# How to Integrate Novel Approaches in the Treatment of Relapsed/ Refractory Multiple Myeloma

## Conference Highlights
## 2021 Virtual ASH Annual Meeting

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# Disclosures

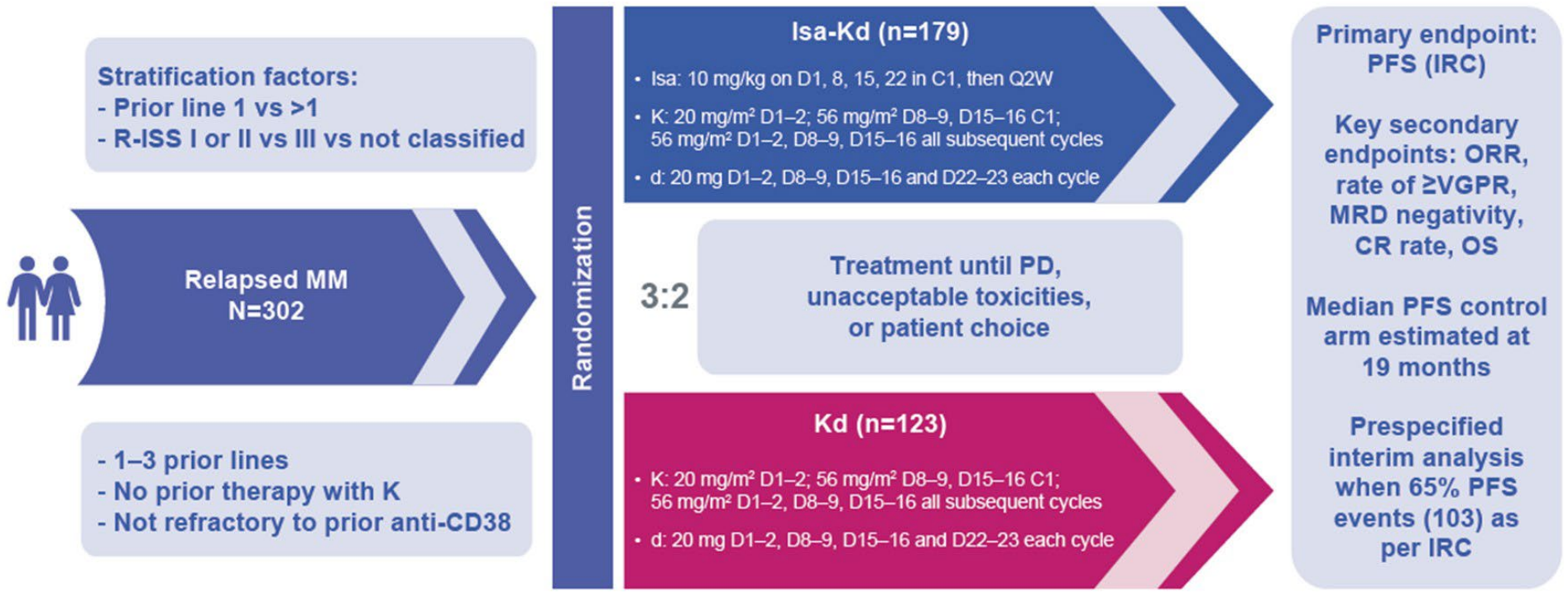
- Consulting: AbbVie, Caelum, Celularity, GlaxoSmithKline, Janssen, Karyopharm, Sanofi, Sorrento, and Takeda
- Research support: Karyopharm and Sanofi
- Shares/ Patent: Caelum

# Novel Approaches in the Treatment of Relapsed/ Refractory Multiple Myeloma presented at ASH 2021

- IKEMA Study in High-Risk Multiple Myeloma
- Bispecific T-Cell Engagers (BITEs)
- Combination Therapy With BITEs
- CAR T-Cell Treatment
- AlloCAR T-Cell Treatment

IKEMA

# Isatuximab plus carfilzomib and dexamethasone in relapsed multiple myeloma patients with high-risk cytogenetics: IKEMA subgroup analysis



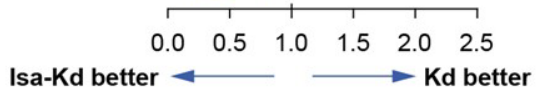

Sample size calculation: ~300 patients and 159 PFS events to detect 41% risk reduction in hazard rate for PFS with 90% power and one-sided 0.025 significance level

IKEMA study: NCT03275285
C, cycle; CD, cluster of differentiation; CR, complete response; D, day; d, dexamethasone; IRC, Independent Response Committee; Isa, isatuximab; K, carfilzomib; MM, multiple myeloma; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Q2W, once every 2 weeks; R-ISS, Revised International Staging System; VGPR, very good partial response

Moreau P, et al. *Future Oncol*. 2020;16:4347–58

# IKEMA
## Progression-free survival

| Subgroup | Isa-Kd Group (n/N) | Kd Group (n/N) | Hazard ratio (95% CI) |
|---|---|---|---|
| **All patients** | 48/179 | 55/123 | 0.531 (0.359–0.786) |
| **High-risk chromosomal abnormality*** | | | |
| At least one | 17/42 | 15/31 | 0.724 (0.361–1.451) |
| None | 27/114 | 35/77 | 0.440 (0.266–0.728) |
| **del(17p)** | | | |
| Present | 6/18 | 7/16 | 0.837 (0.281–2.496) |
| Absent | 39/143 | 43/96 | 0.510 (0.330–0.788) |
| **t(4;14)** | | | |
| Present | 10/22 | 11/20 | 0.549 (0.232–1.301) |
| Absent | 34/137 | 39/89 | 0.491 (0.310–0.778) |
| **t(14;16)** | | | |
| Present | 4/6 | 0/0 | NC |
| Absent | 41/153 | 50/111 | 0.501 (0.331–0.757) |
| **gain(1q21)** | | | |
| Present | 26/75 | 26/52 | 0.569 (0.330–0.981) |
| Absent | 19/84 | 24/55 | 0.443 (0.242–0.812) |
| **Isolated gain(1q21)** | 13/47 | 15/31 | 0.462 (0.219–0.972) |
| **No gain(1q21) and standard risk** | 14/65 | 20/43 | 0.396 (0.199–0.787) |

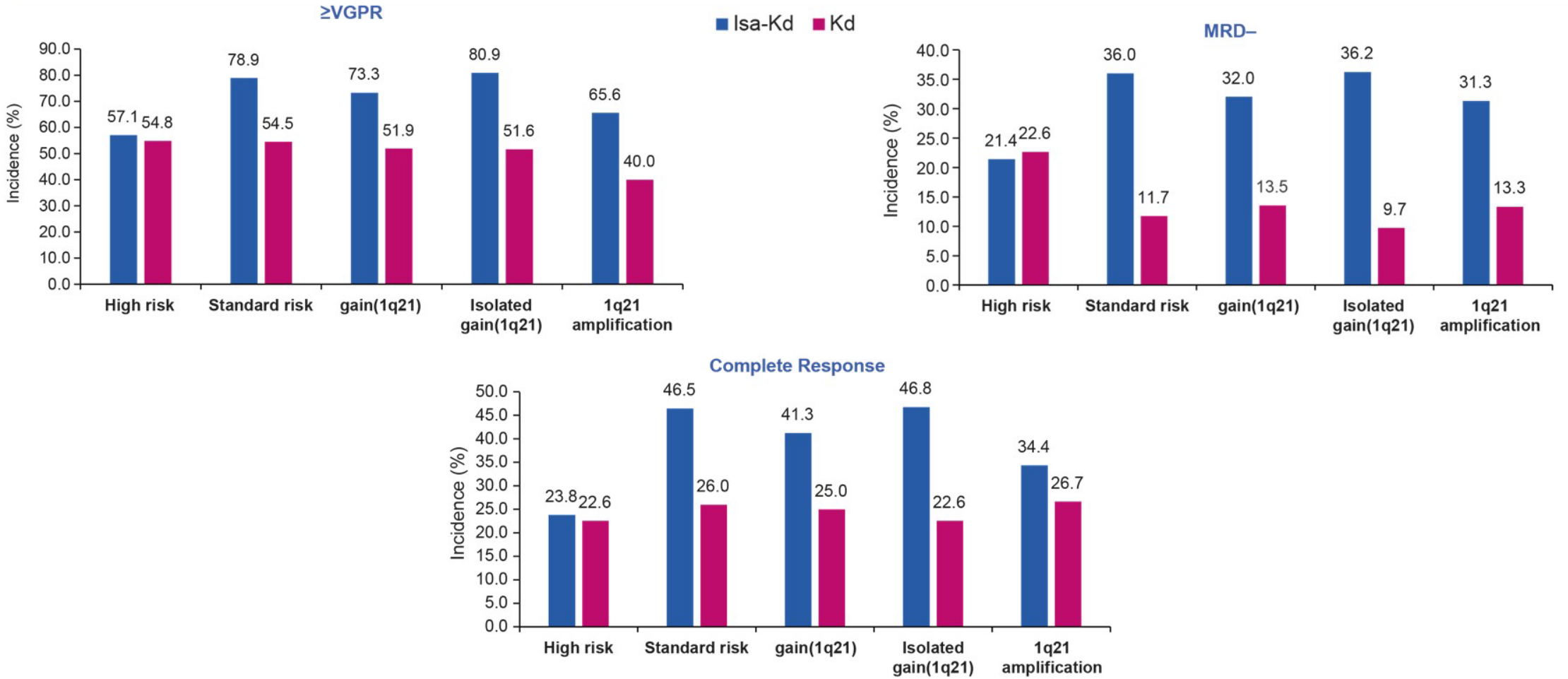



- **Benefit was also observed in patients with 1q21 amplification (HR 0.531; 95% CI 0.150–1.878)**

**PFS benefit in favor of Isa-Kd was seen in patients with high-risk CA, standard-risk CA, gain(1q21), isolated gain(1q21), and 1q21 amplification**

*High-risk cytogenetics defined as the presence of del(17p), t(4;14), and/or t(14;16)
CI, confidence interval; d, dexamethasone; Isa, isatuximab; K, carfilzomib; PFS, progression-free survival

# IKEMA
## Depth of response




**Isa-Kd improved depth of response vs Kd in patients with gain or amplification of 1q21**



d, dexamethasone; Isa, isatuximab; K, carfilzomib; MRD-, minimal residual disease negativity; VGPR, very good partial response

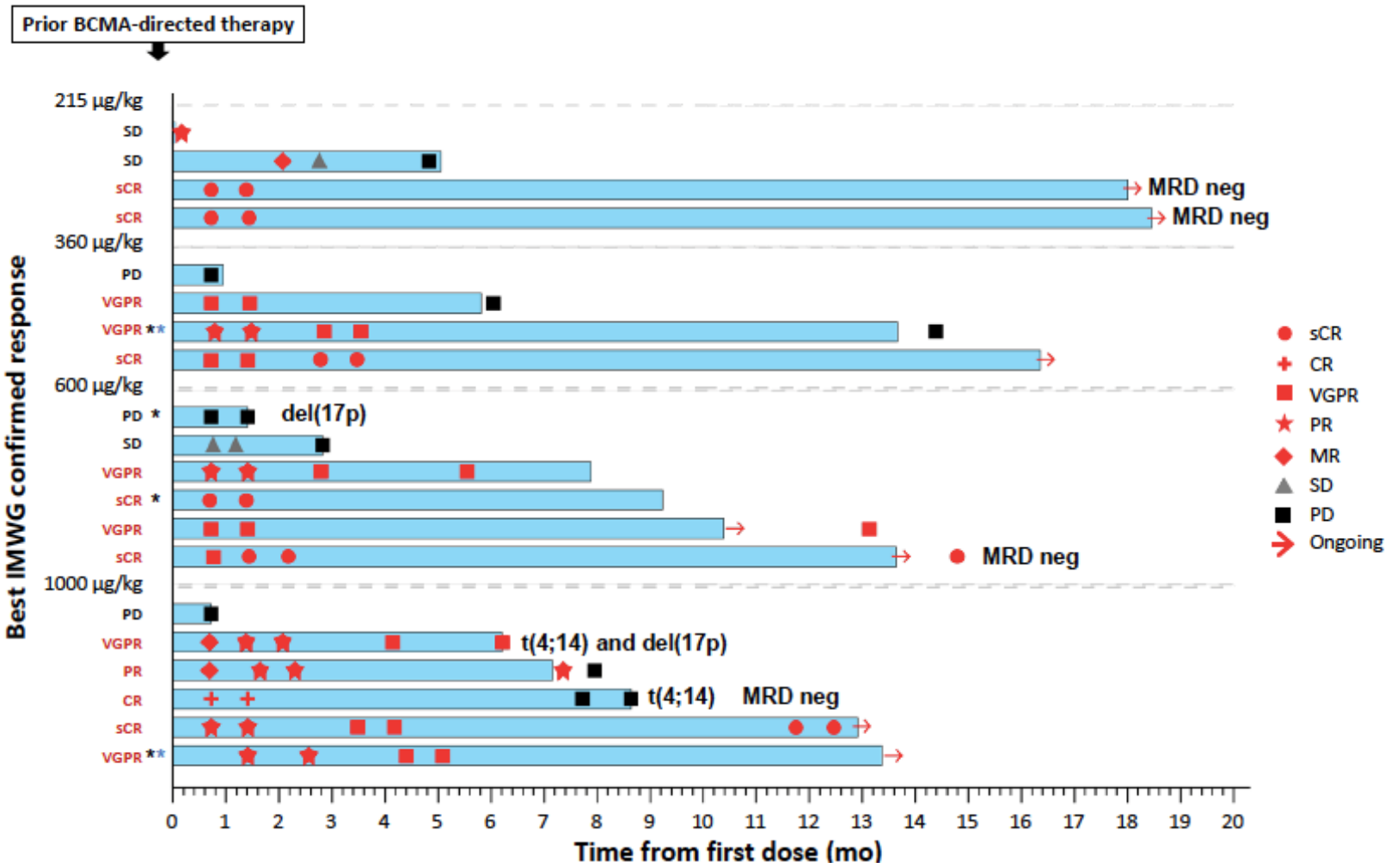
# Bispecific T-Cell Engagers (BITEs)

- MagnetisMM-1: Phase 1/2 Study of Elranatamab (Pfizer)
- Phase 1 Study REGN5458 (Regeneron)
- MajesTEC-1: Phase 1/2 Study of Teclistamab (Janssen)
- Phase 1b Study of TNB-383B (Abbvie)

# MagnetisMM-1: A Study of Elranatamab (PF-06863135), a B-Cell Maturation Antigen (BCMA)-Targeted CD3-Engaging Bispecific Molecule, for Patients With Relapsed or Refractory Multiple Myeloma

- MagnetisMM-1 (NCT03269136), the initial study for the MagnetisMM program, is a multipart phase 1 trial designed to evaluate the safety, PD, PK, and efficacy of elranatamab for patients with RRMM
- Report results for elranatamab as a single agent from SC dose escalation (Part 1), priming cohorts (Part 1.1), and expansion (Part 2A)
- Elranatamab is given SC
- Prior BCMA treatment was permitted

# Escalation (Part 1, ≥ 215 µg/kg, N=20) Duration of Treatment

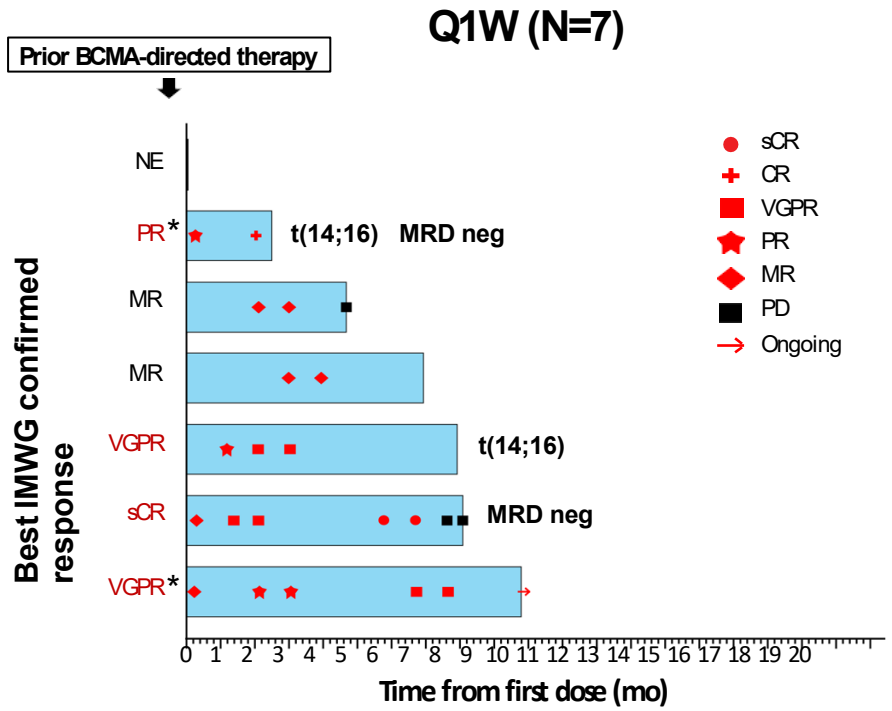


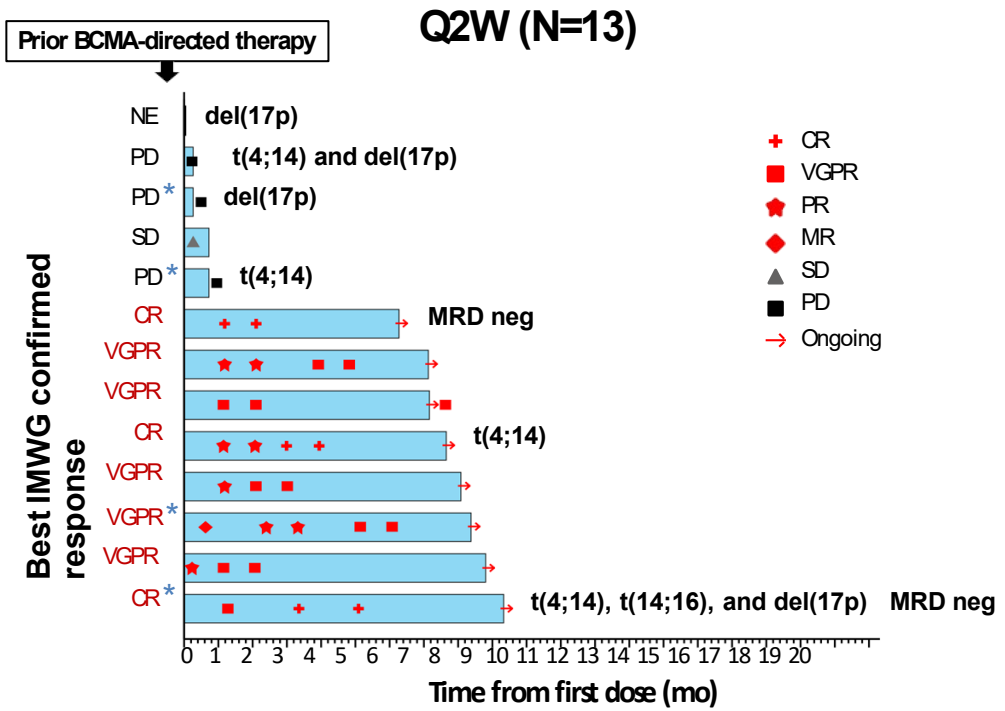

- Median follow-up was 12.5 months.
- 75% (3/4) of patients with prior BCMA-directed therapy achieved response including 1 sCR and 2 VGPR.
- 100% (4/4) of patients assessed were MRD negative.

Data cutoff was July 26, 2021. Swimmer plot depicts disease assessments relevant to first response, confirmation of response, deepening of response, and best response.
MRD status, available for 4 patients, was assessed by next-generation sequencing at a sensitivity of $1x10^{-5}$ in accordance with IMWG criteria for MRD assessment.
* Prior anti-BCMA ADC. * Prior BCMA-targeted CAR-T.
sCR=stringent complete response; CR=complete response; VGPR=very good partial response; PR=partial response; MR=minimal response; SD=stable disease; PD=progressive disease; BCMA=B-cell maturation antigen; MRD=minimal residual disease; neg=negative; IMWG=International Myeloma Working Group; ADC=antibody drug conjugate; CAR-T=chimeric antigen receptor T-cell therapy.

# Priming Cohorts (Part 1.1, N=20) – Duration of Treatment

- Median follow-up was 7.5 months




- 100% (2/2) of patients with prior BCMA-directed therapy achieved response including 1 PR and 1 VGPR
- 100% (2/2) of patients assessed were MRD negative

- 50% (2/4) of patients with prior BCMA-directed therapy achieved response including 1 CR and 1 VGPR
- 100% (2/2) of patients assessed were MRD negative

Data cutoff was July 26, 2021. Swimmer plots depict disease assessments relevant to first response, confirmation of response, deepening of response, and best response.
MRD status, available for 4 patients, was assessed by next-generation sequencing at a sensitivity of $1x10^{-5}$ in accordance with IMWG criteria for MRD assessment.
* Prior anti-BCMA ADC. * Prior BCMA-targeted CAR-T.

Q1W=weekly; Q2W=every 2 weeks; sCR=stringent complete response; CR=complete response; VGPR=very good partial response; PR=partial response; MR=minimal response; SD=stable disease; PD=progressive disease; NE=not evaluable; BCMA=B-cell maturation antigen; MRD=minimal residual disease; neg=negative; IMWG=International Myeloma Working Group; ADC=antibody drug conjugate; CAR-T=chimeric antigen receptor T-cell therapy.

# Conclusions

- Elranatamab monotherapy SC had a manageable safety profile for patients with RRMM
- Elranatamab 1000 µg/kg Q2W achieved exposure associated with anti-myeloma efficacy
- Confirmed ORR was 69% (9/13[a]) at the recommended dose of 1000 µg/kg Q1W
- 70% (7/10) of patients with prior BCMA-directed therapy achieved response
- These results, including both clinical and molecular responses, support continued development of elranatamab for patients with MM

# REGN5458, a BCMAxCD3 Bispecific Antibody, in a Phase 1/2 in RRMM

## Primary objectives (Phase 1)

- Safety, tolerability, and DLTs
- Recommended Phase 2 dose (RP2D)

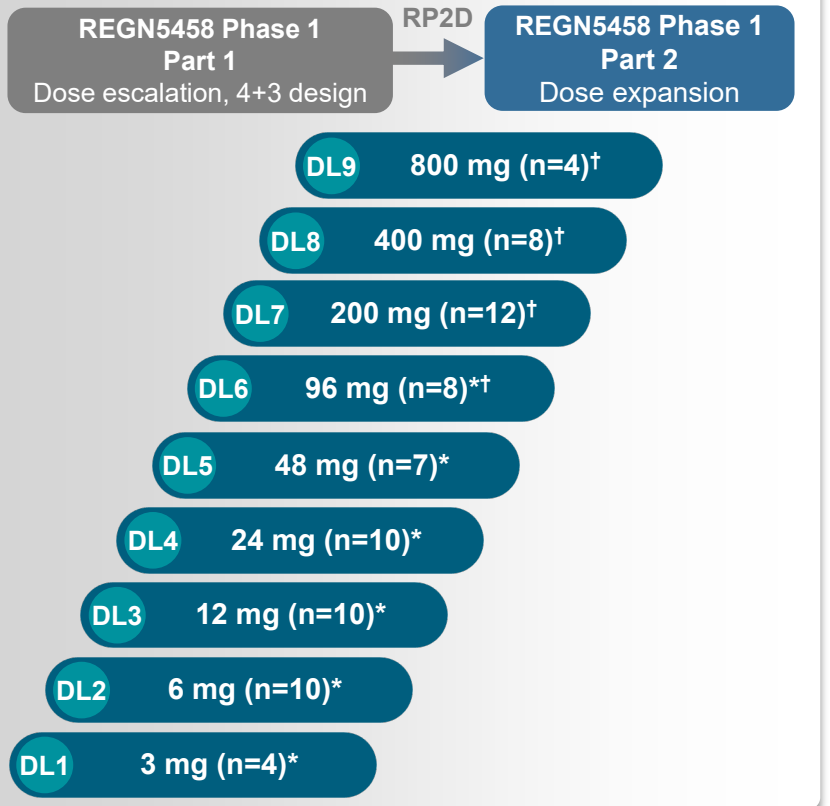
## Secondary objectives (Phase 1)

ORR, DOR, PFS, MRD status, and OS

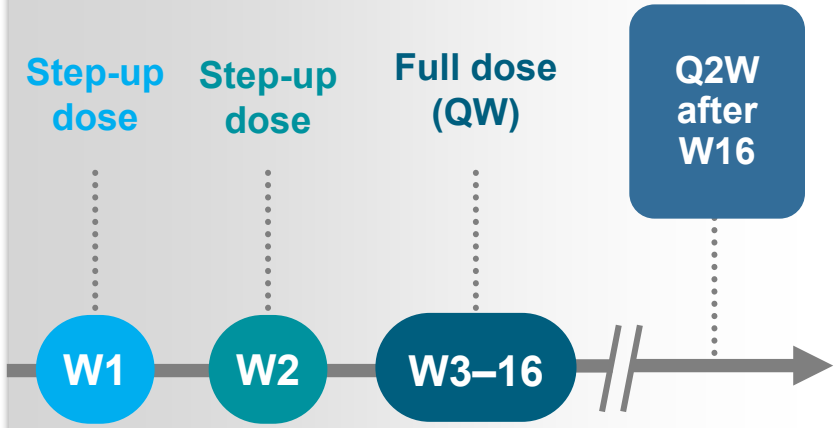
## Patient eligibility

- Active MM by IMWG; non-secretory MM allowed
- Relapsed/refractory (or intolerance) to ≥3 lines of therapy including an IMiD, a PI, and an anti-CD38 Ab, or double-refractory to an IMiD and PI and progressed on or after an anti-CD38 Ab

## REGN5458 IV dose levels

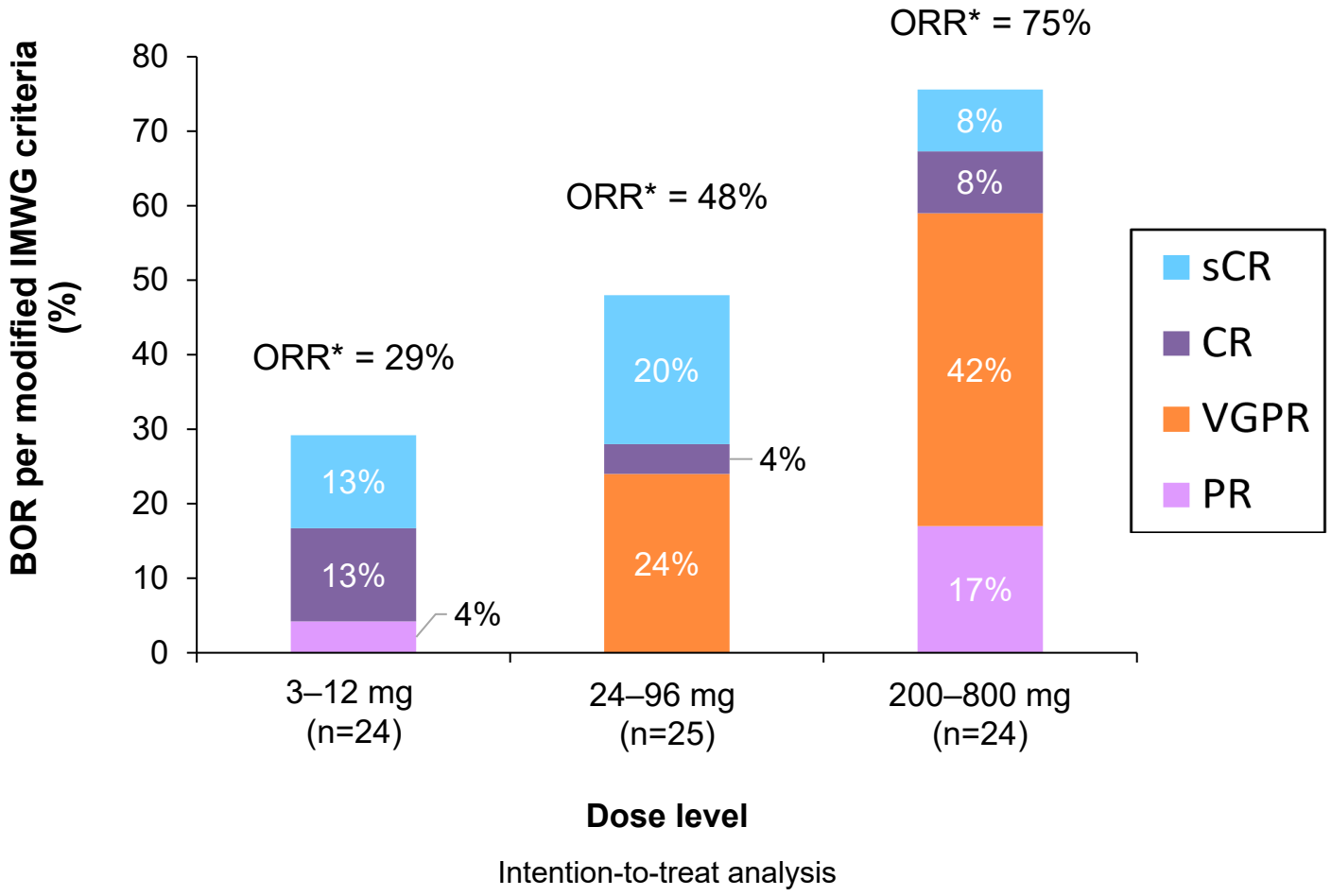



## REGN5458 Phase 1 dosing schedule




*With 1 dose-level specific step-up dose; †With 5 and 25 mg step-up doses
Ab, antibody; CD, cluster of differentiation; DL, dose level; DLT, dose-limiting toxicity; DOR, duration of response; IMiD, immunomodulatory imide drug; IMWG, International Myeloma Working Group; MM, multiple myeloma; MRD, minimal residual disease; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; QW, weekly; Q2W, every 2 weeks; W, week.

# Phase 1 efficacy




- Responses have been observed across all dose levels, with a trend for higher response rates at higher doses
  - 51% ORR among all enrolled patients*
- 75% ORR and 58% ≥VGPR with REGN5458 200–800 mg
- Among all responders, 86% achieved ≥VGPR, 43% ≥CR
- Among CR/sCR with available MRD data:
  - 4/10 MRD negative at $10^{-5}$

Data cut-off: 30 September 2021. *Full analysis set - includes all patients who had opportunity for response assessment at 4 weeks.
BOR, best overall response; CR, complete response; IMWG, International Myeloma Working Group; MRD, minimal residual disease; ORR, objective response rate; PR, partial response; sCR, stringent CR; VGPR, very good partial response.

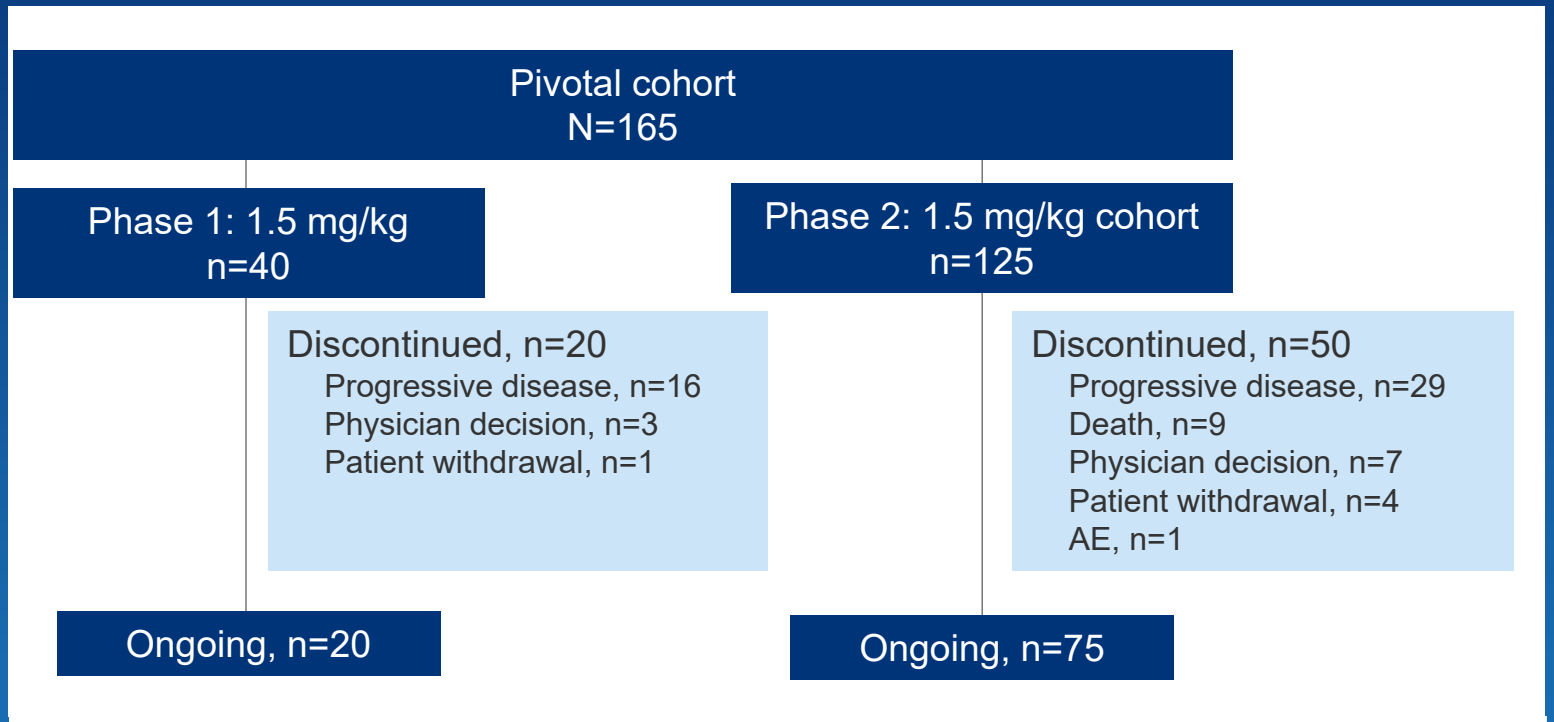
Observed median duration of follow-up (range): 3 months (0.7–22.1)

# REGN5458: Conclusions

- **Early, deep, and durable responses are observed with REGN5458 in patients with RRMM who are at least triple refractory to prior treatment**
  - ORR of 75% and 58% ≥VGPR at higher doses (200–800 mg)
  - 86% of responders achieved VGPR or better; 43% ≥CR
  - Estimated median DOR was not reached
  - Probability of responders being event free at 8 months was 90.2% (95% CI: 72.6, 96.7)
- **REGN5458 shows an acceptable and manageable safety and tolerability profile**
  - Maximum tolerated dose has not been reached
  - CRS was reported in 38% of the patients
    - The majority of events were Grade 1, occurred within the first 2 weeks, and resolved within 1 day
    - No correlation between CRS and dose level was observed
- **REGN5458 showed promising efficacy and manageable safety in patients with heavily pretreated RRMM**
- **These results support further development as monotherapy. Phase 2 portion of the study is recruiting**

CI, confidence interval; CR, complete response; CRS, cytokine release syndrome; DOR, duration of response; ORR, objective response rate; RRMM, relapsed/refractory multiple myeloma; VGPR, very good partial response.

# MajesTEC-1: Phase 1/2 Study of Teclistamab, a B-Cell Maturation Antigen x CD3 Bispecific Antibody in RRMM




| | Phase 1 Cohort | Phase 2 Cohort | Patients, n |
|---|---|---|---|
| Primary efficacy analysis[b] | 40 | 110 | 150 |
| Primary safety analysis[c] | 40 | 125 | 165 |

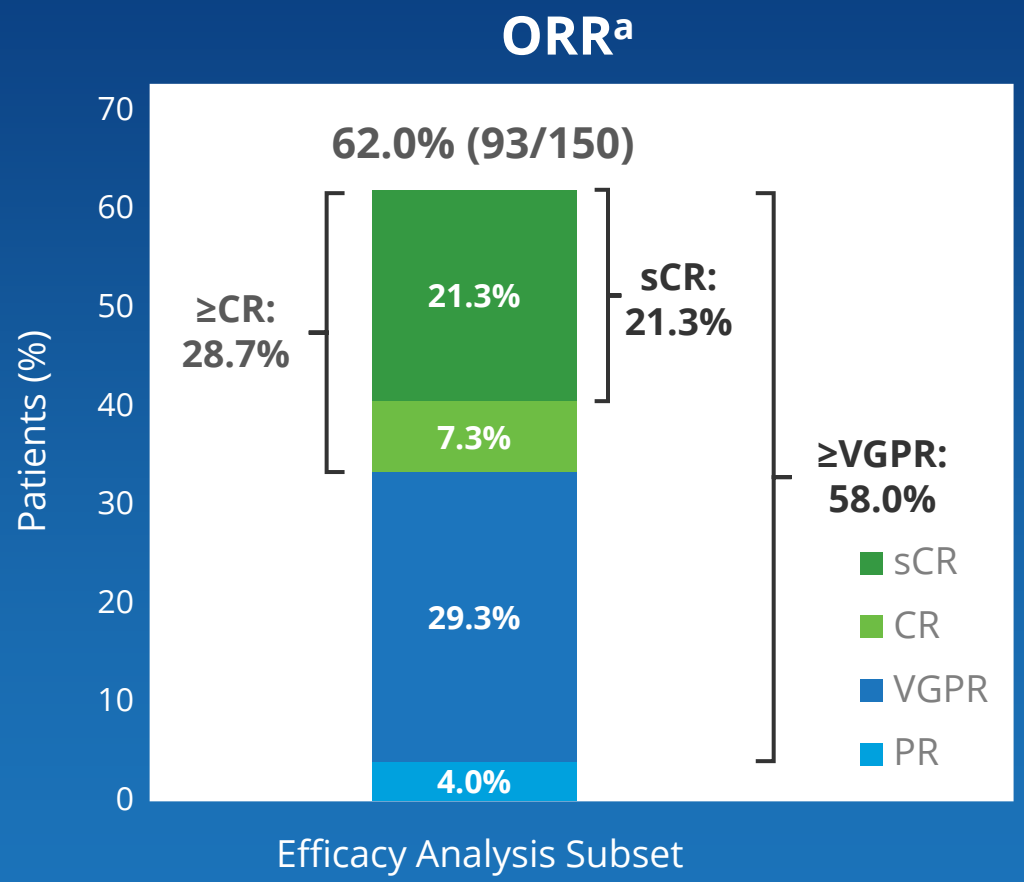
## Teclistamab Exposure

(as of CCO 07 Sept 2021)

- Median treatment duration was 5.9 months (range: 0.2–18.0) for patients included in the primary safety analysis
- 77 patients (46.7%) received ≥6 months of treatment, and 27 patients (16.4%) received ≥9 months of treatment
- No patients had a teclistamab dose reduction

[a]Phase 1 and 2 had similar inclusion criteria. [b]Includes all enrolled patients who received ≥1 dose on or before 18 March 2021; [c]Includes patients enrolled in pivotal RP2D cohorts on or before the CCO of 7 Sep 2021.
AE, adverse event; CCO, clinical cutoff; RP2D, recommended phase 2 dose

# MajesTEC-1: Overall Response Rate for Teclistamab Monotherapy




- At a median follow-up of 7.8 months (range: 0.5+–18):
  - ORR of 62.0% (95% CI: 53.7–69.8) represents a substantial benefit for patients with triple-class exposed disease
- Median time to first response: 1.2 months (range: 0.2–5.5)
- MRD negativity rate[b]
  - 24.7% (37/150; 95% CI: 18.0–32.4) at a threshold of $10^{-5}$
  - 16.7% (25/150; 95% CI: 11.1–23.6) at a threshold of $10^{-6}$[,c]
- In patients who achieved ≥CR, the MRD-negativity rate was 41.9%

[a]PR or better, IRC assessed; ORR was assessed in efficacy analysis population, which includes all patients who received their first dose on or before March 18, 2021 (n=150); [b] Baseline clones were obtained for all patients All MRD assessments were done by next-generation sequencing; [c]Patients who were not negative at the $10^{-6}$ threshold were indeterminate.

CR, complete response; IRC, independent review committee; MRD, minimal residual disease; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

# MajesTEC-1: Phase 1/2 Conclusions

**In MajesTEC-1, teclistamab was efficacious and tolerable in patients with triple-class exposed RRMM**

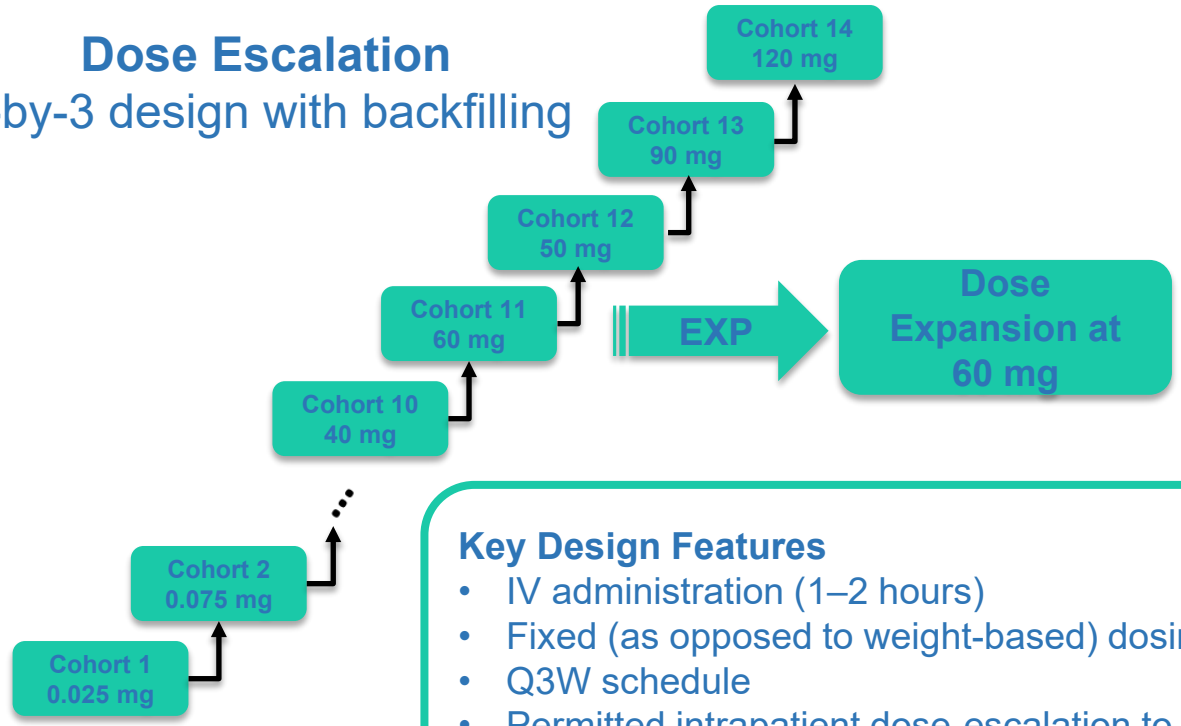
- **62% ORR with responses that were durable and deepened over time in this heavily pre-treated population**
- **Teclistamab was well tolerated; no patients required dose reduction**
  - The most common AEs were CRS and hematologic events; CRS events were low grade, with the exception of 1 grade 3 event which resolved without discontinuation
  - ICANS events were rare, were all grade 1/2, and resolved without discontinuation
- **These data support teclistamab as a promising new, off-the-shelf, T-cell redirecting therapy targeting BCMA for patients with RRMM**
- Ongoing studies (NCT04722146, NCT04586426, NCT04108195) are evaluating teclistamab in earlier-line settings and in combination with other agents, including a phase 3 study, MajesTEC-3 (NCT05083169); data in patients with prior BCMA exposure will be presented at an upcoming congress

AE, adverse event; BCMA, B-cell maturation antigen; CRS, cytokine release syndrome; ICANS, immune effector cell–associated neurotoxicity syndrome; ORR, overall response rate; RRMM, relapsed/refractory multiple myeloma

# A Phase 1 Study of TNB-383B (Abbvie) in RRMM

## Dose Escalation

3-by-3 design with backfilling




**Key Design Features**

- IV administration (1–2 hours)
- Fixed (as opposed to weight-based) dosing
- Q3W schedule
- Permitted intrapatient dose-escalation to 60 mg

**Key Eligibility Criteria**

- Patients with RRMM (≥3 prior lines including a PI, an IMiD, and an anti-CD38 mAb)
- Not considered candidates for therapies known to provide clinical benefit
- Hgb ≥8 g/dL, ANC ≥1 × $10^9$/ L, platelets ≥50 × $10^9$/ L
- ECOG ≤2
- eGFR ≥30 mL/min
- Prior BCMA-targeted therapy prohibited

**Primary Objectives**

- Safety/tolerability, PK, and determination of RP2D

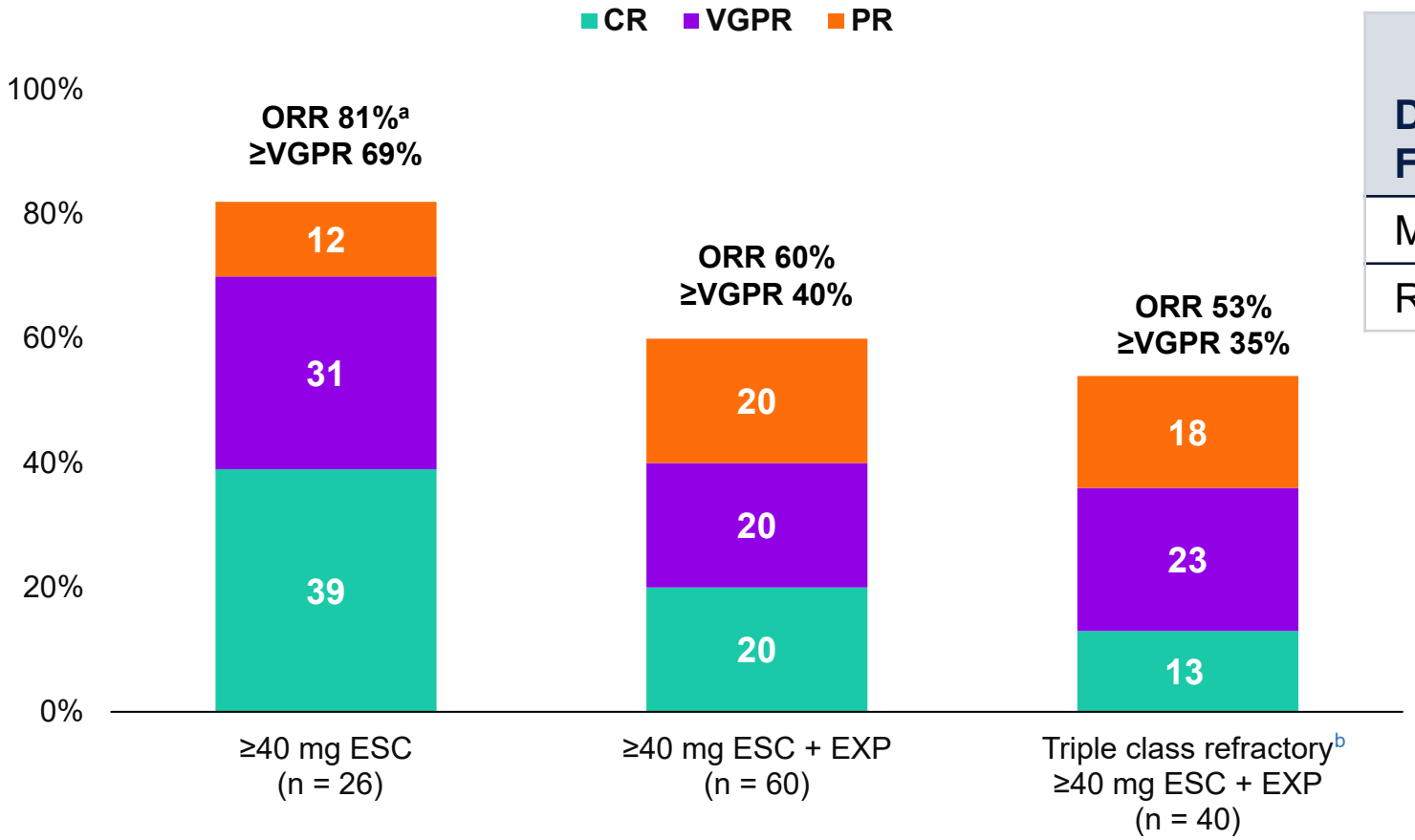
**Secondary Objectives**

- Clinical activity (per IMWG criteria 2016)

ANC, absolute neutrophil count; BCMA, B-cell maturation antigen; ECOG, Eastern Cooperative Oncology Group; eGFR, estimated glomerular filtration rate; EXP, dose-expansion; Hgb, hemoglobin; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; IV, intravenous; mAb, monoclonal antibody; PI, proteasome inhibitor; PK, pharmacokinetics; Q3W, every 3 weeks; RP2D, recommended phase 2 dose; RRMM, relapsed/refractory multiple myeloma.

# A Phase 1 Study of TNB-383B in RRMM

## Response Rates by IMWG Criteria




| Duration of Follow-up, mo | ≥40 mg ESC n = 26 | ≥40 mg ESC + EXP n = 60 |
|---|---|---|
| Median | 8.0 | 4.3 |
| Range | 0.8–12.8 | 0.6–12.8 |

Data cutoff date: Aug 9, 2021.
Modified efficacy-evaluable population includes patients who have received ≥1 dose of ABBV-383 and have ≥1 postdose disease assessment and/or discontinued treatment for any reason by data cutoff date.
[a]Total values due to rounding. [b]Refractory to an immunomodulatory drug, a proteasome inhibitor, and anti-CD38 antibody; programmatically derived confirmed or unconfirmed response (IMWG 2016).

CR, complete response; ESC, dose escalation; EXP, dose expansion; IMWG, International Myeloma Working Group; ORR, objective response rate; PR, partial response; VGPR, very good partial response; ≥VGPR, VGPR or better.

# Conclusion

- ABBV-383 is well tolerated at all Q3W doses administered with a predictable and manageable CRS rate, as well as low incidence of cytopenias
- An ORR of 81% was observed at doses ≥40 mg in the dose-escalation cohorts (median follow-up: 8.0 months) with a similar trend also observed at the ≥40-mg dose in the combined dose-escalation/expansion cohorts (ORR: 60%; median follow-up: 4.3 months)
- Promising efficacy of ABBV-383 Q3W regimen will be further explored

# Combination BITE and Daratumumab

- Phase 1b Study Teclistamab in Combination With Daratumumab for Relapsed/Refractory Multiple Myeloma
- Phase 1b Study Talquetamab in Combination With Daratumumab for Relapsed/Refractory Multiple Myeloma

# Phase 1b Study: Subcutaneous Teclistamab (CD3 x BCMA) in Combination With Daratumumab in RRMM

## TRIMM-2: Overall Response Rate

| Response categories | Evaluable patients[a], n (%) | | |
|---|---|---|---|
| | Dara 1800 mg SC: Cycle 1-2: QW, Cycles 3-6: Q2W; Cycles 7+: monthly | | |
| | Tec SC QW 1.5 mg/kg (n=19) | Tec SC QW 3 mg/kg (n=4) | Tec SC Q2W 3 mg/kg (n=5) |
| **ORR[c]** | **16 (84.0)** | **4 (100.0)** | **3 (60.0)** |
| CR | 6 (31.6) | 3 (75.0) | 0 (0) |
| VGPR | 7 (36.8) | 1 (25.0) | 2 (40.0) |
| PR | 3 (15.8) | 0 (0) | 1 (20.0) |
| SD | 1 (5.3) | 0 (0) | 2 (40.0) |
| PD | 2 (10.5) | 0 (0) | 0 (0) |

- Median follow-up was 5.1 months (range: 0.3–12.9)
- Median time to first confirmed response: 1.0 month (range: 1.0–8)
- ORR across all dose levels was improved compared to RP2Ds for teclistamab monotherapy

[a]Patients have received at least one study treatment and have at least one postbaseline response evaluation by investigator. Includes unconfirmed responses.
[b]PR or better in response-evaluable patients; includes unconfirmed responses.

CR, complete response; Dara, daratumumab; ORR, overall response rate; PR, partial response; QW, weekly; Q2W, every other week; SC, subcutaneous; SD, stable disease; PD, progressive disease; RP2D, recommended phase 2 dose; Tec, teclistamab; VGPR, very good partial response

# Phase 1b Results for Subcutaneous Talquetamab (GPRC5D x CD3) Plus Daratumumab in RRMM

## TRIMM-2: Overall Response Rate

| Response Categories | Evaluable patients[a], n (%) | | |
|---|---|---|---|
| | Dara 1800 mg SC: Cycle 1-2: QW, Cycles 3-6: Q2W; Cycles 7+: monthly | | |
| | Tal 400 µg/kg SC Q2W (n=5) | Tal 400 µg/kg SC QW (n=7) | Tal 800 µg/kg SC Q2W (n=9) |
| **ORR[b]** | **4 (80.0)** | **6 (85.7)** | **7 (77.8)** |
| sCR/CR | 1 (20.0) | 2 (28.6) | 1 (11.1) |
| VGPR | 2 (40.0) | 3 (42.9) | 5 (55.6) |
| PR | 1 (20.0) | 1 (14.3) | 1 (11.1) |
| MR | 0 (0) | 0 (0) | 0 (0) |
| SD | 0 (0) | 1 (14.3) | 2 (22.2) |
| PD | 1 (20.0) | 0 (0) | 0 (0) |

- Median follow-up was 4.2 months
- Median time to first confirmed response: 1.0 month (range: 0.9–2.4)
- ORR across all dose levels was improved compared to RP2Ds for talquetamab monotherapy

[a]Patients have received at least one study treatment and have at least one post-baseline response evaluation by investigator. Includes unconfirmed responses;
[b]PR or better in response-evaluable patients; includes unconfirmed responses.

CR, complete response; Dara, daratumumab; MR, minimal response; ORR, overall response rate; PR, partial response; QW, weekly; Q2W, every other week; SC, subcutaneous; sCR, stringent complete response; SD, stable disease; PD, progressive disease; Tal, talquetamab; VGPR, very good partial response.

# TRIMM-2: Conclusions

**The combination of tal + dara appears tolerable, with no overlapping toxicity**

- Safety profiles appear consistent with each agent given as a monotherapy and no new AEs were observed
- 55% of patients experienced CRS, all grade 1 and 2, with median time to onset of 2 days and 2 days duration

**Preliminary efficacy data suggest a promising ORR (77-85%) in these heavily pre-treated patients**

- Responses were observed in both CD38–exposed and –refractory patients
- Responses were durable and appeared to deepen over time, with the majority of patients remaining on treatment

**Tal-mediated induction of cytotoxic T cells (CD38+/CD8+) in the presence of dara, supports the rationale for this synergistic combination regimen**

**These data support tal + dara as a novel immunotherapy-based approach for the treatment of patients with MM**

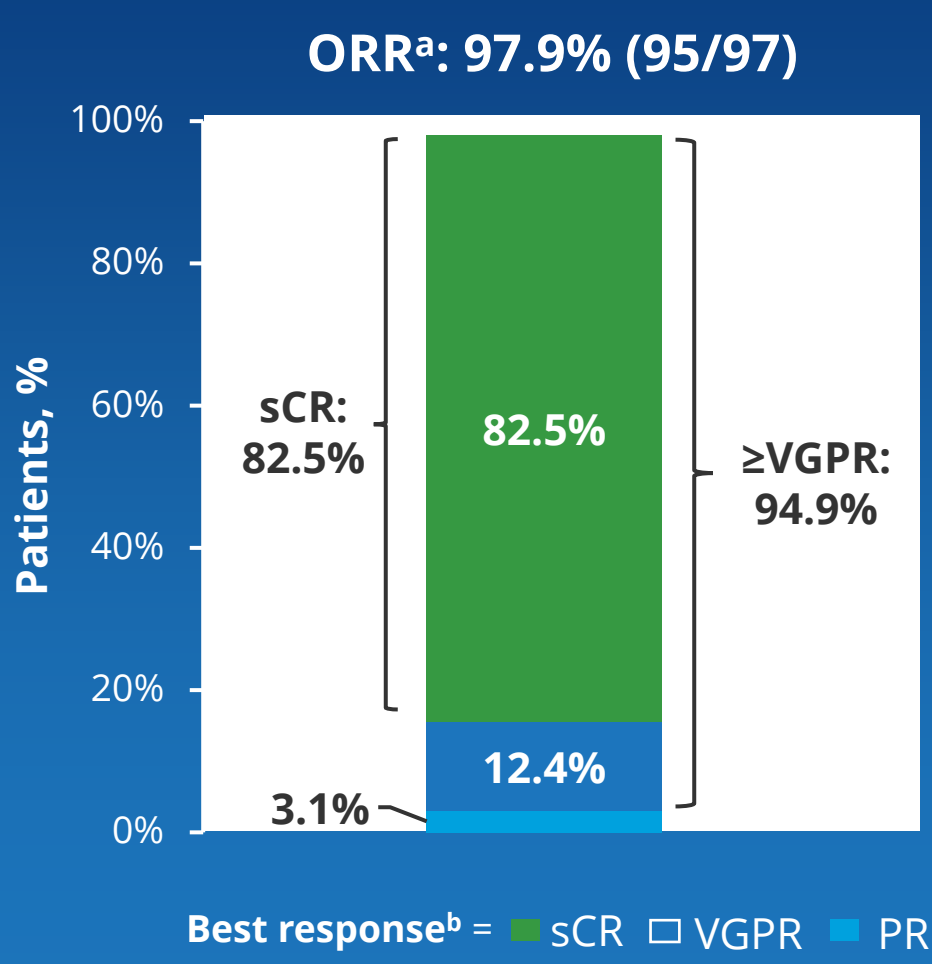
Dara, daratumumab; MM, multiple myeloma; MOA, mechanism of action; ORR, overall response rate; Tal, talquetamab; RRMM, relapsed/refractory MM; VGPR, very good partial response.

# CAR T-Cell Therapy Trials

- **Updated Results From CARTITUDE-1: Phase 1b/2 Study of Ciltacabtagene Autoleucel, a B-cell Maturation Antigen–Directed Chimeric Antigen Receptor T Cell Therapy, in Patients With Relapsed/Refractory Multiple Myeloma**

- **UNIVERSAL Updated Phase 1 Data Validates the Feasibility of Allogeneic Anti-BCMA ALLO-715 Therapy for Relapsed/Refractory Multiple Myeloma**

# Updated Results From CARTITUDE-1: Phase 1b/2 Ciltacabtagene Autoleucel in RRMM




## CARTITUDE-1: Efficacy Response

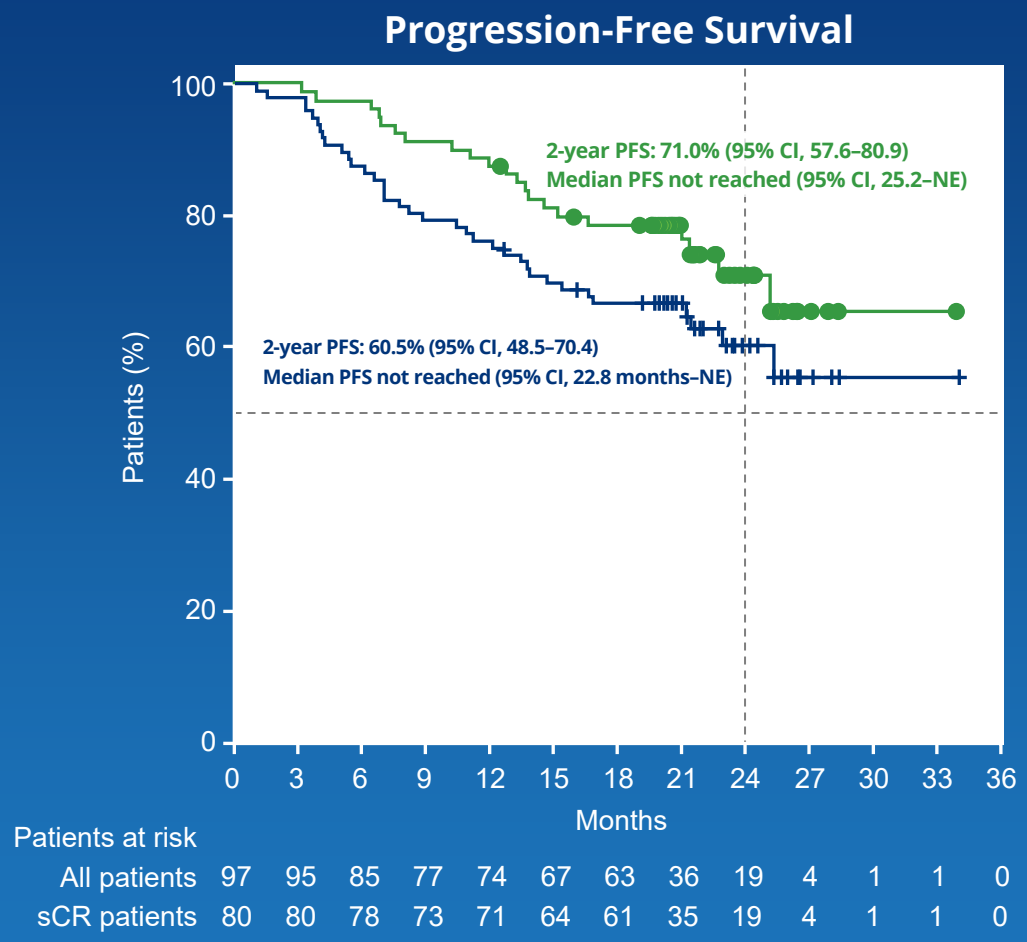
**Responses deepened over time from the 1-year follow-up**

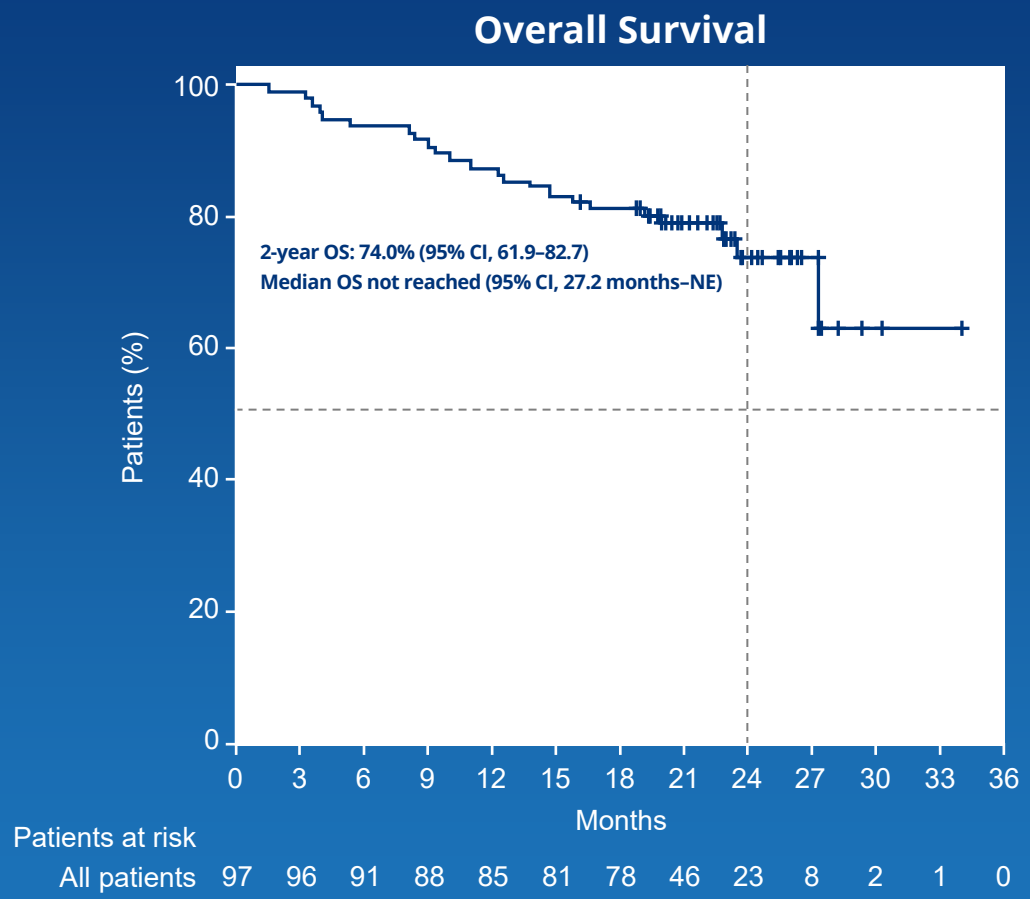
| Best response at any time | Median–1 year follow-up | Median–2 years follow-up |
|---|---|---|
| sCR, % | 67 | 83 |

- Median time to first response was 1 month (range, 0.9–10.7)
- Median time to best response was 2.6 months (range, 0.9–17.8)
- Median time to CR or better was 2.9 months (range, 0.9–17.8)
- Median duration of response was not estimable (21.8 months–NE)

[a]ORR assessed by independent review committee; [b]No patient had CR or stable disease as best response.
CR, complete response; NE, not estimable; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

# CARTITUDE-1: Progression-Free Survival and Overall Survival




All patients  sCR patients

NE, not estimable; OS, overall survival; PFS, progression-free survival; sCR, stringent complete response

# CARTITUDE-1: Conclusions

**At a median follow-up of ~2 years, patients treated with cilta-cel showed durable and deepening responses**

- ORR remained at 98%, with sCR rates higher at a median of ~2 years than at median of ~1 year (83% vs 67%)
- 2-year PFS and OS rates were 60.5% and 74.0%, respectively
- MRD negativity (at $10^{-5}$) was achieved in 92% of evaluable patients
- PFS and OS was improved in patients with MRD-negativity sustained for ≥6 and ≥12 months

**Cilta-cel has a manageable safety profile with no new safety signals observed with longer follow-up**

**These encouraging data suggest cilta-cel will be an important treatment option for patients with MM**

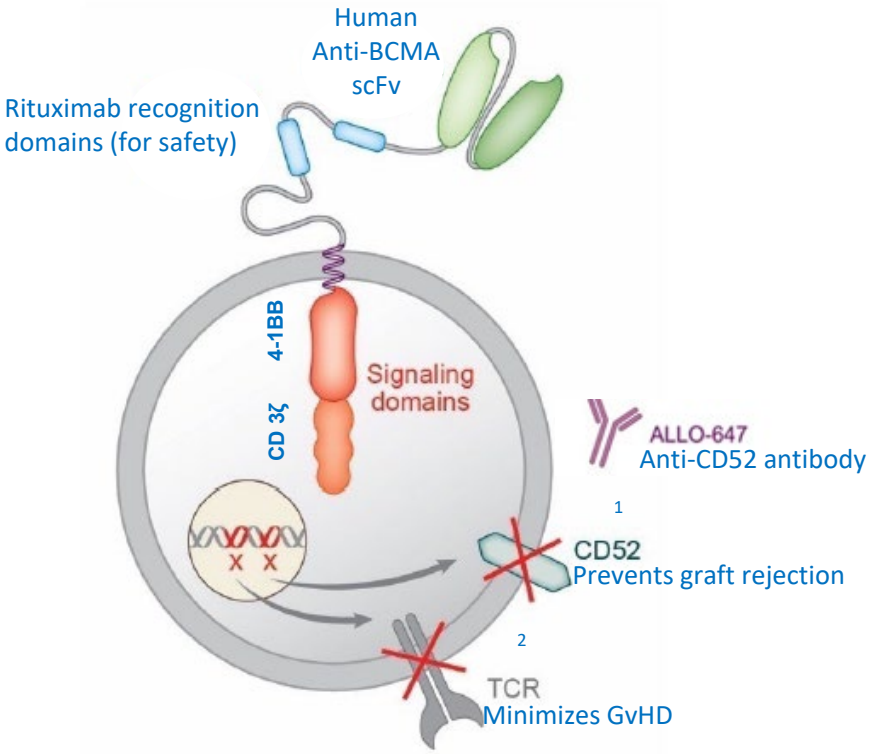
- Cilta-cel is currently under further investigation in patients with MM in earlier-line settings, including patients with newly diagnosed MM (CARTITUDE-2[a], CARTITUDE-4[b], CARTITUDE-5[c])
- Outpatient administration of cilta-cel is being explored in these studies

ClinicalTrials.gov [a]NCT04133636; [b]NCT04181827; [c]NCT04923893.

cilta-cel, ciltacabtagene autoleucel; MRD, minimal residual disease; MM, multiple myeloma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RRMM, relapsed/refractory multiple myeloma; sCR, stringent complete response.

# The First Allogeneic anti-BCMA CAR T Study for R/R Multiple Myeloma

- BCMA cell therapy has demonstrated unprecedented efficacy, but is not readily available to all patients
- Allogeneic chimeric antigen receptor (CAR) T-cell therapy has the potential for all eligible patients to receive therapy on demand and supports re-dosing
- ALLO-715 (anti-BCMA) is an allogeneic CAR T-cell product utilizing TALEN® gene editing specifically designed to
  - Disrupt TCRα constant gene – to reduce the risk of graft-versus-host disease (GvHD)
  - Edit CD52 gene – permits use of ALLO-647 (a humanized anti-CD52 mAb) to selectively deplete host T cells while protecting donor cells




1. TALEN-mediated CD52 KO allows selective lymphodepletion with ALLO-647
2. TALEN-mediated TRAC KO eliminates TCRα expression to minimize risk of GvHD

# ALLO-715 and ALLO-647 Demonstrated Manageable Safety Profile

| TEAE of Interest* (N=43) | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 | All Grades |
|---|---|---|---|---|---|---|
| | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| Cytokine Release Syndrome | 13 (30) | 10 (23) | 1 (2) | 0 | 0 | 24 (56) |
| Neurotoxicity† | 4 (9) | 2 (5) | 0 | 0 | 0 | 6 (14) |
| Graft-versus-Host Disease | 0 | 0 | 0 | 0 | 0 | 0 |
| Infection‡ | 3 (7) | 10 (23) | 7 (16) | 0 | 3 (7) | 23 (54) |
| Infusion Reaction to ALLO-647 | 7 (16) | 5 (12) | 0 | 0 | 0 | 12 (28) |

- **Manageable safety profile with low-grade and reversible neurotoxicity and no GvHD**
  - 14% of patients with AEs of potential low-grade neurotoxicity
  - Low use of tocilizumab 23% and steroids 14%

- 20 (47%) patients with an SAE
- 30 (70%) patients experienced Gr3+ neutropenia
- 3 Gr5 infections; 2 previously reported and an additional one due to sepsis

* Number of patients with AE occurring from the start of study drug up to subsequent anti-cancer therapy. For patients reporting more than one AE within a preferred term, only one AE with the maximum grade is reported.
† Analysis done using a broad SMQ of noninfectious encephalopathy/delirium with adjudication by clinical review.
‡ All infections (bacterial, fungal, and viral) included.

# Encouraging Efficacy Seen With Additional Patients at DL3

| Cell Dose & LD Regimen | DL3 (320M CAR+ T Cells)* | | | | DL4 (480M CAR+ T Cells) | |
|---|---|---|---|---|---|---|
| | FCA39 N=11 | FCA60 N=10 | FCA90 N=3 | FCA ALL N=24 | FCA39 N=3 | FCA60 N=3 |
| ORR†, n (%) (95% CI) | **7 (64)** (31, 89) | **8 (80)** (44, 98) | **2 (67)** (9, 99) | **17 (71)** (49, 87) | **1 (33)** (0.8, 91) | **2 (67)** (9, 99) |
| VGPR+ Rate, n (%) | 5 (46) | 5 (50) | 1 (33) | 11 (46) | 0 | 2 (67) |
| CR/sCR Rate, n (%) | 3 (27) | 3 (30) | 0 | 6 (25) | 0 | 0 |
| mDOR, months (95% CI) | 8.3 (3.4, 11.3) | NE (5.6, NE) | 3.1 (2.4, 3.1) | 8.3 (3.4, 11.3) | 1.4 (NE, NE) | NE (1.5, NE) |
| Median follow-up, months (range)** | 3.3 (0.5, 3.8) | 3.8 (3.1, 11.2) | -- | 3.8 (0.5, 11.2) | -- | 7.4 (7.4, 7.4) |

- In the FCA 320M CAR+ cell dose group, 17 patients **(71%) achieved an overall response rate (ORR)**
- 11 (46%) were VGPR+, of those 6 (25%) were CR/sCR

* Three patients treated with 320M CAR+ cells and the CA LD regimen are not included above. Two of those responded with one pt achieving a CR.
† Clinical response evaluation was based on IMWG response criteria, Kumar et al, 2016.
** Median follow-up is for censored pts.

# Conclusion

- ALLO-715 UNIVERSAL Trial is the first allogeneic anti-BCMA CAR T study to demonstrate safety and substantial efficacy in MM
- “Off-the-shelf” AlloCAR Ts have potential to addresses significant unmet need in patients with rapidly progressive disease
  - No bridging therapy required
  - Median time from enrollment to start of therapy of 5 days
  - 90% enrolled patients received treatment
- ALLO-715 with ALLO-647 is well tolerated with low-grade CRS, low-grade reversible neurotoxicity, no GvHD, and manageable safety
- 71% ORR and 46% VGPR+ with 320M cell dose and FCA comparable to approved autologous CAR T therapy
  - 92% VGPR+ responses were MRD negative
  - 8.3 months median durability of response
- ALLO-715 consolidation with two doses and ALLO-715 in combination with nirogacestat are also being evaluated; next-generation anti-BCMA TurboCAR (ALLO-605) currently in Phase 1 development

# Summary

- IKEMA Study showed that Isa-Kd is very effective in high-risk multiple myeloma
- Several bispecific T-cell engagers (BITEs) are in clinical trials→ winner is unclear
- Combination of BITEs with Daratumumab as a steroid-free combination is safe and promising
- CAR T-cell treatment results in durable responses but production capacity reduces availability
- AlloCAR T cells - off the shelf - might overcome production problem