) show significant progress in prolonging disease control post-transplant

# Important takeaways from the ASH 2024 meeting IV

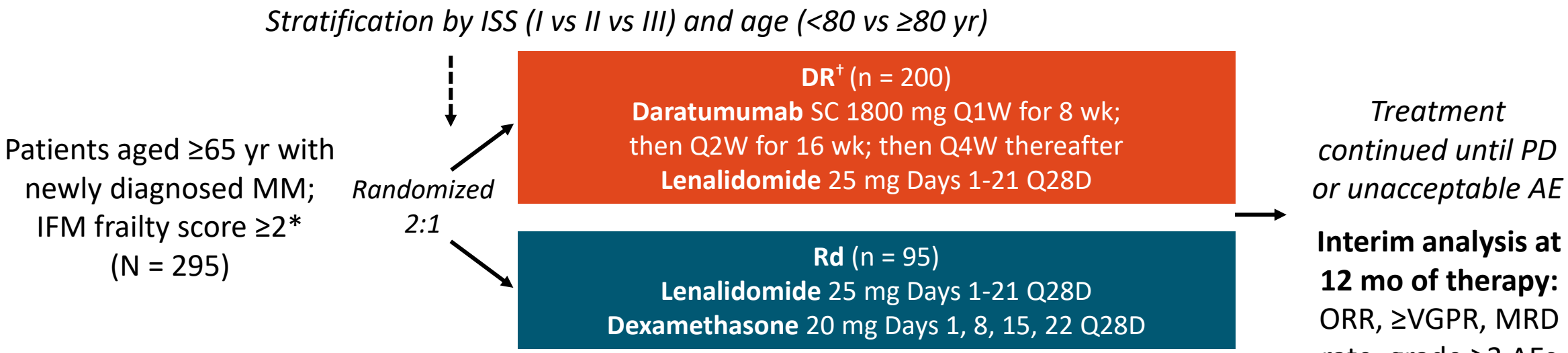
- **Therapies for specific populations:** Trials targeting elderly and frail patients (IFM2017-03) with de-escalating regimens offer effective and tolerable treatment options

- **Refinement of diagnostic criteria:** Re-evaluating the IMWG criteria and using advanced techniques like mass spectrometry emphasize the need for precise response assessments in the evolving treatment landscape

- Elderly and frail patients : (IFM2017-03) NDMM
- Maintenance with doublet combinations : EMN30/MajesTEC-4

# IFM2017-03: Study Design

- Randomized, open-label, multicenter phase III trial[1]




*IFM frailty score (age, ECOG PS, Charlson index)[2]: 0-1 = fit; ≥2 = frail.

†DR included low-dose dexamethasone 20 mg/wk during cycles 1,2, along with SC daratumumab dosing.

- **Primary endpoint:** PFS
- **Secondary endpoints:** ORR, rate of ≥VGPR, rate of MRD negativity, OS, safety

1. Manier. ASH 2024. Abstr 774. 2. Facon. Leukemia. 2020;34:224.

# IFM2017-03: Baseline Characteristics

| Characteristic | DR (n = 200) | Rd (n = 95) |
|---|---|---|
| Median age, yr (range) | 81 (68-92) | 81 (68-90) |
| Age category, n (%) | | |
| ▪ 65 to <70 yr | 2 (1) | 2 (2) |
| ▪ 70 to <75 yr | 30 (15) | 13 (14) |
| ▪ 75 to <80 yr | 49 (24) | 19 (20) |
| ▪ ≥80 yr | 119 (60) | 61 (64) |
| Female, n (%) | 101 (51) | 49 (52) |
| ECOG PS 0/1/2/≤3, % | 10/46/44/6 | 10/50/40/3 |
| Charlson ≤1, n (%) | 117 (58) | 57 (60) |
| IFM frailty score, n (%) | | |
| ▪ ≤1 | 0 | 0 |
| ▪ 2 | 58 (29) | 35 (37) |
| ▪ 3 | 80 (40) | 26 (28) |
| ▪ 4 | 46 (23) | 24 (25) |
| ▪ 5 | 16 (8) | 9 (9) |

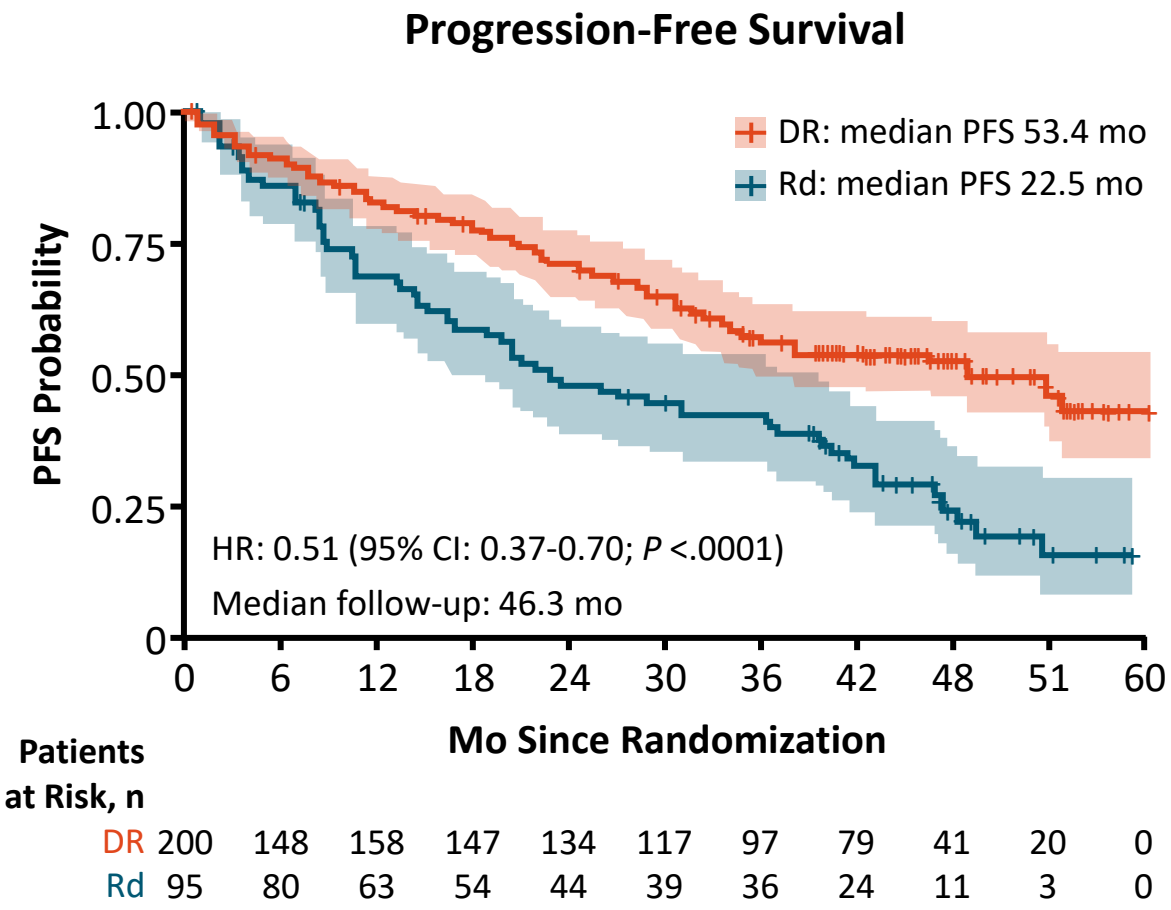
| Characteristic | DR (n = 200) | Rd (n = 95) |
|---|---|---|
| ISS disease stage I/II/III, % | 16/52/32 | 20/52/28 |
| Measurable disease type, n (%) | | |
| ▪ IgG | 113 (57) | 50 (53) |
| ▪ IgA | 36 (18) | 20 (21) |
| ▪ BJP only | 6 (3) | 7 (7) |
| ▪ SFLC only | 26 (13) | 10 (11) |
| Cytogenetics profile,* n (%) | | |
| ▪ Standard risk | 146 (84) | 56 (77) |
| ▪ High risk | 28 (16) | 17 (23) |
| – del17p | 16 (9) | 11 (14) |
| – t(4;14) | 9 (5) | 5 (6) |
| – t(14;16) | 5 (3) | 2 (3) |
| Creatinine clearance, n (%) | | |
| ▪ <30 mL/min | 1 (1) | 3 (3) |
| ▪ 30 to <60 mL/min | 120 (59) | 50 (53) |
| ▪ ≥60 mL/min | 79 (40) | 41 (44) |

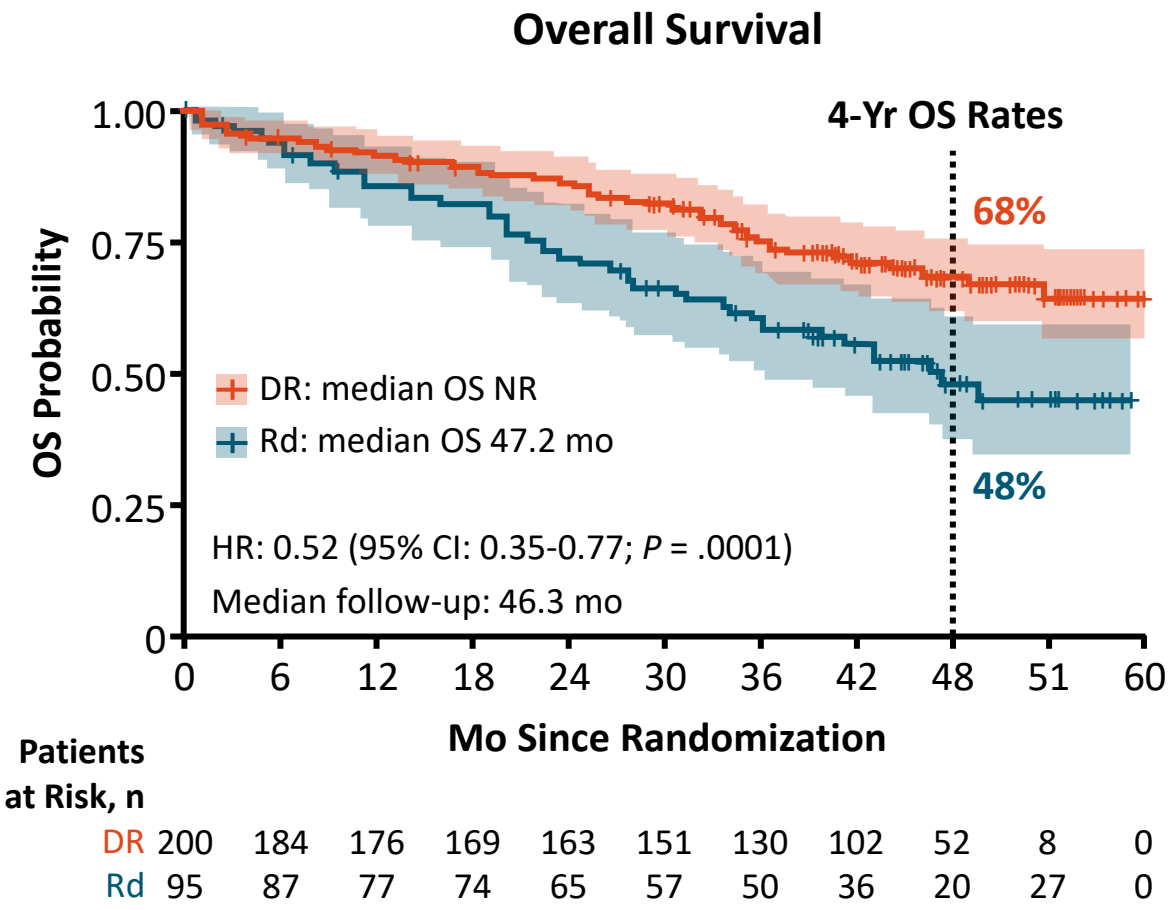
*Cytogenetic profile NA for DR (n=26); Rd (n=22)

Manier. ASH 2024. Abstr 774.

Slide credit: clinicaloptions.com

# IFM2017-03: PFS (Primary Endpoint) and OS



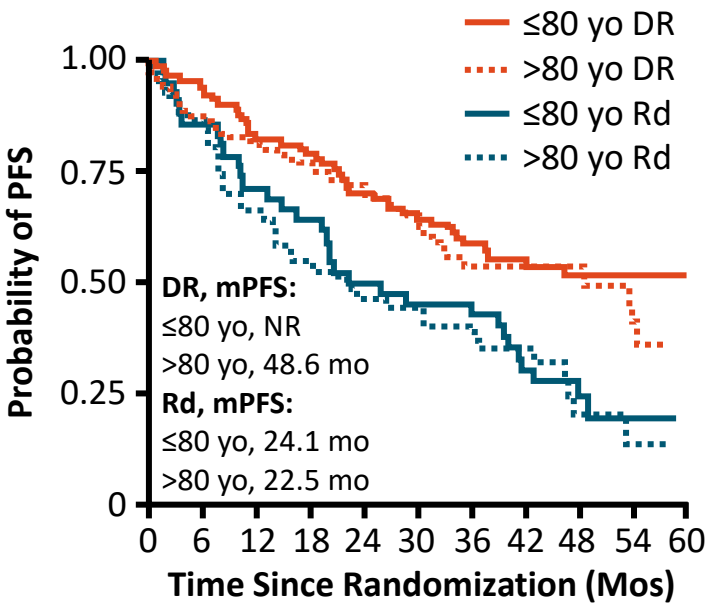




Manier. ASH 2024. Abstr 774. Reproduced with permission.

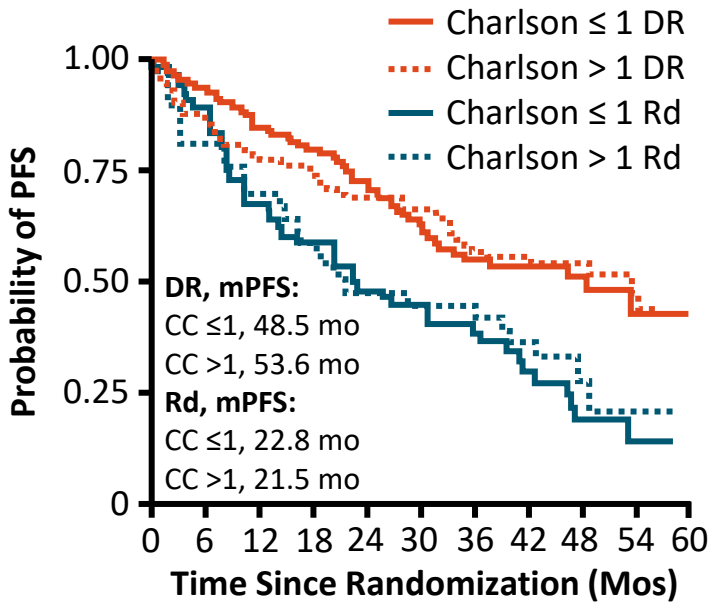
Slide credit: clinicaloptions.com

# IFM2017-03: PFS by Age, Charlson Index, and Frailty

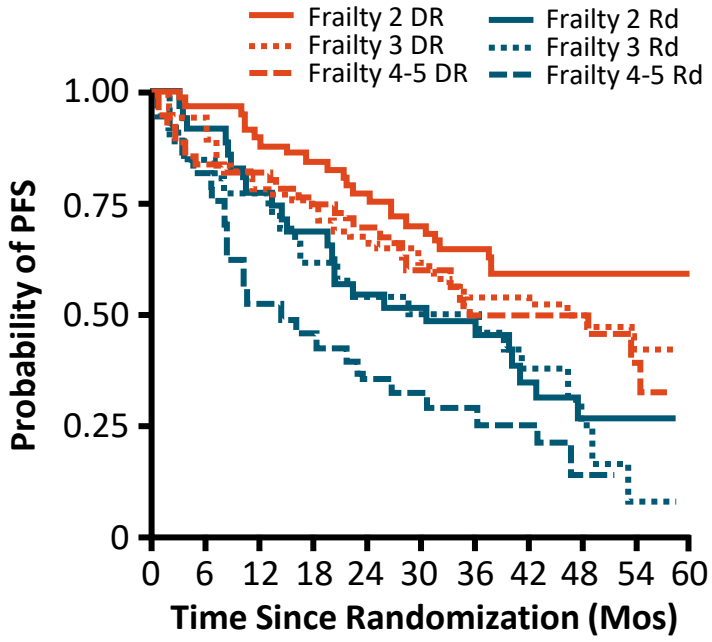
**PFS per Age, ≤80 vs. >80**




**PFS per Charlson, ≤1 vs. >1**




**PFS per Frailty Score, 2 vs. 4-5**



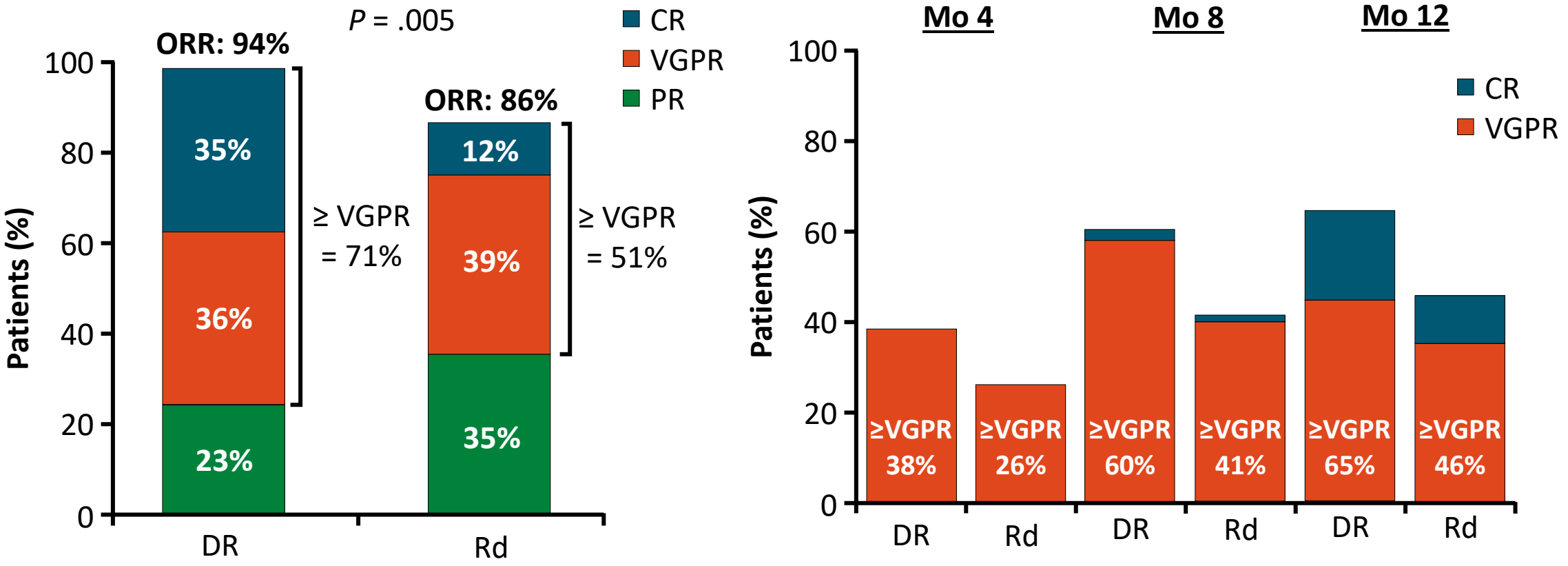

| DR, mPFS: | Rd, mPFS: |
|---|---|
| Frailty 2, NR mo | Frailty 2, 30.6 mo |
| Frailty 3, 46.2 mo | Frailty 3, 32.6 mo |
| Frailty 4-5, 35.3 mo | Frailty 4-5, 14.3 mo |

**Age and Charlson Index did not affect PFS, but the degree of frailty matters**

Manier. ASH 2024. Abstr 774. Reproduced with permission.

Slide credit: clinicaloptions.com

# IFM2017-03: Response Rates




- VGPR or better rate was substantially greater in the DR group
- DR was associated with deeper responses at all time points, including early time points

Manier. ASH 2024. Abstr 774. Reproduced with permission.

Slide credit: clinicaloptions.com

# IFM2017-03: Most Common Grade ≥3 AEs

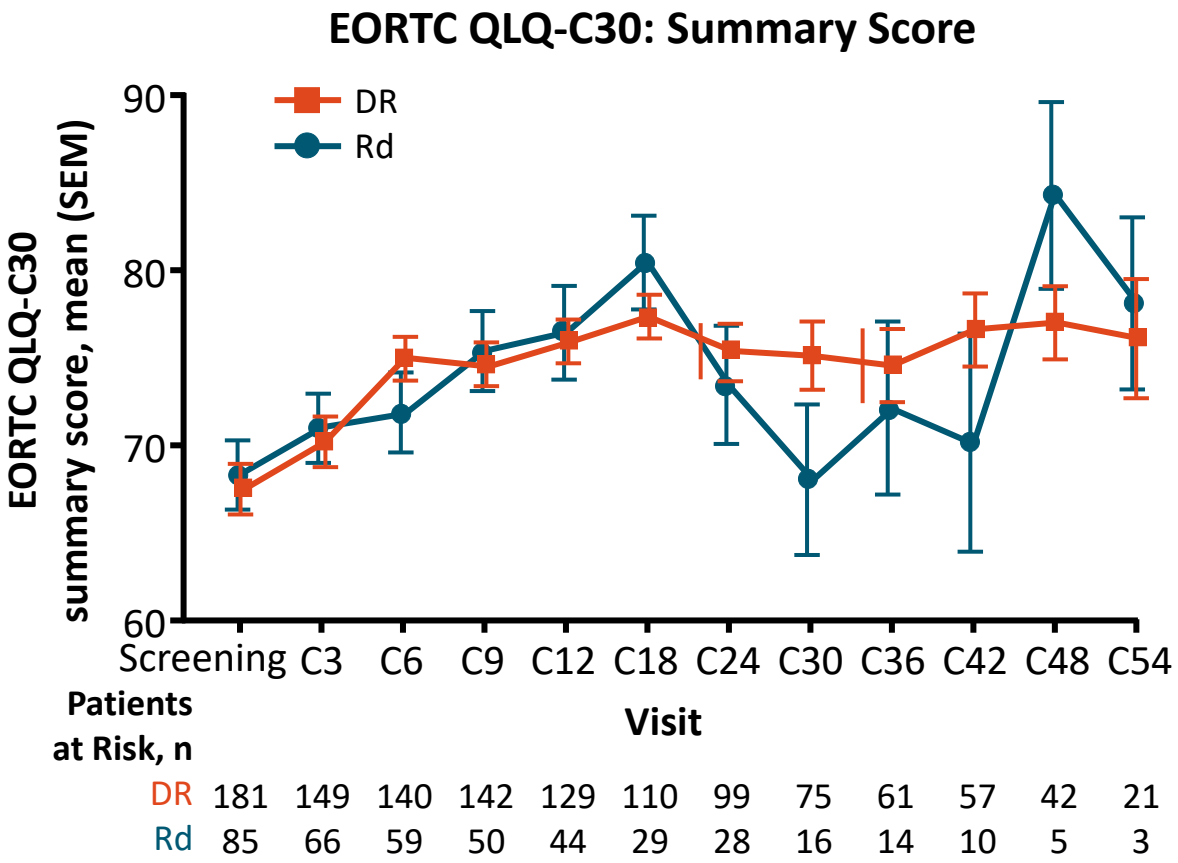
| Outcome | Grade ≥3 AEs | |
|---|---|---|
| | DR (n = 200) | Rd (n = 95) |
| Median treatment duration, mo | 31.6 | 14.3 |
| All grade ≥3 AEs, n (%) | 178 (89) | 75 (79) |
| All grade 5 AEs, n (%) | 23 (12) | 12 (13) |
| Grade 3 hematologic AEs, n (%)<br>▪ Neutropenia<br>▪ Anemia<br>▪ Thrombocytopenia | 123 (62)<br>110 (55)<br>24 (12)<br>19 (10) | 32 (34)<br>23 (24)<br>3 (3)<br>5 (5) |
| Nonhematologic AEs, n (%) | 132 (66) | 68 (72) |
| Infection, n (%)<br>▪ Pneumonia | 38 (19)<br>11 (6) | 20 (21)<br>8 (8) |
| Infection rate per patient-yr | 0.07 | 0.09 |
| Treatment discontinuation due to AE, n (%) | 60 (30) | 32 (34) |

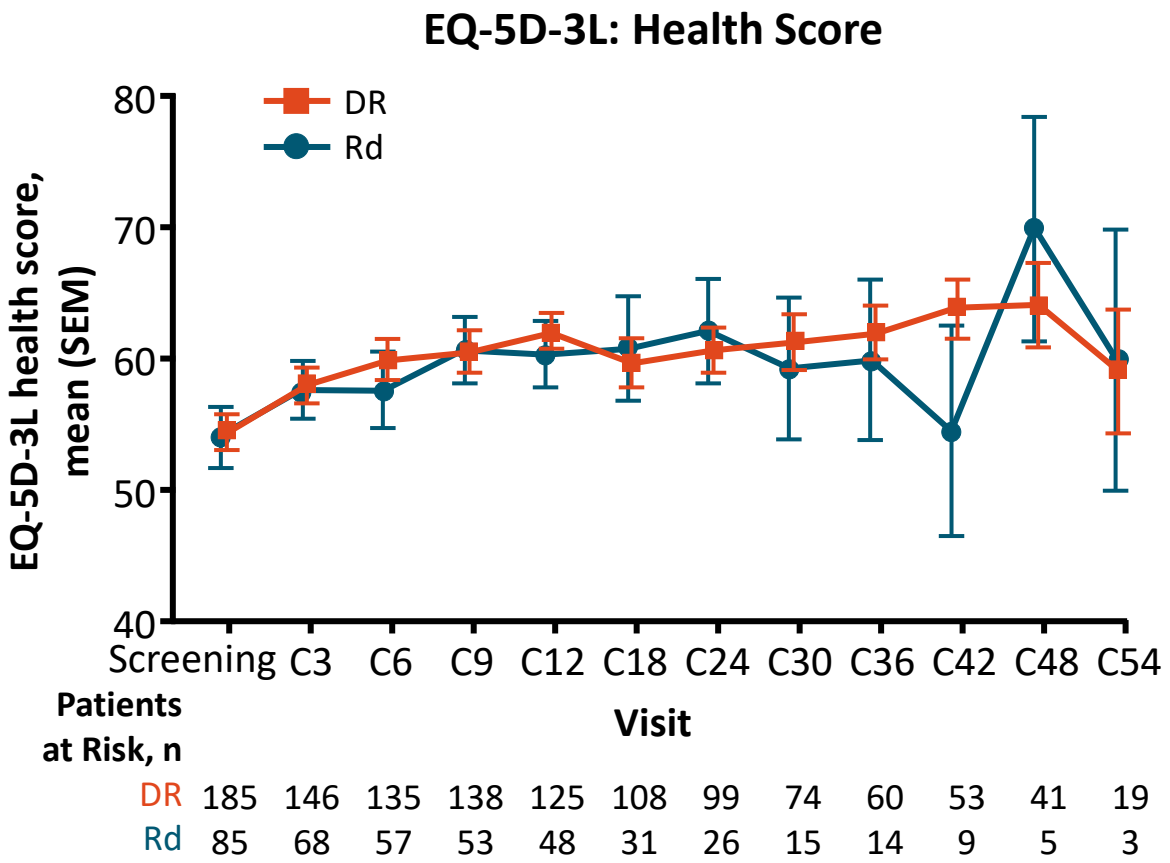
- Patients receiving DR experienced no increased rates of infection or treatment discontinuation

Manier. ASH 2024. Abstr 774.

Slide credit: clinicaloptions.com

# IFM2017-03: Quality of Life



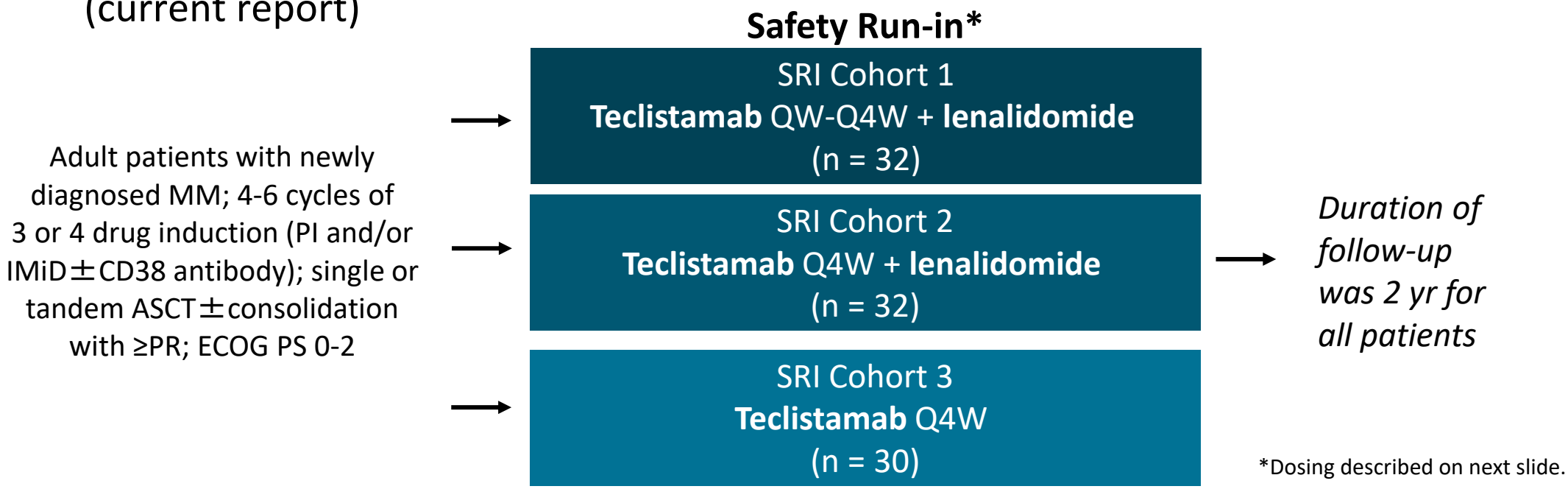

- Patients receiving DR experienced improved quality of life and remained stable

Manier. ASH 2024. Abstr 774. Reproduced with permission.

Slide credit: clinicaloptions.com

# EMN30/MajesTEC-4 SRI: Study Design

- Multicenter, open-label, randomized phase III trial with nonrandomized safety run-in (current report)




- **Primary endpoints (full trial):** PFS, 12 mo MRD-negative CR
- **Key secondary endpoints (full trial):** OS, CR, MRD-negativity, PFS2, TTNT, safety

Zamagni. ASH 2024. Abstr 494.

# EMN30/MajesTEC-4 SRI: Dosing

| SRI Cohort | Cycle 1 | Cycle 2 | Cycles 3-6 | Cycles 7-26 |
|---|---|---|---|---|
| Cohort 1: Tec-Len (Tec QW → Q4W) | Teclistamab step up* + teclistamab 1.5 mg/kg on Days 8, 15, 22 | Teclistamab 1.5 mg/kg QW + lenalidomide | Teclistamab 3.0 mg/kg Q2W + lenalidomide | Teclistamab 3.0 mg/kg Q4W + lenalidomide |
| Cohort 2: Tec-Len (Tec Q4W) | Teclistamab step-up* + teclistamab 1.5 mg/kg Days 8, 15 | Teclistamab 3.0 mg/kg Q4W + lenalidomide | | |
| Cohort 3: Tec Q4W | Teclistamab step-up* + teclistamab 1.5 mg/kg Days 8, 15 | Teclistamab 3.0 mg/kg Q4W | | |

*Step-up doses: 0.06 and 0.3 mg/kg.

- Lenalidomide dosing: 10 mg/day in cycles 2-4, then 15 mg/day in cycles 5-26, if tolerated
- 2-yr fixed-duration maintenance regimen defined as: patients who achieved CR after 1 yr discontinued teclistamab but continued lenalidomide for 1 yr later

Zamagni. ASH 2024. Abstr 494.

# EMN30/MajesTEC-4 SRI: Baseline Characteristics

| Characteristic | SRI Cohort 1 Tec-Len (QW → Q4W) (n = 32) | SRI Cohort 2 Tec-Len (Q4W) (n = 32) | SRI Cohort 3 Tec (Q4W) (n = 30) |
|---|---|---|---|
| Median age, yr (range)<br>▪ ≥65 yr, n (%) | 58.5 (31-73)<br>12 (37.5) | 58.0 (38-73)<br>5 (15.6) | 58.5 (34-72)<br>9 (30.0) |
| Male, n (%) | 21 (65.6) | 21 (65.6) | 22 (73.3) |
| White, n (%) | 32 (100) | 32 (100) | 30 (100) |
| ISS stage at diagnosis, n/N (%)<br>▪ I<br>▪ II<br>▪ III | <br>18/32 (56.3)<br>7/32 (21.9)<br>7/32 (21.9) | <br>8/32 (25.0)<br>9/32 (28.1)<br>15/32 (46.9) | <br>9/28 (32.1)<br>11/28 (39.3)<br>8/28 (28.6) |
| High cytogenetic risk at diagnosis, n/N (%) | 7/25 (28.0) | 5/29 (17.2) | 6/25 (24.0) |
| MM induction, n (%)<br>▪ PI + IMiD<br>▪ PI + IMiD + CD38 antibody | <br>28 (87.5)<br>11 (34.4) | <br>28 (87.5)<br>19 (59.4) | <br>30 (100)<br>20 (66.7) |
| Prior consolidation, n (%) | 6 (18.8) | 12 (37.5) | 10 (33.3) |

- Median time from ASCT to maintenance (all patients): 4.7 mo (range: 1.8-7.4)
- All patients had ECOG PS 0/1

Zamagni. ASH 2024. Abstr 494.

Slide credit: clinicaloptions.com

# EMN30/MajesTEC-4 SRI: Hematologic TEAEs

| TEAEs, n (%) | SRI Cohort 1 Tec-Len (QW → Q4W) (n = 32) | | SRI Cohort 2 Tec-Len (Q4W) (n = 32) | | SRI Cohort 3 Tec (Q4W) (n = 30) | |
|---|---|---|---|---|---|---|
| | Any Grade | Grade 3/4 | Any Grade | Grade 3/4 | Any Grade | Grade 3/4 |
| Any | 32 (100) | 32 (100) | 32 (100) | 27 (84.4) | 30 (100) | 17 (56.7) |
| Hematologic TEAE | | | | | | |
| ▪ Neutropenia | 30 (93.8) | 30 (93.8) | 21 (65.6) | 20 (62.5) | 17 (56.7) | 14 (46.7) |
| ▪ Leukopenia | 9 (28.1) | 3 (9.4) | 1 (3.1) | 0 | 1 (3.3) | 1 (3.3) |
| ▪ Lymphopenia | 2 (6.3) | 1 (3.1) | 4 (12.5) | 4 (12.5) | 4 (13.3) | 4 (13.3) |
| ▪ Thrombocytopenia | 6 (18.8) | 2 (6.2) | 0 | 0 | 2 (6.7) | 0 |
| ▪ Febrile neutropenia | 3 (9.4) | 3 (9.4) | 3 (9.4) | 3 (9.4) | 0 | 0 |
| ▪ Anemia | 3 (9.4) | 0 | 1 (3.1) | 1 (3.1) | 1 (3.3) | 0 |
| ▪ Eosinophilia | 1 (3.1) | 1 (3.1) | 1 (3.1) | 1 (3.1) | 0 | 0 |

*Median follow-up: cohort 1, 21.1 mo; cohort 2, 9.2 mo; cohort 3, 9.2 mo.

- Incidence of grade 3/4 neutropenia at Mo 6: cohort 1, 81.3%; cohort 2, 56.3%; cohort 3, 40.0%
- Median relative dose intensity: teclistamab, 95.5%-99.7%; lenalidomide, 58.4%-61.5%
- Treatment discontinuation due to TEAEs: 5.3% overall
- Less grade 3/4 neutropenia with cohort 2 vs cohort 1

Zamagni. ASH 2024. Abstr 494.

# EMN30/MajesTEC-4 SRI: Nonhematologic TEAEs

| TEAEs, n (%) | SRI Cohort 1 Tec-Len (QW → Q4W) (n = 32) | | SRI Cohort 2 Tec-Len (Q4W) (n = 32) | | SRI Cohort 3 Tec (Q4W) (n = 30) | |
|---|---|---|---|---|---|---|
| | Any Grade | Grade 3/4 | Any Grade | Grade 3/4 | Any Grade | Grade 3/4 |
| Nonhematologic AEs | | | | | | |
| ▪ CRS | 16 (50.0) | 0 | 13 (40.6) | 0 | 13 (43.3) | 0 |
| ▪ URTI | 20 (62.5) | 1 (3.1) | 13 (40.6) | 0 | 8 (26.7) | 0 |
| ▪ Cough | 15 (46.9) | 0 | 6 (18.8) | 0 | 8 (26.7) | 0 |
| ▪ Diarrhea | 13 (40.6) | 3 (9.4) | 9 (28.1) | 1 (3.1) | 6 (20.0) | 0 |
| ▪ Injection-site erythema | 7 (21.9) | 0 | 12 (37.5) | 0 | 8 (26.7) | 0 |
| ▪ COVID-19 | 12 (37.5) | 1 (3.1) | 5 (15.6) | 0 | 9 (30.0) | 1 (3.3) |
| ▪ Fatigue | 10 (31.3) | 1 (3.1) | 8 (25.0) | 1 (3.1) | 5 (16.7) | 0 |
| ▪ Pneumonia | 9 (28.1) | 4 (12.5) | 3 (9.4) | 0 | 2 (6.7) | 1 (3.3) |

- Low rates of grade 3/4 nonhematologic TEAEs
- CRS events all grade 1/2 (no discontinuations due to CRS), mostly during teclistamab step-up dosing: after step-up dose 1: 37.2%; after step-up dose 2: 8.5%; after treatment dose 1: 5.3%
- No ICANS

Zamagni. ASH 2024. Abstr 494.

# EMN30/MajesTEC-4 SRI: Infections and Hypogammaglobulinemia

| TEAEs, n (%) | SRI Cohort 1 Tec-Len (QW → Q4W) (n= 32) | | SRI Cohort 2 Tec-Len (Q4W) (n = 32) | | SRI Cohort 3 Tec (Q4W) (n = 30) | |
|---|---|---|---|---|---|---|
| | Any Grade | Grade 3/4 | Any Grade | Grade 3/4 | Any Grade | Grade 3/4 |
| Any infection | 30 (93.8) | 12 (37.5) | 25 (78.1) | 9 (28.1) | 23 (76.7) | 6 (20.0) |
| Most common infections | | | | | | |
| ▪ URTI | 20 (62.5) | 1 (3.1) | 13 (40.6) | 0 | 8 (26.7) | 0 |
| ▪ COVID-19 | 12 (37.5) | 1 (3.1) | 5 (15.6) | 0 | 9 (30.0) | 1 (3.3) |
| ▪ Pneumonia | 9 (28.1) | 4 (12.5) | 3 (9.4) | 0 | 2 (6.7) | 1 (3.3) |
| ▪ Nasopharyngitis | 6 (18.8) | 0 | 0 | 0 | 3 (10.0) | 0 |

- Hypogammaglobulinemia: cohort 1: 31 (96.9%); cohort 2: 25 (78.1%); cohort 3: 28 (93.3%); all received ≥1 dose IVIg or SCIg
- 1 grade 5 COVID-19 TEAE in cohort 2
- Infection prophylaxis was strongly recommended, including immunoglobulin replacement

Zamagni. ASH 2024. Abstr 494.

# EMN30/MajesTEC-4 SRI: Response, MRD Negativity, and PFS

| Response, % | SRI Cohort 1 Tec-Len (QW → Q4W) (n = 32) | | SRI Cohort 2 Tec-Len (Q4W) (n = 32) | | SRI Cohort 3 Tec (Q4W) (n = 30) | |
|---|---|---|---|---|---|---|
| | Post ASCT* | Best on Maint | Post ASCT* | Best on Maint | Post ASCT* | Best on Maint |
| sCR | 18.8 | 90.6 | 12.5 | 65.6 | 3.3 | 70.0 |
| CR | 18.8 | 9.4 | 12.5 | 25.0 | 30.0 | 23.3 |
| VGPR | 40.6 | -- | 56.3 | 9.4 | 43.3 | 6.7 |
| PR | 21.9 | -- | 18.8 | -- | 23.3 | -- |
| ≥CR | 37.6 | 100 | 25.0 | 90.6 | 33.3 | 93.3 |
| **MRD Negative, %** | **Post ASCT† (n = 27)** | **At 12 Mo (n = 28)** | **Post ASCT† (n = 30)** | **At 6 Mo (n = 26)** | **Post ASCT† (n = 30)** | **At 6 Mo (n = 22)** |
| Rate | 63.0 | 100 | 83.3 | 100 | 73.3 | 100 |

*ASCT and consolidation. †MRD negative defined as proportion who achieved MRD negativity ($10^{-5}$) regardless of response.

- Median PFS was not reached in all cohorts

Zamagni. ASH 2024. Abstr 494.

Slide credit: clinicaloptions.com