
# NUOVE TERAPIE NEI LINFOMI B AGGRESSIVI E NEL MIELOMA MULTIPLO

## *Bispecifici nella terapia di salvataggio del Mieloma Multiplo*

**Dott.ssa Anna Furlan**
**UOC Ematologia di Treviso**

CRO Aviano (PN) - 9 ottobre 2024

# Disclosures of Anna Furlan

| Company name | Research support | Employee | Consultant | Stockholder | Speakers bureau | Advisory board | Other |
|---|---|---|---|---|---|---|---|
| Janssen | | | | | x | x | x |
| Sanofi | | | | | x | x | |
| GSK | | | | | x | x | |
| Takeda | | | | | x | x | x |
| Bristol Myers Squibb | | | | | x | | |
| Menarini | | | | | | x | |
| Amgen | | | | | | x | |

# Topics

Anticorpi bispecifici (BsAbs): meccanismi d'azione e target

I BsAbs approvati: Teclistamab, Talquetamab. Elranatanab. Updates

I BsAbs sono in grado di rispondere agli attuali unmet needs? Efficacia nelle popolazioni ad alto rischio

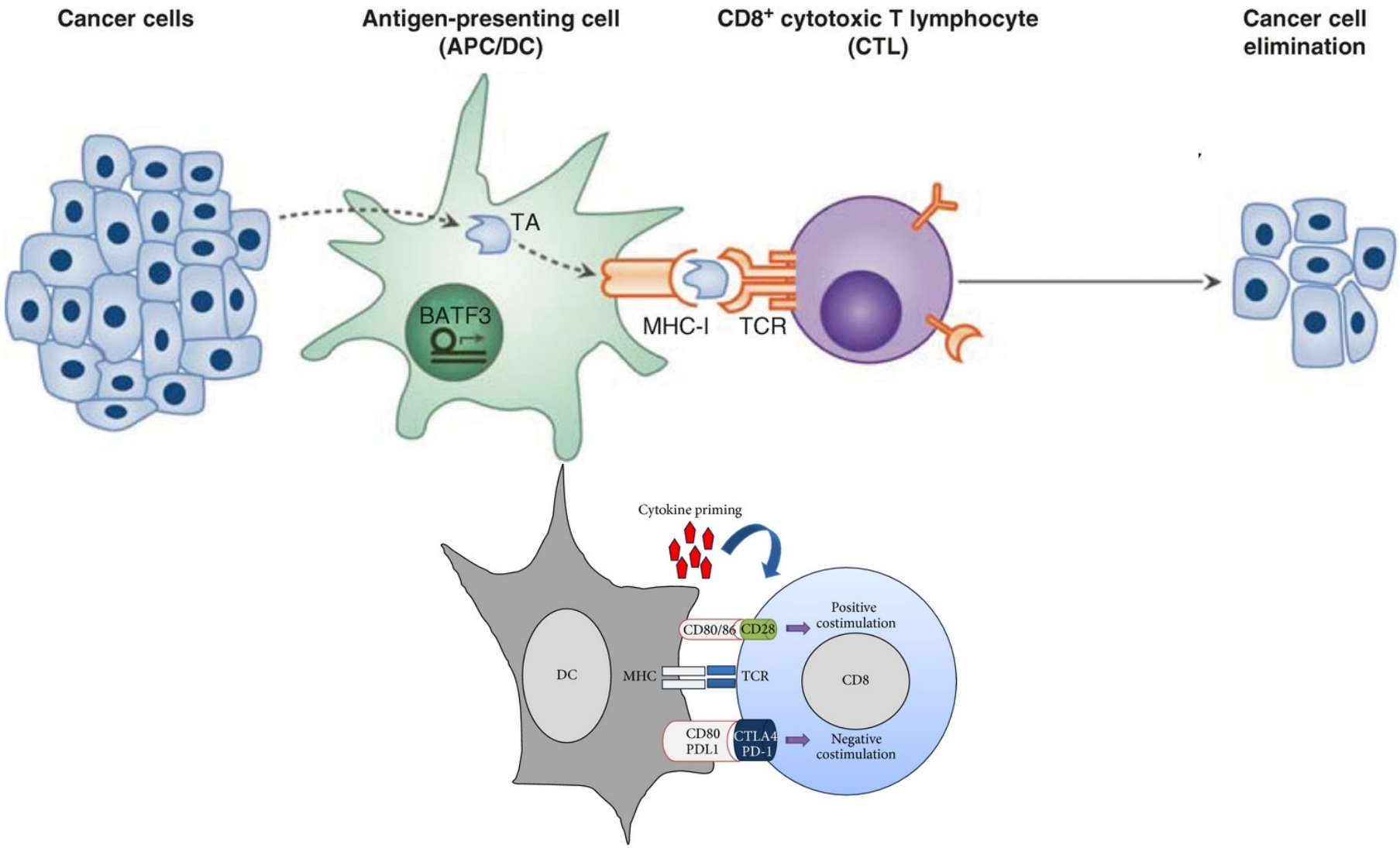
Meccanismi di resistenza e potenziali limiti all'utilizzo, correlati a:
- Caratteristiche del microambiente
- Caratteristiche delle cellule T
- Caratteristiche della cellula tumorale

Strategie volte a ottimizzare l'efficacia dei BsAbs
- Dual targeting: Associazioni di BsAbs con target differenti
- Combinazioni con agenti ad azione immunomodulante
- Aumento dei livelli di Ag target
- Timing precoce di utilizzo

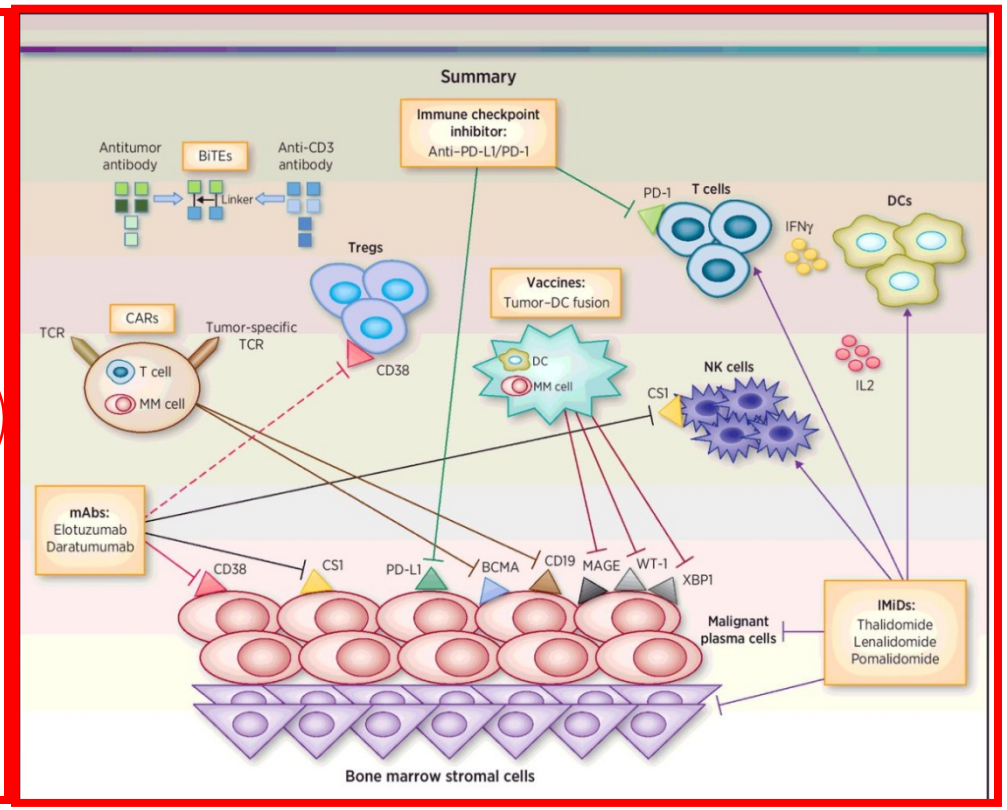
Sequencing: impatto delle terapie precedenti sull'efficacia dei BsAbs e dei BsAbs sull'efficacia delle terapie successive

Safety: strategie per contenere la tossicità (infezioni, CRS)

# Immunità anti-tumorale



# Immunoterapia anti-tumorale

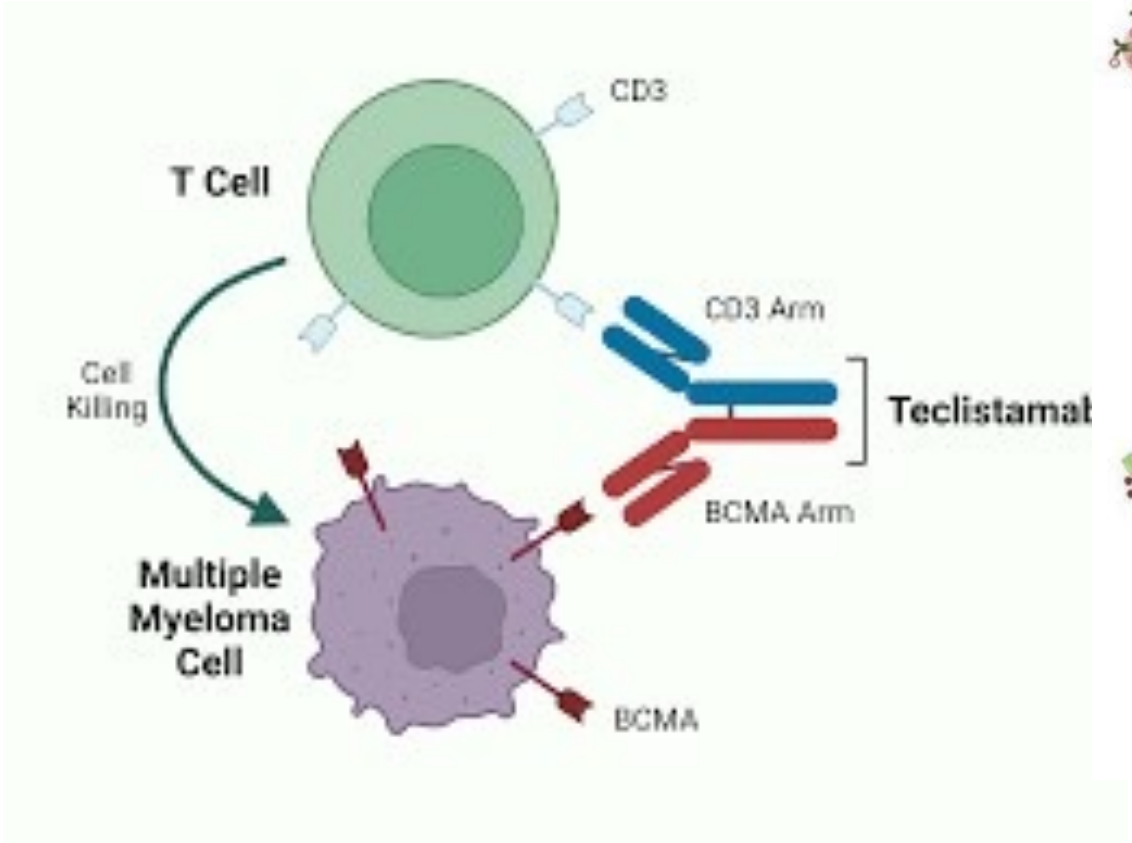



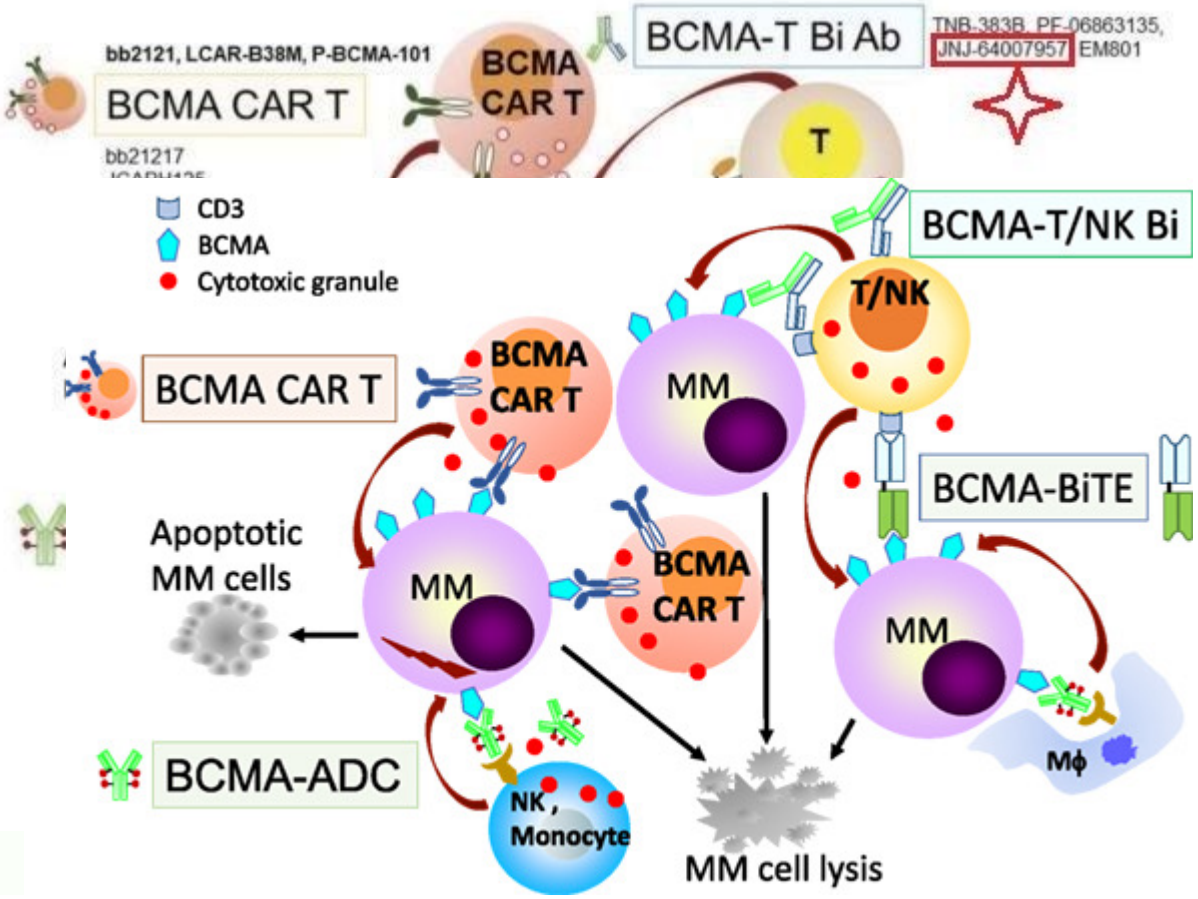

- Modulazione del microambiente immune nelle sue componenti cellulare e solubile
→ripristino dell'immunosorveglianza verso il tumore (**IMIDs, Checkpoint Inhibitors**)

- Reclutamento del microambiente immune al fine indurre/potenziare azione citotossica sulle cellule tumorali (immunoterapie NK/T cell mediate: **MoAbs, CAR-T cells, BsAbs**)

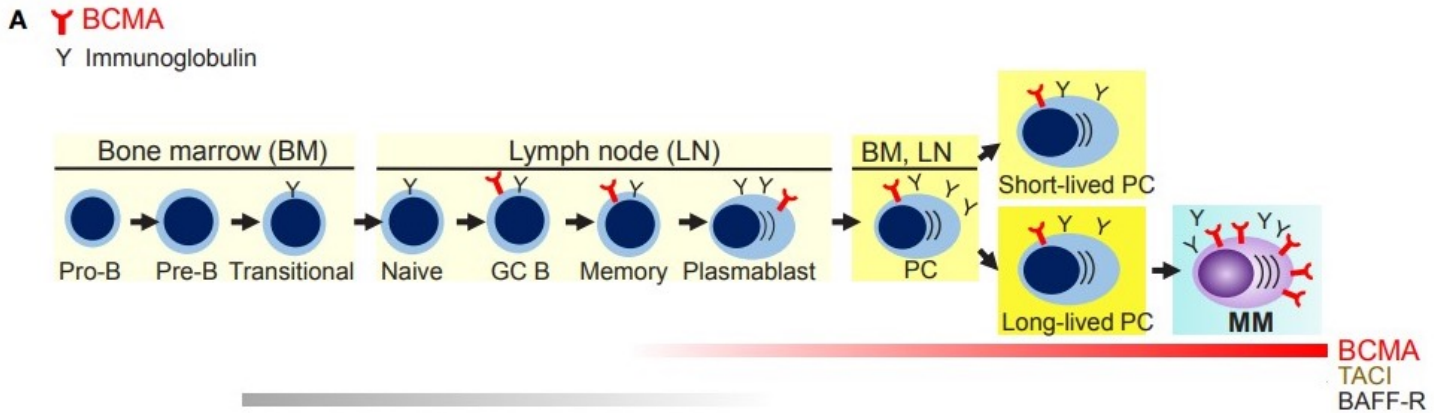
Da Rodriguez-OteroP., Hematologica 2017

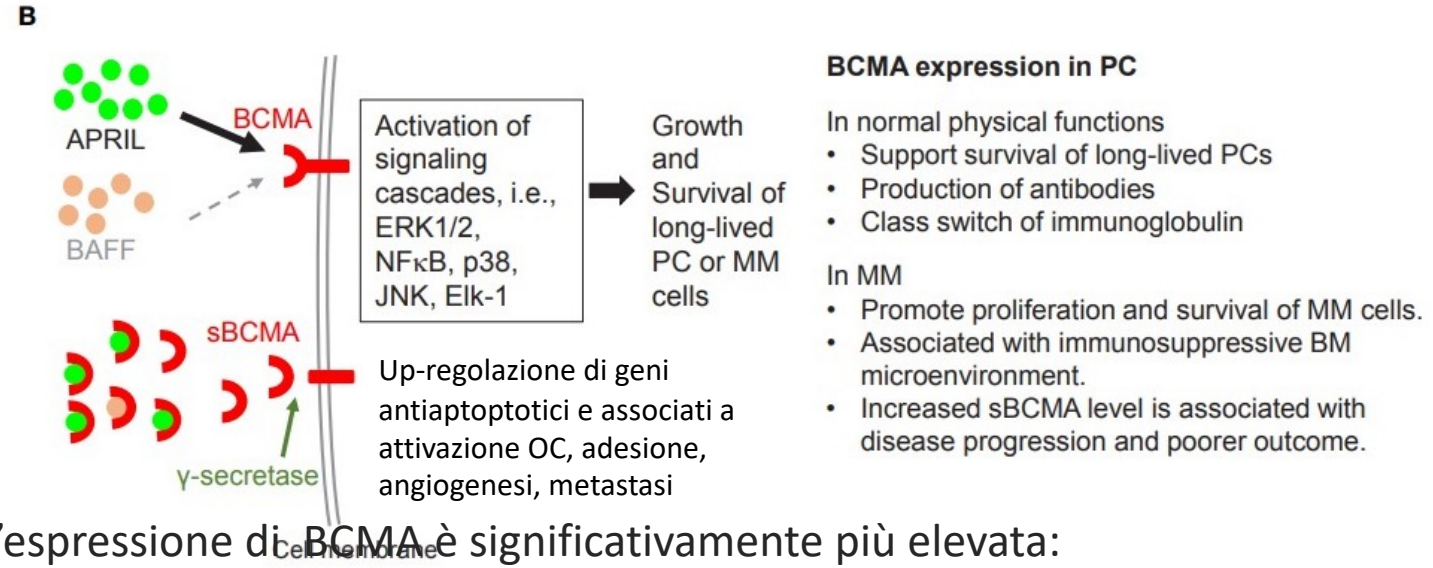
# BsAbs anti-BCMA: Teclistamab, Elranatamab



# BCMA (B Cell Maturation Antigen)




E' un recettore di superficie indotto selettivamente durante la differenziazione PC e si associa a perdita di BAFF-R

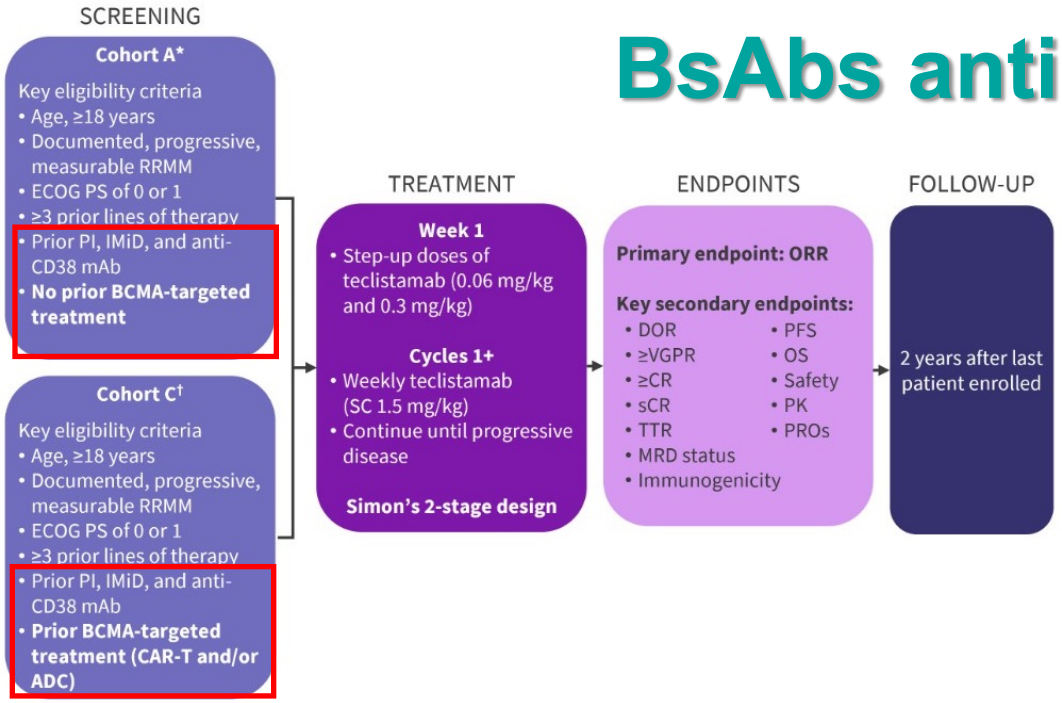
Espresso sulle cellule B late-stage, plasmablasti proliferanti, short and long-lived PC virtualmente assente nelle cellule B naive e memory

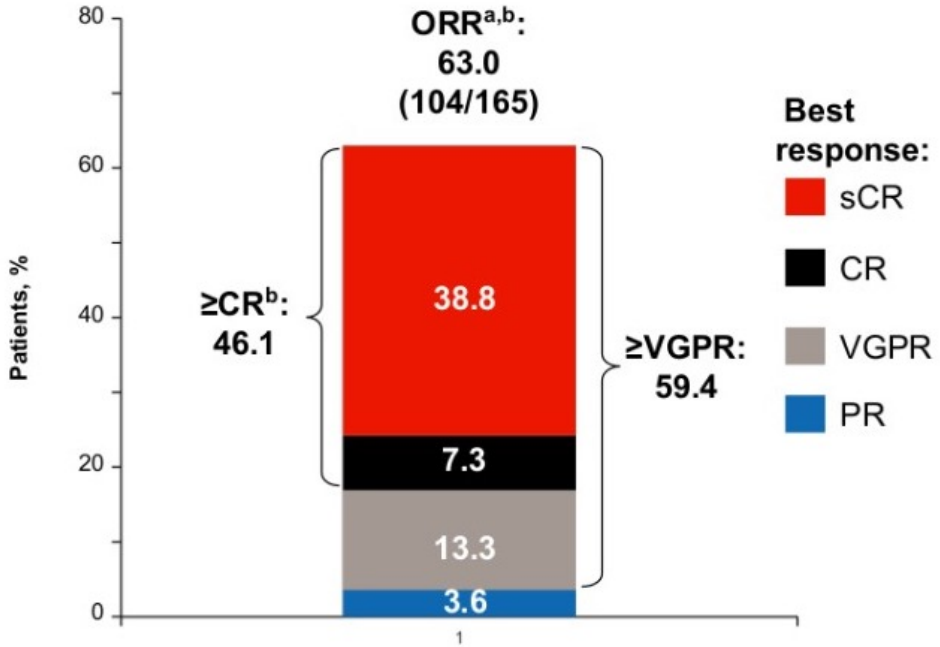
L'espressione di BCMA è significativamente più elevata:
- sulle PC tumorali del MM vs PC normali
- nel RRMM vs NDMM

Il progressivo incremento della espressione di BCMA con la progressione della malattia è legato alla perdita di PC che esprimono livelli inferiori

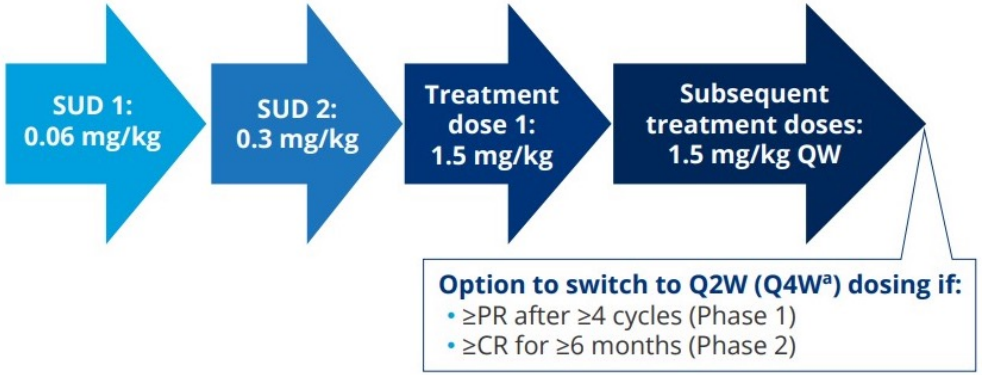
Una più elevata espressione di BCMA potrebbe infatti conferire un vantaggio selettivo di sopravvivenza

# BsAbs anti-BCMA, Teclistamab: MajesTEC-1 (Phase 1/2). Efficacia




## Long-Term Follow-Up From the Phase 1/2 MajesTEC-1 Trial of Teclistamab in Patients With Relapsed/Refractory Multiple Myeloma




Al data cut-off (Aug 22, 2023, follow-up mediano 30.4 m):

165 pz avevano ricevuto Tec alla RP2D (1.5 mg/kg QW)
65 pz erano passati a 1.5 mg/kg Q2W
38 pz rimanevano in trattamento (di cui 37 Q2W)

Garfall AL et al, ASCO 2024. P7540

# Long-Term Follow-Up From the Phase 1/2 MajesTEC-1 Trial of Teclistamab in Patients With Relapsed/Refractory Multiple Myeloma

**Figure 3: DOR**

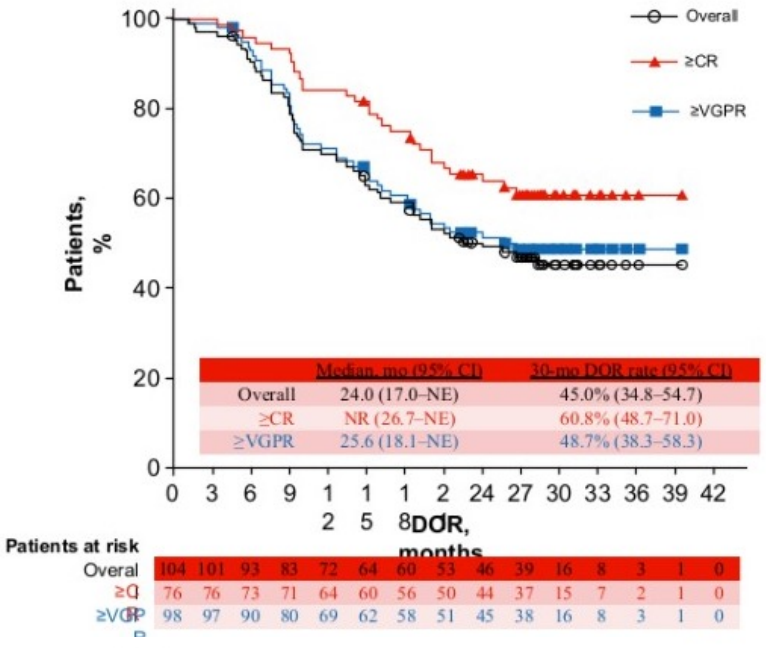
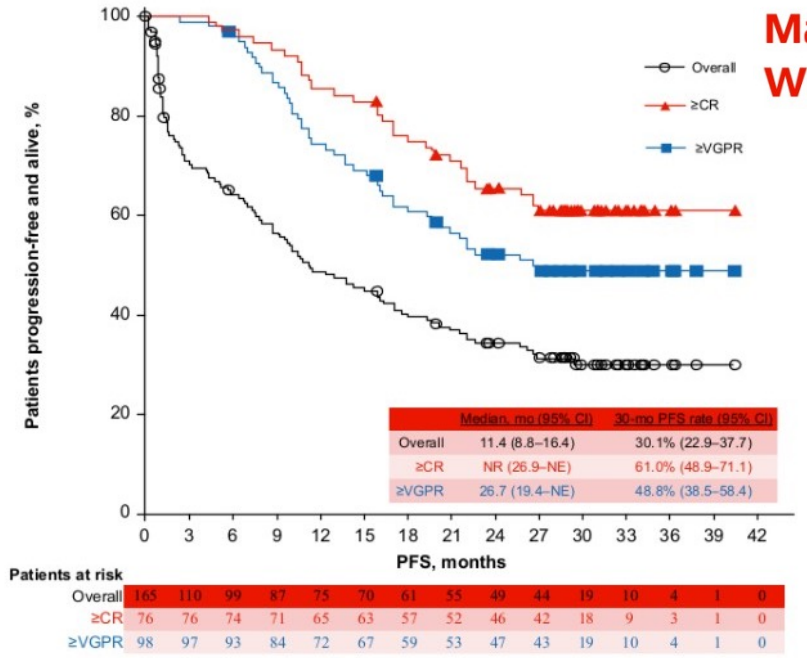
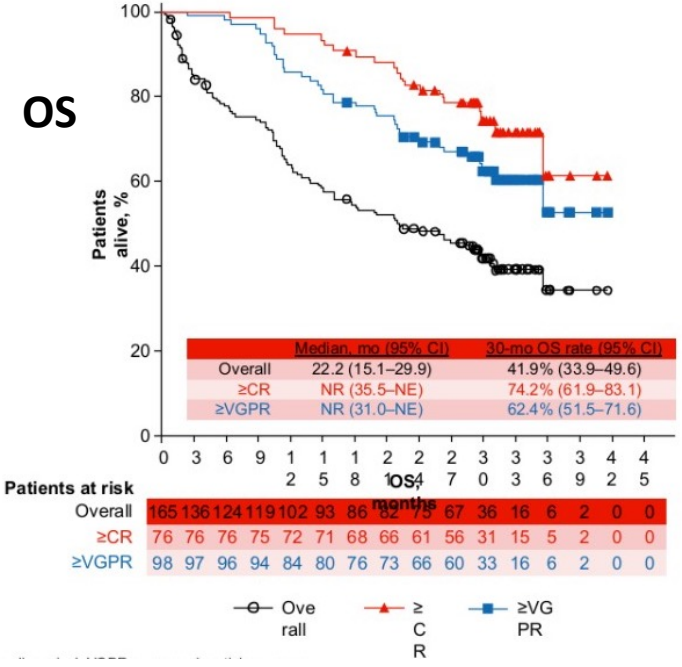



**Figure 4: PFS**




**OS**




DOR, PFS e OS correlano con la profondità della risposta

**mDOR** complessiva 24 m
mDOR in pz in ≥CR NR (30-month DOR rate, 60.8%)

**mPFS** complessiva 11.4 m
mPFS in pz in ≥CR NR

**mOS** complessiva 22.2 m
mOS in pz in ≥CR NR

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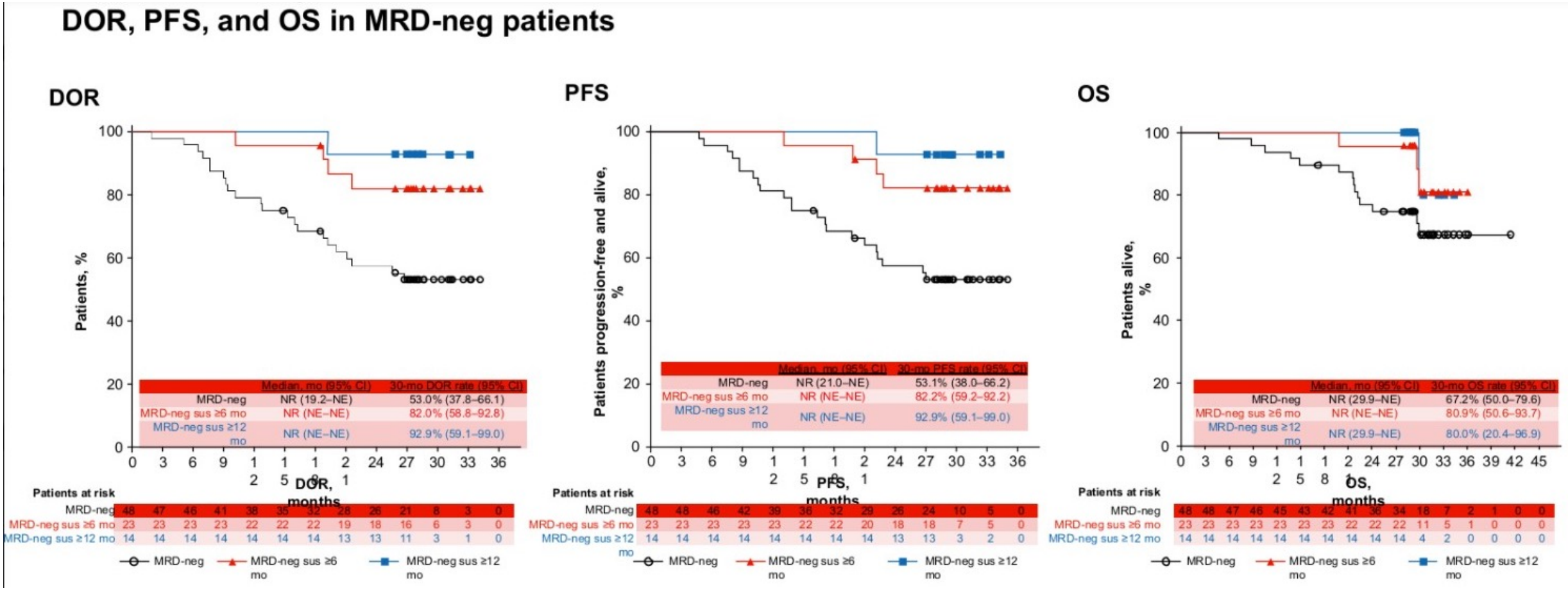
# Teclistamab. Efficacia

## Long-Term Follow-Up From the Phase 1/2 MajesTEC-1 Trial of Teclistamab in Patients With Relapsed/Refractory Multiple Myeloma




DOR, PFS e OS correlano con la profondità della risposta, con ulteriore miglioramento nei pz con MRD-neg sostenuta

**MRD-neg** 85.7% dei pz valutabili ad almeno un time point, **MRD-neg sostenuta ≥6** m 56.1%, **MRD neg-sostenuta ≥12 m** 38.9%

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# Teclistamab. Safety

## Long-Term Follow-Up From the Phase 1/2 MajesTEC-1 Trial of Teclistamab in Patients With Relapsed/Refractory Multiple Myeloma

**Table 2: TEAEs occurring in ≥20% of patients in MajesTEC-1**

| TEAEs, n (%) | N=165 | |
|---|---|---|
| | Any grade | Grade 3/4 |
| **Any TEAE** | **165 (100)** | **156 (94.5)** |
| **Hematologic** | | |
| Neutropenia | 118 (71.5) | 108 (65.5) |
| Anemia | 91 (55.2) | 62 (37.6) |
| Thrombocytopenia | 69 (41.8) | 38 (23.0) |
| Lymphopenia | 60 (36.4) | 57 (34.5) |
| Leukopenia | 33 (20.0) | 15 (9.1) |
| **Nonhematologic** | | |
| Infections | 130 (78.8) | 91 (55.2) |
| COVID-19 | 48 (29.1) | 35 (21.2) |
| CRS | 119 (72.1) | 1 (0.6) |
| Diarrhea | 57 (34.5) | 6 (3.6) |
| Pyrexia | 51 (30.9) | 1 (0.6) |
| Fatigue | 50 (30.3) | 4 (2.4) |
| Cough | 46 (27.9) | 0 |
| Nausea | 45 (27.3) | 1 (0.6) |
| Injection site erythema | 44 (26.7) | 0 |
| Arthralgia | 42 (25.5) | 2 (1.2) |
| Headache | 40 (24.2) | 1 (0.6) |
| Constipation | 37 (22.4) | 0 |
| Hypogammaglobulinemia | 36 (21.8) | 3 (1.8) |
| Back pain | 33 (20.0) | 4 (2.4) |

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Non nuovi segnali di tossicità

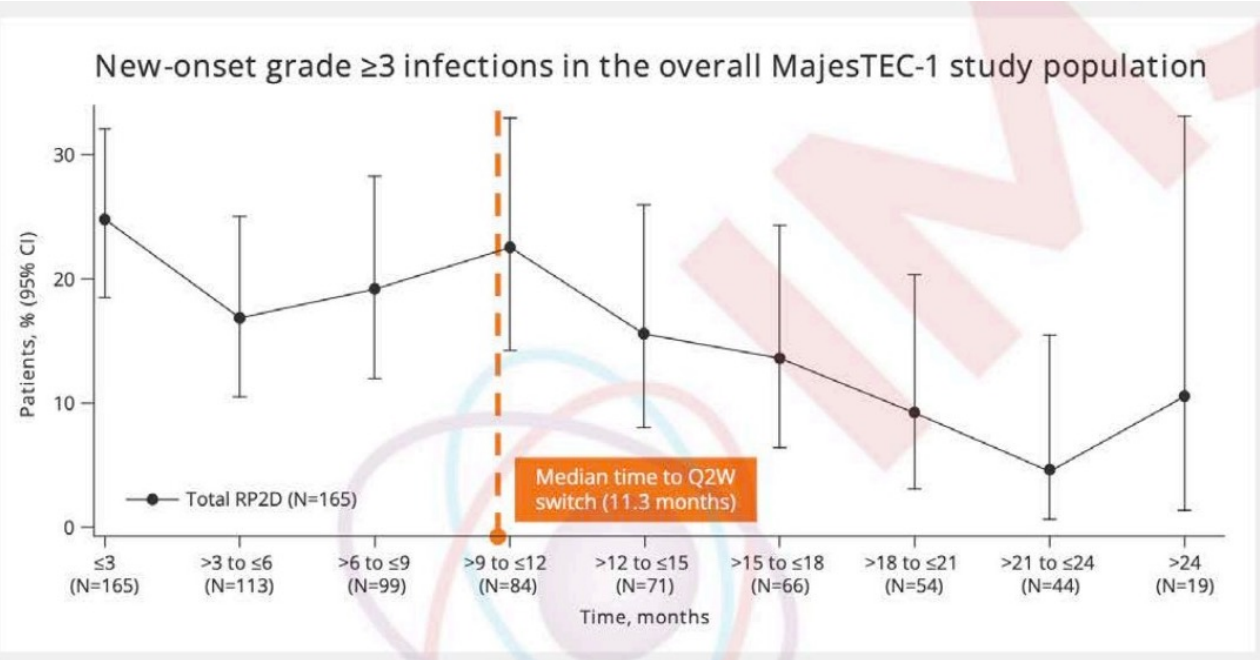
**TEAEs G3/4** 94.5%
**TEAEs ematologici G3/4**
Neutropenia 65.5%
Anemia 37.6%,
Trombocitopenia 23.0%
Linfopenia 34.5%

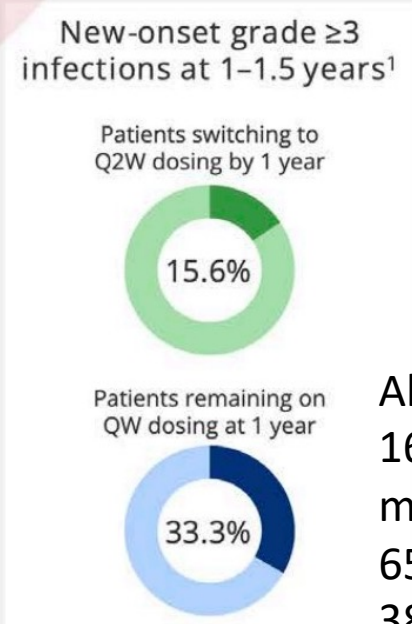
**Infezioni G3/4** 55.2%

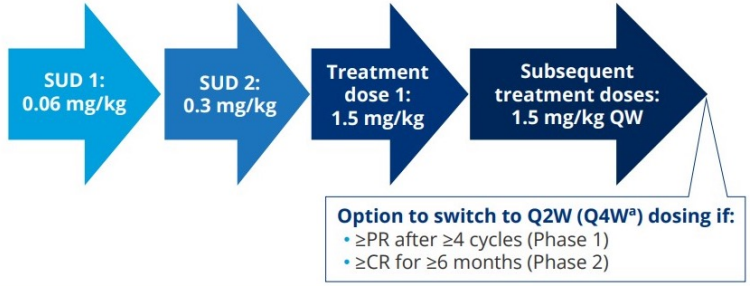
**CRS** di ogni grado 72.1%
(G3/4 0.6%)

**TEAEs che portano a riduzione di dose** 0.6%;
**discontinuazione** 4.8%
(5 casi correlati a infezione)

# Teclistamab. Safety. Infezioni




Al data cut-off (follow-up mediano 30.4 m):
165 pz avevano ricevuto Tec alla RP2D (1.5 mg/kg QW)
65 pz erano passati a 1.5 mg/kg Q2W
38 pz rimanevano in trattamento (di cui 37 Q2W)

L'incidenza di infezioni G ≥3 tende a ridursi nel tempo, in particolare dopo i primi 9-12 mesi di trattamento (switch a Q2W; incremento dell'utilizzo di Ig)

**E' stata approvata la somministrazione di Tec 1.5 mg/kg s.c. Q2W nei pz con di ≥RC sostenuta per ≥6 mesi**

Quota di pz con almeno ≥1 infezione G≥3:

| | | | |
|---|---|---|---|
| <6 m | 35.2% | da >6 a ≤12 m | 33.3% |
| da >12 a ≤18 m | 25.4% | da >18 a ≤24 m | 13.0% |
| da > 24 m | 10.5% | | |

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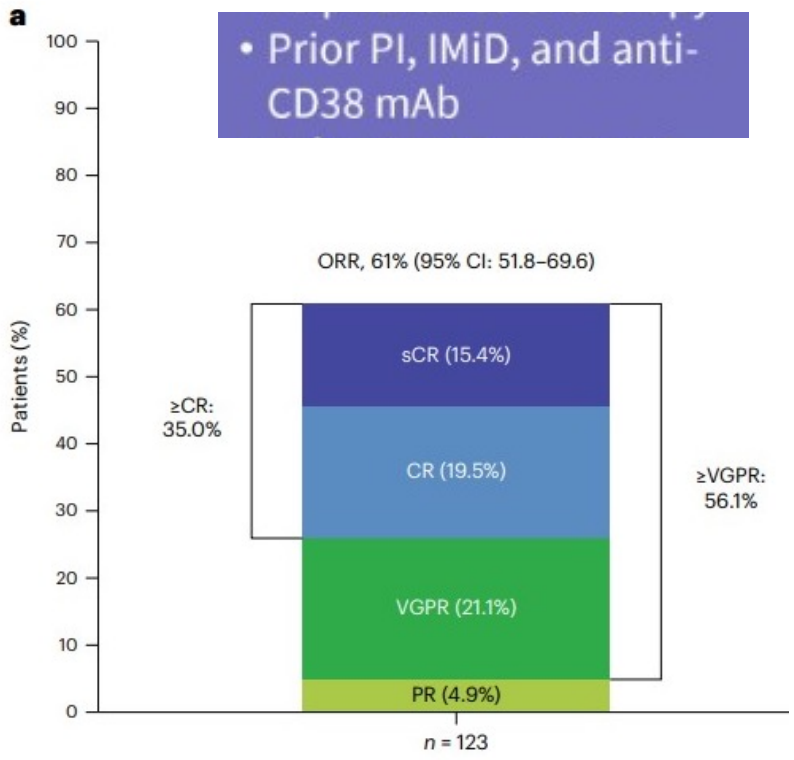
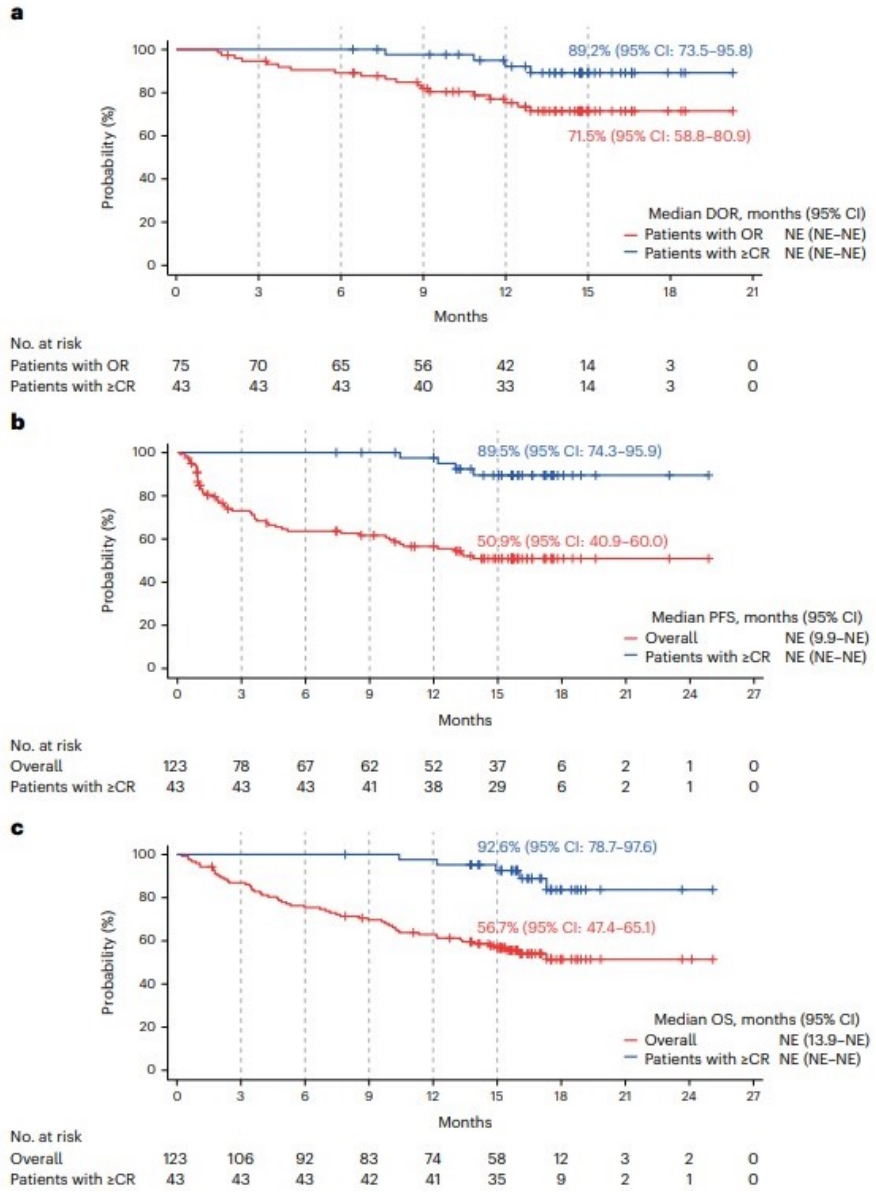
Usmani SZ et al, JCO 2023

# BsAbs anti-BCMA, Elranatamab: MagnetisMM-3 (Phase 2). Efficacia




Coorte A: 123 pz senza precedente BCMA.TT
Elr somministrato QW dopo 2 dosi di step up.
Nei pz responsivi switch a Q2W dopo 6 cicli
(50 pz di cui 80% hanno migliorato o mantenuto la risposta ≥6 m)
Triple-class refractory 96.7 %, HCR 25.2%




Follow-up mediano 14.7 m

mDOR, mPFS, mOS NR
15-m DOR 71.5%
15-m PFS 50.9%
15-m OS 56.7%

Lesokhim AM et al, Nat Med 2023

# Elranatamab: MagnetisMM-3 (Phase 2). Safety

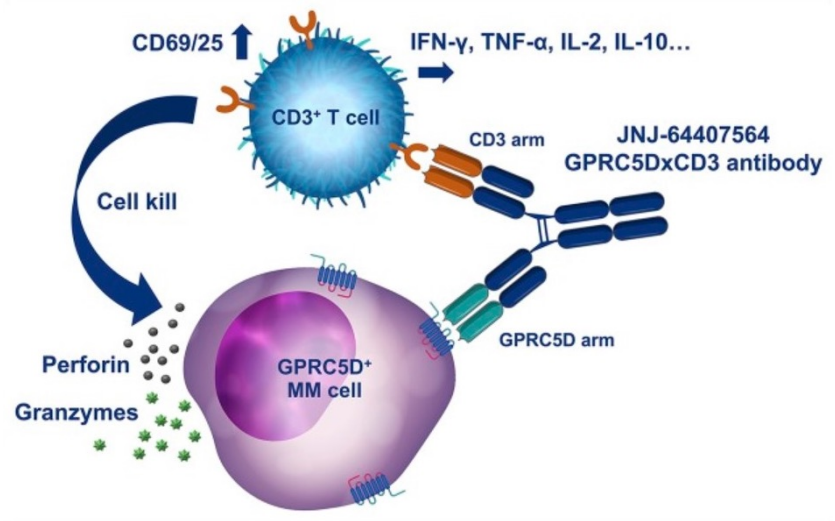
| Treatment-emergent adverse events, *n* (%) | *n*=123 | |
|---|---|---|
| | Any grade | Grade 3 or 4 |
| Any treatment-emergent adverse event | 123 (100) | 87 (70.7) |
| Hematologic[a] | | |
| Anemia | 60 (48.8) | 46 (37.4) |
| Neutropenia | 60 (48.8) | 60 (48.8) |
| Thrombocytopenia | 38 (30.9) | 29 (23.6) |
| Lymphopenia | 33 (26.8) | 31 (25.2) |
| Nonhematologic | | |
| Cytokine release syndrome | 71 (57.7) | 0 |
| Diarrhea | 52 (42.3) | 2 (1.6) |
| Fatigue | 45 (36.6) | 4 (3.3) |
| Decreased appetite | 41 (33.3) | 1 (0.8) |
| Pyrexia | 37 (30.1) | 5 (4.1) |
| COVID-19 related[b] | 36 (29.3)[c] | 19 (15.4) |
| Injection site reaction | 33 (26.8) | 0 |
| Nausea | 33 (26.8) | 0 |
| Hypokalemia | 32 (26.0) | 13 (10.6) |
| Cough | 31 (25.2) | 0 |
| Headache | 29 (23.6) | 0 |

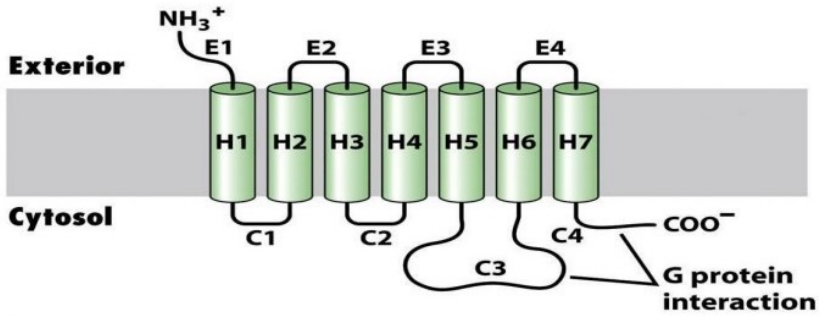
**CRS** 57.7% (limitate a G<3)
**Infezioni** 69.9% (G3/4 39.8%)

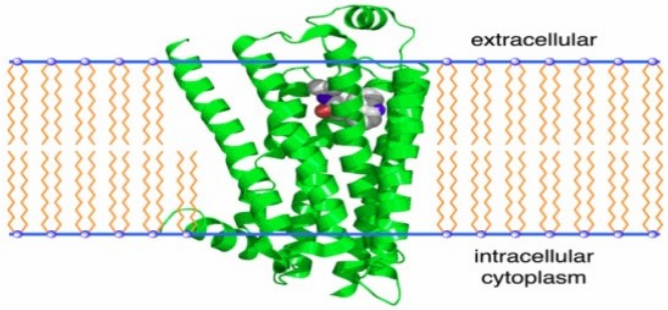
AEs G3/4 ridotti da 58.6% a 46.6% con la schedula Q2W

Lesokhim AM et al, Nat Med 2023

# BsAbs anti-GPRC5D (G protein-coupled receptor, class C, group 5, member D): Talquetamab




GPRC5D è espresso nelle PC di MM e in diverse linee cellulari di MM; PC normali, **follicoli piliferi e tessuti cheratinizzati**

L'espressione negli altri tessuti normali, comprese le cellule emopoietiche, è limitata

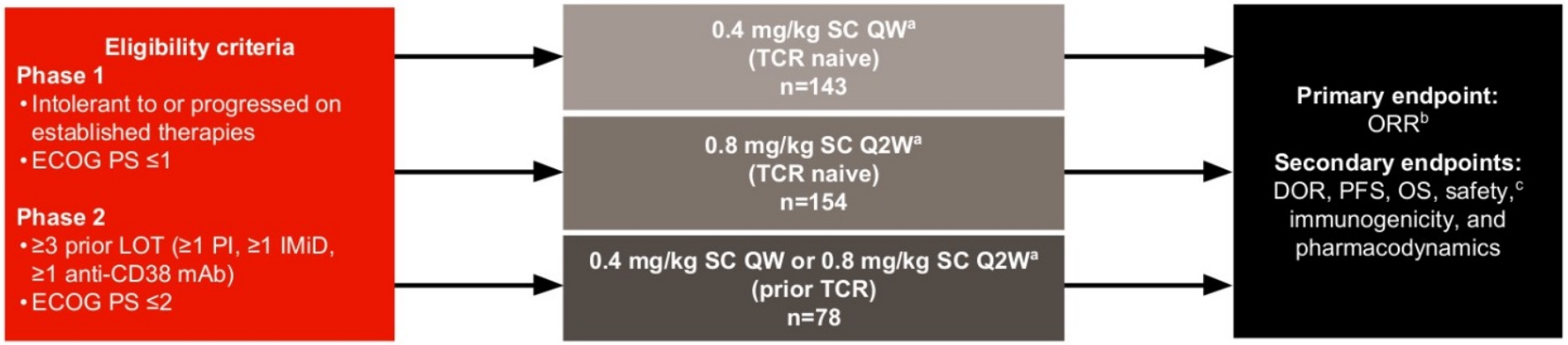
La sua funzione nei tessuti umani non è nota

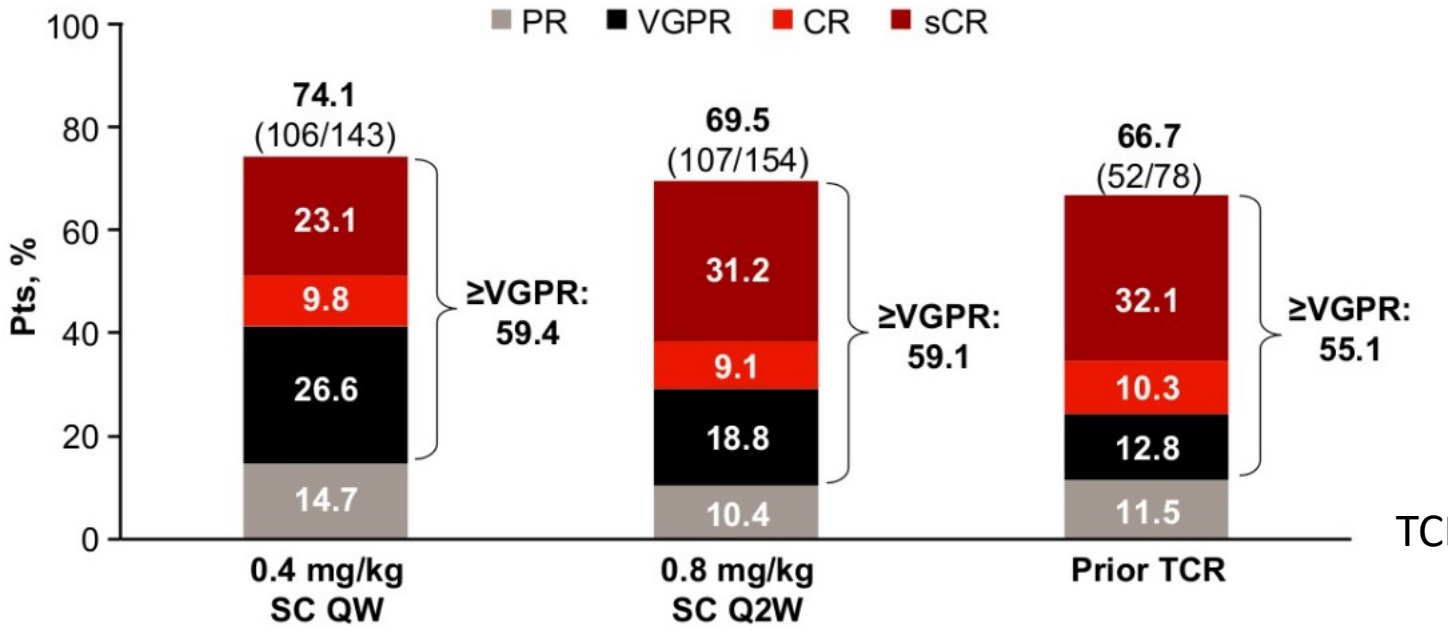
Proteina transmembrana a 7 passaggi con **ridotta probabilità di passaggio nel siero ("shedding")** che potrebbe interferire con l'effetto terapeutico

**La prossimità degli epitopi esposti alla membrana plasmatica** facilita la formazione di immunosinapsi più strette tra cellule T e cellule target

# BsAbs anti-GPRC5D, Talquetamab: MonumenTAL-1 (Phase 1/2). Efficacia

**Long-Term Efficacy and Safety Results From the Phase 1/2 MonumenTAL-1 Study of Talquetamab, a GPRC5D×CD3 Bispecific Antibody, in Patients With Relapsed/Refractory Multiple Myeloma**




TCR: T-cell redirecting therapy

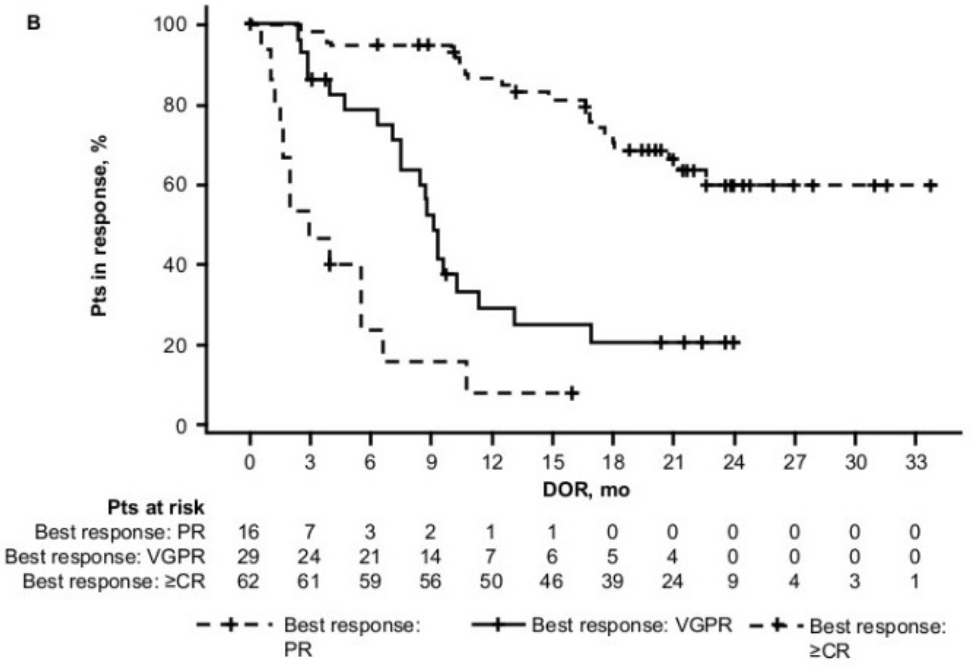
**Follow-up mediano 29.8 m, 23.4 m, 20.5 m**

Rasche L et al, EHA 2024. P915

# Talquetamab. Efficacia

**Long-Term Efficacy and Safety Results From the Phase 1/2 MonumenTAL-1 Study of Talquetamab, a GPRC5D×CD3 Bispecific Antibody, in Patients With Relapsed/Refractory Multiple Myeloma**

| Outcome | 0.4 mg/kg SC QW (n=143) | 0.8 mg/kg SC Q2W (n=154) | Prior TCR (n=78) |
|---|---|---|---|
| mFU, mo | 29.8 | 23.4 | 20.5 |
| mDOR (95% CI),[a] mo | 9.5 (6.7–13.4) | 17.5 (12.5–NE) | N/A[b] |
| mDOR in pts with ≥CR (95% CI), mo | 28.6 (19.4–NE) | NR (21.2–NE) | N/A[b] |
| mPFS (95% CI), mo | 7.5 (5.7–9.4) | 11.2 (8.4–14.6) | 7.7 (4.1–14.5) |
| 24-mo OS rate (95% CI), % | 60.6 (51.7–68.4) | 67.1 (58.3–74.4) | 57.3 (43.5–68.9) |




DOR correla con la profondità della risposta
**mDOR** complessiva 9.5 m, 17.5 m, N/A
mDOR in pz in ≥CR 28.6 m, NR, N/A

**mPFS** 7.5 m, 11.2 m, 7.7 m

OS a 24 m 60.6%, 67.1%, 57.3%

TCR: T-cell redirecting therapy

Rasche L et al, EHA 2024. P915

# Talquetamab. Safety

**Long-Term Efficacy and Safety Results From the Phase 1/2 MonumenTAL-1 Study of Talquetamab, a GPRC5D×CD3 Bispecific Antibody, in Patients With Relapsed/Refractory Multiple Myeloma**

| Any-grade AE, n (%) | 0.4 mg/kg SC QW (n=143) | 0.8 mg/kg SC Q2W (n=154) | Prior TCR (n=78) |
|---|---|---|---|
| Taste-related[a] | | | |
| Total | 103 (72.0) | 110 (71.4) | 59 (75.6) |
| Leading to dose reduction | 10 (7.0) | 6 (3.9) | 4 (5.1) |
| Leading to discontinuation | 0 | 3 (1.9) | 0 |
| Skin-related[b] | | | |
| Total | 81 (56.6) | 113 (73.4)[e] | 50 (64.1) |
| Leading to dose reduction | 5 (3.5) | 1 (0.6) | 2 (2.6) |
| Leading to discontinuation | 2 (1.4) | 1 (0.6) | 0 |
| Nail-related[c] | | | |
| Total | 79 (55.2) | 82 (53.2) | 46 (59.0) |
| Leading to dose reduction | 1 (0.7) | 1 (0.6) | 1 (1.3) |
| Leading to discontinuation | 0 | 0 | 0 |
| Rash-related[d] | | | |
| Total | 57 (39.9)[f] | 46 (29.9)[g] | 25 (32.1)[h] |
| Leading to dose reduction | 1 (0.7) | 1 (0.6) | 0 |
| Leading to discontinuation | 0 | 0 | 0 |

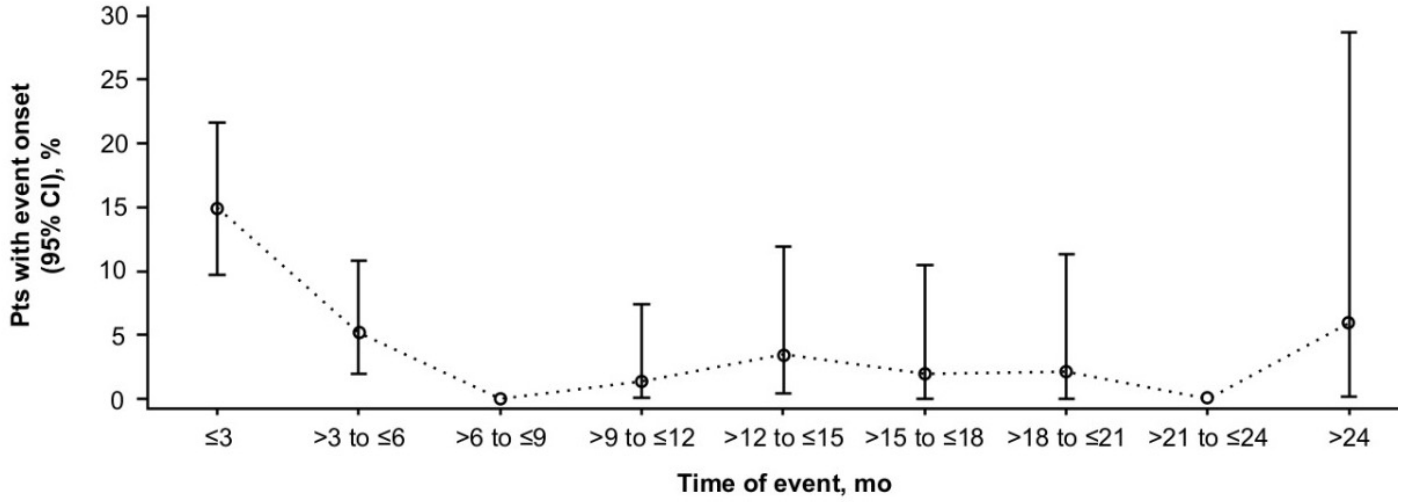
Non nuovi segnali di tossicità
L'incidenza complessiva riduzione di dose/discontinuazione per AEs è limitata: 15%, 10%, 12%/5%, 10%, 5%
0 morti correlate al trattamento

**AEs correlati a GPRC5D** (disgeusia, alterazioni cutanee/unguali) sono frequenti ma raramente associati a riduzione di dose/discontinuazione

Rasche L et al, EHA 2024. P915

# Long-Term Efficacy and Safety Results From the Phase 1/2 MonumenTAL-1 Study of Talquetamab, a GPRC5D×CD3 Bispecific Antibody, in Patients With Relapsed/Refractory Multiple Myeloma

**Figure 5: New-onset grade ≥3 infections over time in the Q2W cohort**



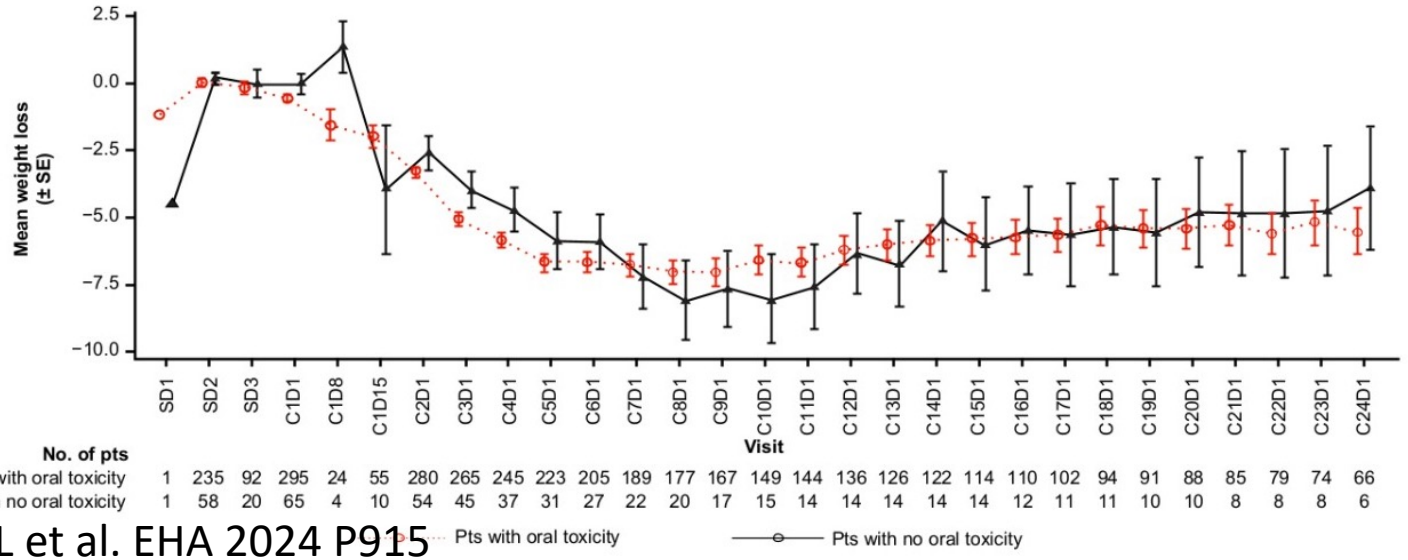

| | ≤3 | >3 to ≤6 | >6 to ≤9 | >9 to ≤12 | >12 to ≤15 | >15 to ≤18 | >18 to ≤21 | >21 to ≤24 | >24 |
|---|---|---|---|---|---|---|---|---|---|
| No. of pts (with event) | 154 (23) | 117 (6) | 89 (0) | 73 (1) | 58 (2) | 51 (1) | 47 (1) | 37 (0) | 17 (1) |

Incidenza di **infezioni G≥3** 19.6/14.5%

L'incidenza di nuove infezioni G≥3 tende a ridursi mantenendosi limitata dopo i primi 3-6 mesi di trattamento

Non è stato osservato incremento delle **infezioni G3/4** con follow-up prolungato

**Figure 4: Weight loss in pts with oral toxicity[a] in the QW and Q2W cohorts**




**Calo ponderale** 39%, 34%, 39%
E' precoce e tende a miglioramento/stabilizzazione, anche nei pz con tossicità orale

Rasche L et al. EHA 2024 P915

Rasche L et al, EHA 2024. P915

# Teclistamab nei pazienti con caratteristiche di alto rischio

**Figure 2: ORR in patients with HR features in MajesTEC-1**

**Efficacy and Safety of Teclistamab in Patients With Relapsed/Refractory Multiple Myeloma With High-Risk Features: A Subgroup Analysis From the Phase 1/2 MajesTEC-1 Study**

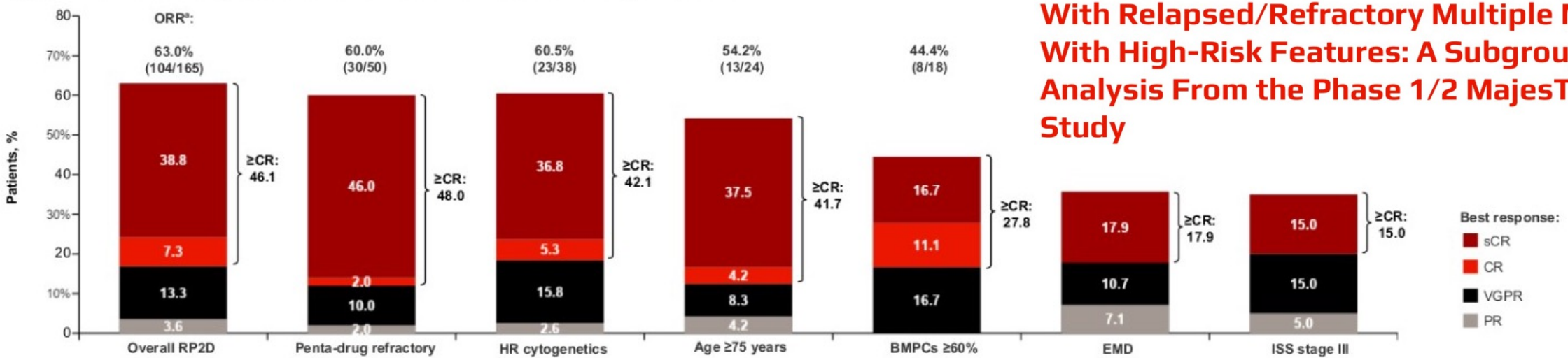
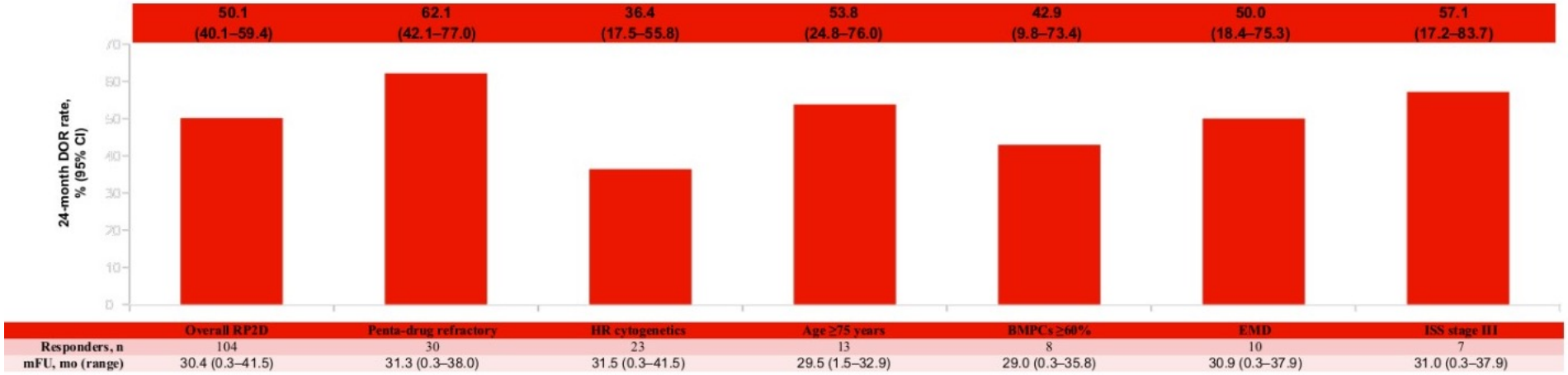



**Figure 3: DOR to teclistamab in patients with HR features in MajesTEC-1**




Nei pz 5-refrattari, con HCR, età ≥75: ORR e ≥CR sovrapponibili alla popolazione complessiva RP2D

Nei pz con elevato burden (BMPCs ≥60% e ISS III) e EMD: ORR inferiori

Nella maggior parte dei sottogruppi ad alto rischio, DOR simile alla popolazione complessiva RP2D

Costa LJ et al, EHA 2024. P923

# Talquetamab nei pazienti con caratteristiche di alto rischio

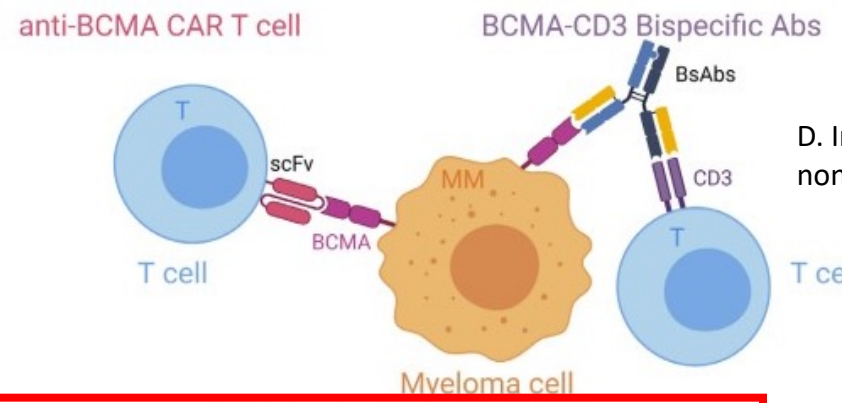
**Long-Term Efficacy and Safety Results From the Phase 1/2 MonumenTAL-1 Study of Talquetamab, a GPRC5D×CD3 Bispecific Antibody, in Patients With Relapsed/Refractory Multiple Myeloma**

| ORR in subgroups, % (95% CI) | 0.4 mg/kg SC QW (n=143) | 0.8 mg/kg SC Q2W (n=154) | Prior TCR (n=78) |
|---|---|---|---|
| Age ≥75, years | 71.4 (47.8–88.7) | 75.8 (57.7–88.9) | 80.0 (28.4–99.5) |
| High-risk cytogenetics[a] | 70.7 (54.5–83.9) | 75.0 (58.8–87.3) | 52.0 (31.3–72.2) |
| ISS stage III | 64.3 (44.1–81.4) | 59.5 (42.1–75.2) | 76.9 (46.2–95.0) |
| Baseline renal function, ≤60 mL/min/1.73 $m^2$ | 65.0 (48.3–79.4) | 65.2 (49.8–78.6) | 63.2 (38.4–83.7) |
| Refractory status | | | |
| Triple-class[b] | 72.9 (63.4–81.0) | 67.3 (57.7–75.9) | 65.2 (52.4–76.5) |
| Penta-drug[c] | 71.1 (55.7–83.6) | 69.2 (52.4–83.0) | 58.8 (40.7–75.4) |
| ≥1 extramedullary plasmacytoma[d] | 48.5 (30.8–66.5) | 41.5 (26.3–57.9) | 44.0 (24.4–65.1) |

Nei pz con ISS III, IR, EMD: ORR inferiori  rispetto alla popolazione complessiva

Rasche L et al, EHA 2024. P915

# Meccanismi di resistenza e potenziali limiti all'utilizzo di terapie T cell-dipendenti

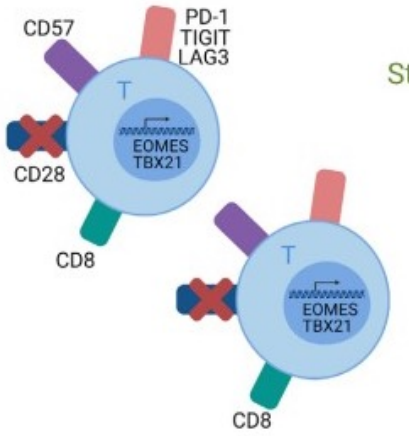


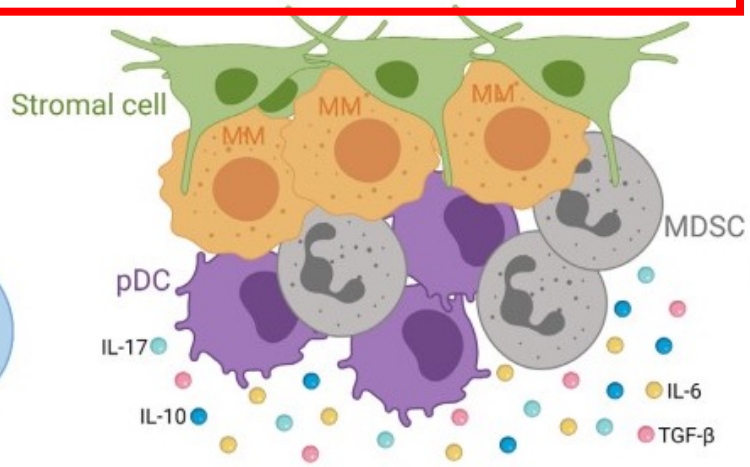

D. Immune response against the Ab construct and non human scFv of CAR-T

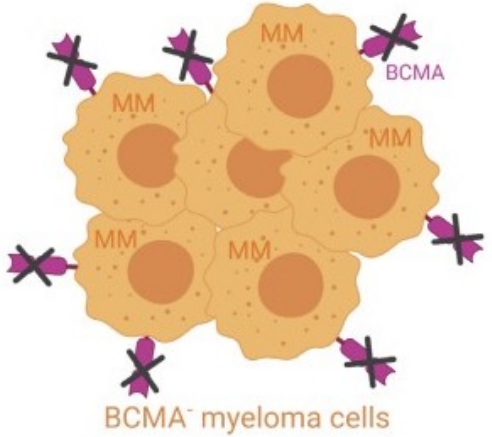
**A. T cell Features**
- T cell expansion/persistance
- T cell phenotype
- T cell fitness

**B. BM environment Features**
- Inhibitory mechanisms
- Suppressive cells
- Inhibitory cytokines

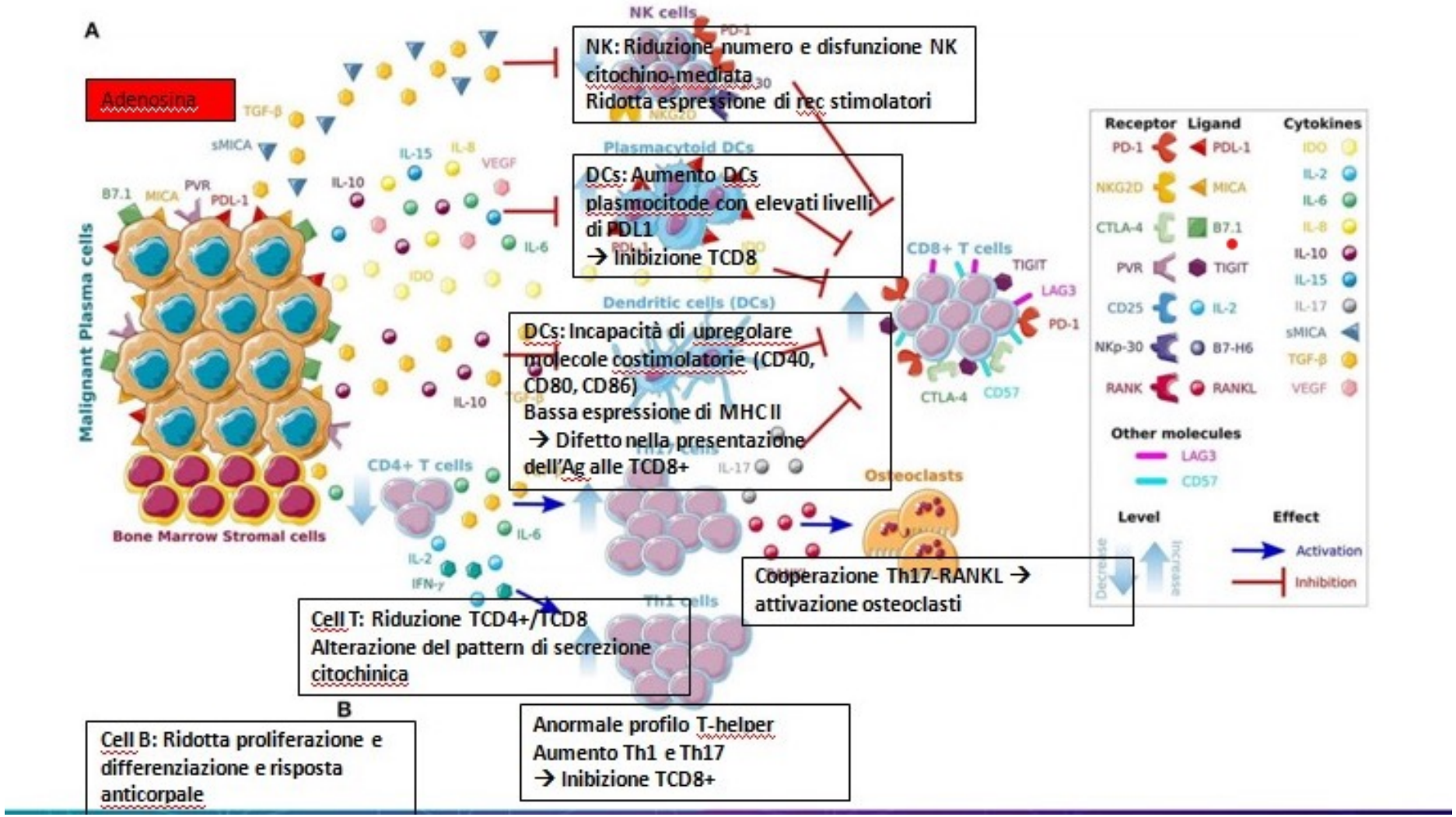
**C. Tumor Features**
- Genetic abnormality
- Tumor heterogeneity → Antigen escape
- Therapeutic selection



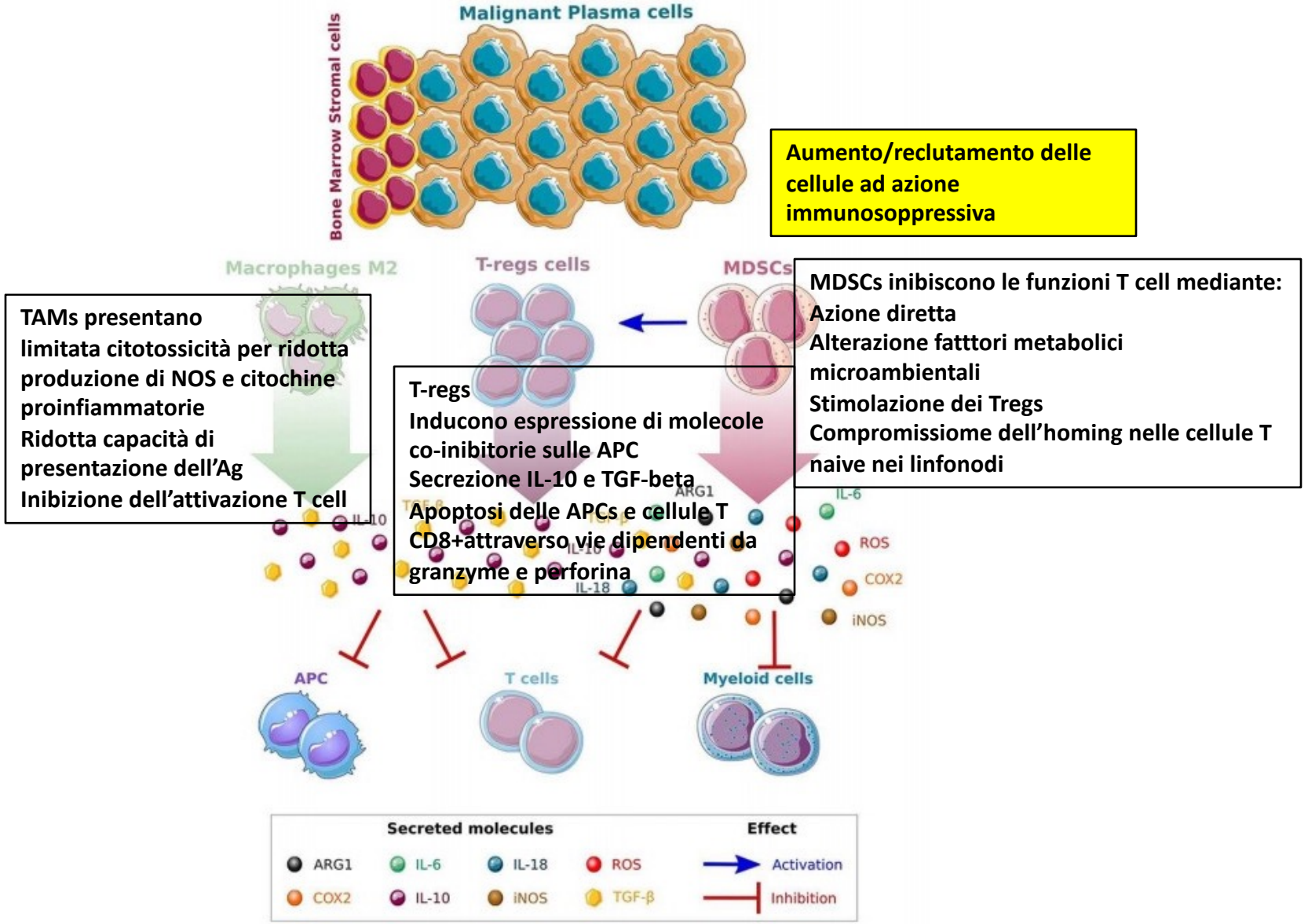



# Meccanismi di evasione immune nel MM



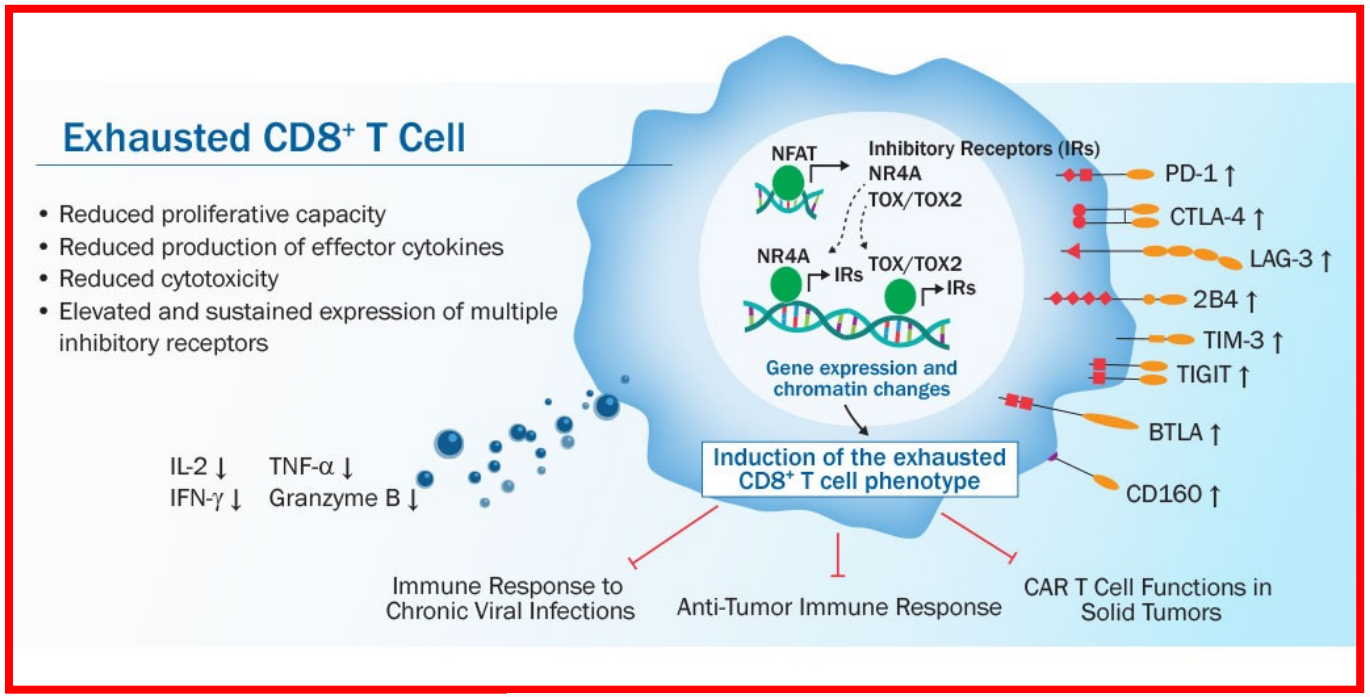

Da: Leblay et al, Front Oncol 2020

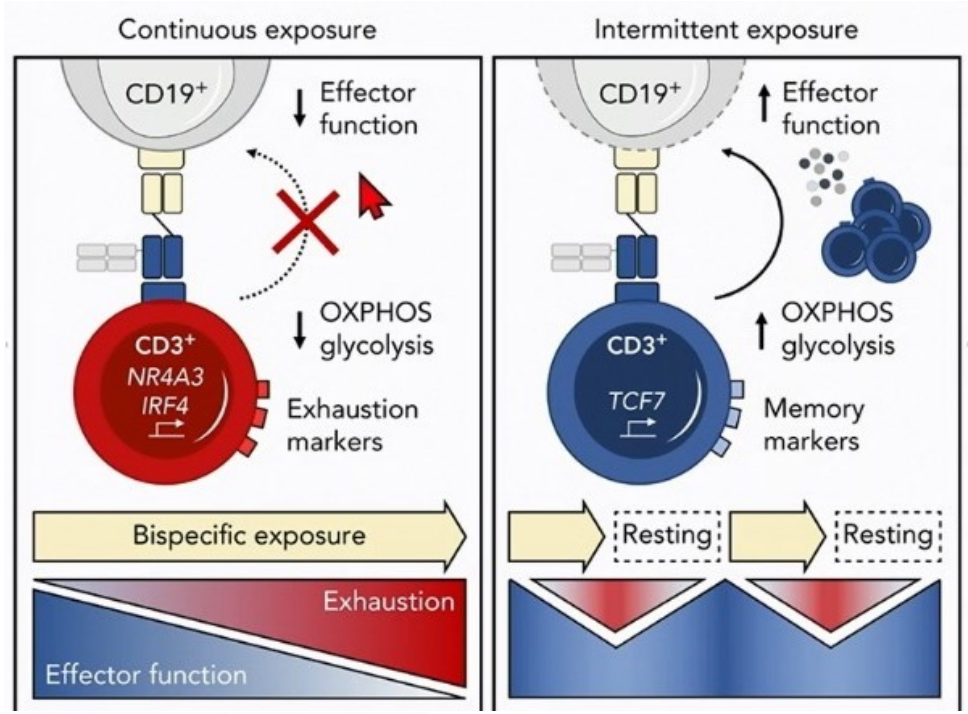
# Meccanismi di evasione immune nel MM

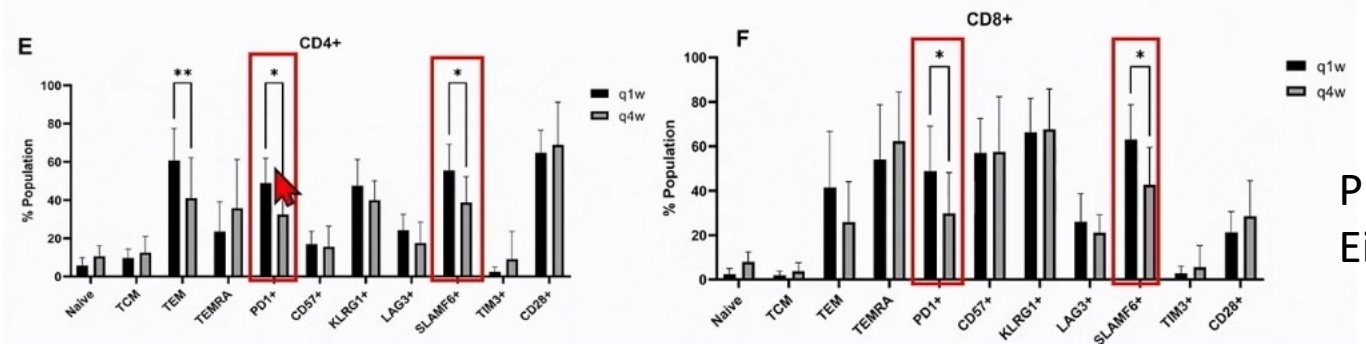



Da: Leblay et al., Front Oncol 2020

# T cell exhaustion




Philipp N et al, Blood 2022
Einsele F et al, ASH 2023

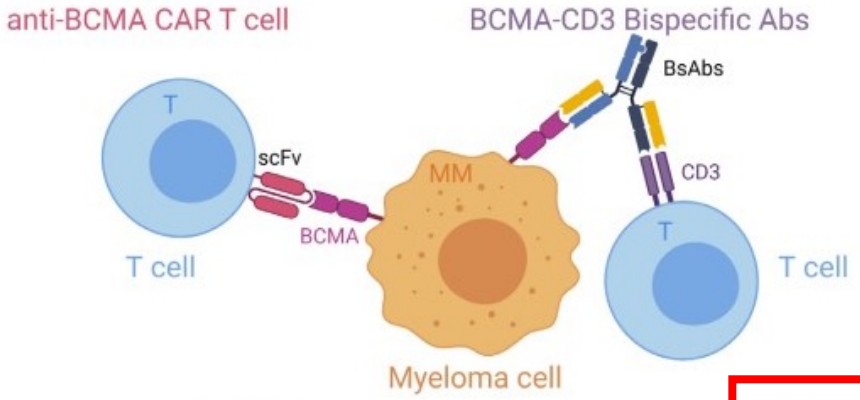
T cell exhaustion è un meccanismo regolatorio finalizzato a limitare l'attività delle cellule T, in particolare in presenza di una stimolazione antigenica cronica

La esposizione continua delle cellule T a BsAbs induce T cell exhaustion (riduzione di funzione effettrice e fitness metabolica)

**L'esposizione intermittente (resting delle cellule T) si associa a** miglioramento di funzione effettrice e fitness metabolica

# Meccanismi di resistenza e potenziali limiti all'utilizzo di terapie T cell-dipendenti

Immune response against the Ab construct and non human scFv of CAR-T




**A. T cell Features**
- T cell expansion/persistance
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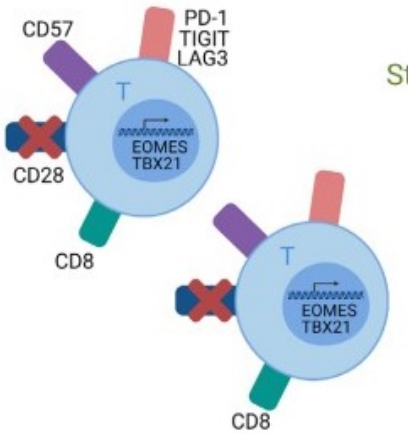
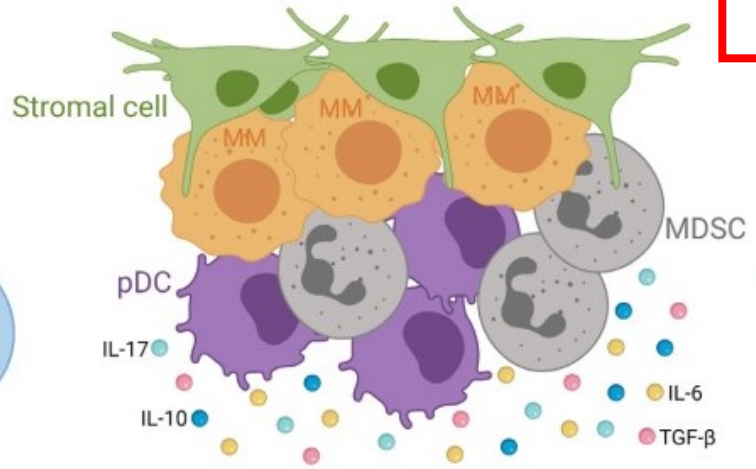
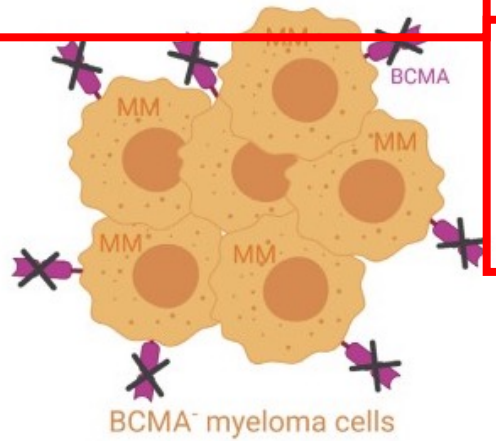


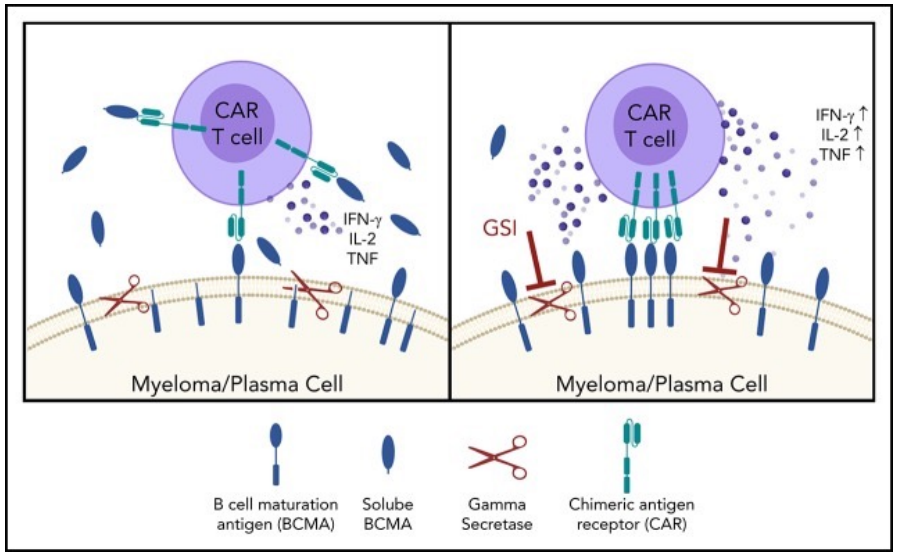




**Acquired resistance:**
**Antigen loss:**
- Ag downregulation
- Ag escape (loss of target epitope)
- Phenotypic switch
- Shedding and interference of soluble BCMA

**Intrinsec resistance:**
- Genetically determined apoptosis resistance (i.e. del *p53 double hit*)
- Apoptosis resistance of metabolically active cells in MRD+

# Strategie per ottimizzare l'efficacia dei BsAbs

## Modulazione farmacologica dell'espressione antigenica sulle cellule tumorali




Gli inibitori delle gamma-secretasi (GSI) limitano lo shedding di BCMA e determinano un aumento della densità di BCMA sulla superficie cellulare

γ-secretase inhibitors augment efficacy of BCMA-targeting bispecific antibodies against multiple myeloma cells without impairing T-cell activation and differentiation

Chen H et al, Blood Cancer J 2022

HemaSphere

EHA EUROPEAN HEMATOLOGY ASSOCIATION

**S194 TECLISTAMAB (TEC) + NIROGACESTAT (NIRO) IN RELAPSED/REFRACTORY MULTIPLE MYELOMA (RRMM): THE PHASE 1B MAJESTEC-2 STUDY**

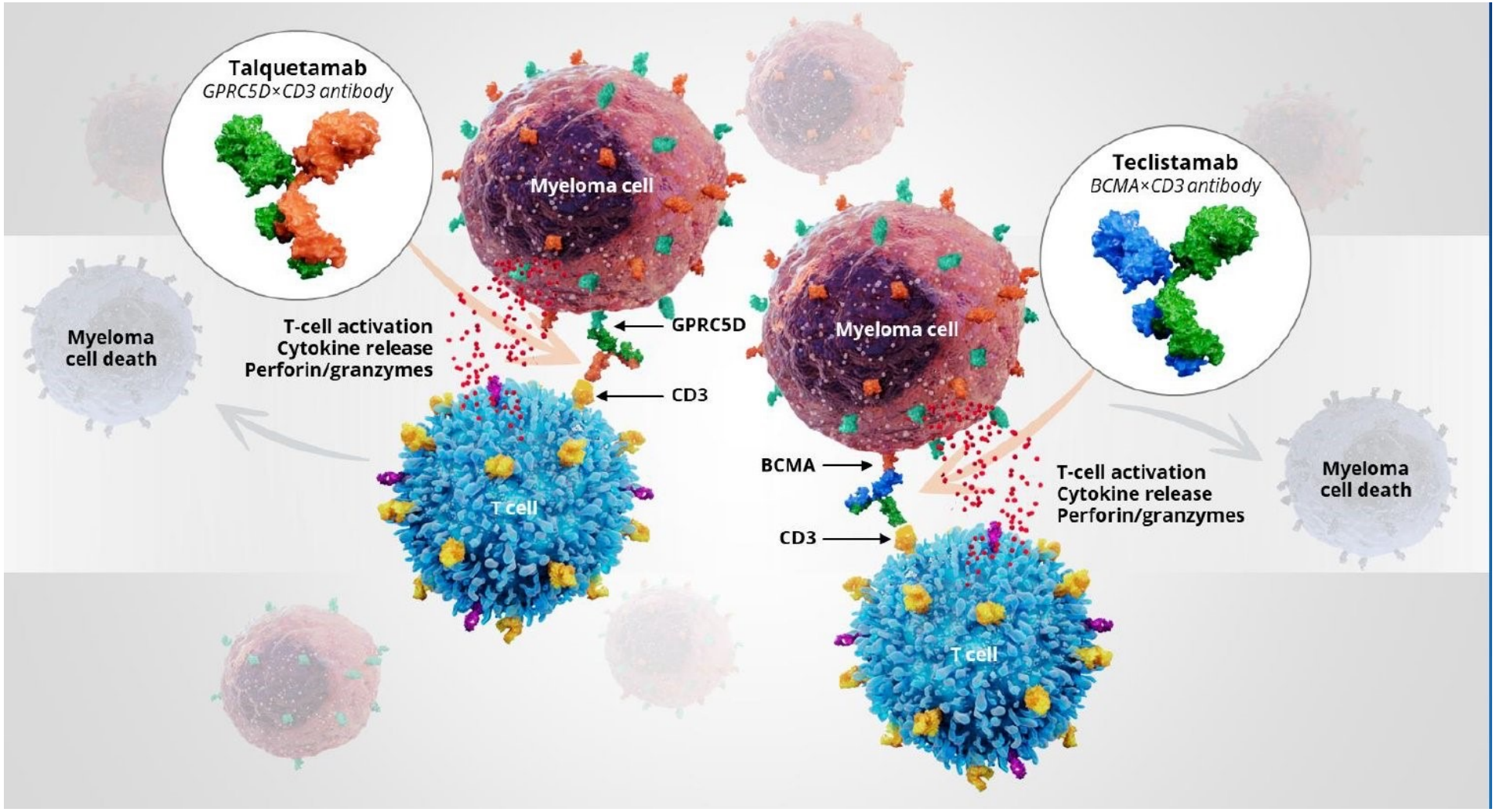
**Table: Response rates by dose level**

| | Tec 720 µg/kg QW + concurrent niro (n=8) | Tec 720 µg/kg QW + QD delayed low-dose niro (n=7) | Tec 1500 µg/kg QW + QD delayed low-dose niro (n=13) | Total (N=28) |
|---|---|---|---|---|
| Follow-up, median (range), mo | 19.3 (0.5[a]–19.7) | 15.3 (1.6[a]–18.6) | 11.3 (4.3[a]–14.2) | 11.96 (0.5[a]–19.7) |
| Response, n (%) | | | | |
| Overall response | 5 (71.4)[b] | 4 (57.1) | 12 (92.3) | 21 (77.8)[c] |
| ≥Very good partial response | 5 (71.4)[b] | 4 (57.1) | 12 (92.3) | 21 (77.8)[c] |
| ≥Complete response | 3 (42.9)[b] | 4 (57.1) | 7 (53.8) | 14 (51.9)[c] |

Offner F et al, EHA 2023

# Strategie per ottimizzare l'efficacia dei BsAbs

## Dual targeting: combinazione di BsAbs con target differenti

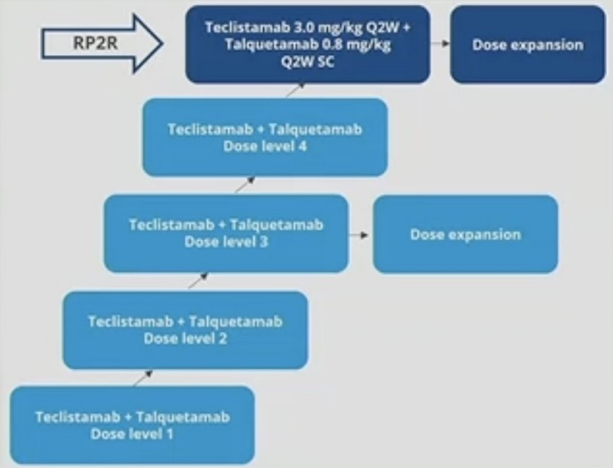


# Tec + Tal: RedirecTT-1 (Phase 1b). Caratteristiche dei pazienti

**Primary objectives**
- Evaluate safety
- Identify RP2R(s) and schedule for the combination

**Secondary objectives**
- Preliminary anticancer activity of each study treatment at RP2R(s) in Part 2, PK, immunogenicity

**Key eligibility criteria**
- Measurable MM
- RR or intolerant to established therapies, including last LOT
- Exposed to a PI, IMiD, and anti-CD38 mAb



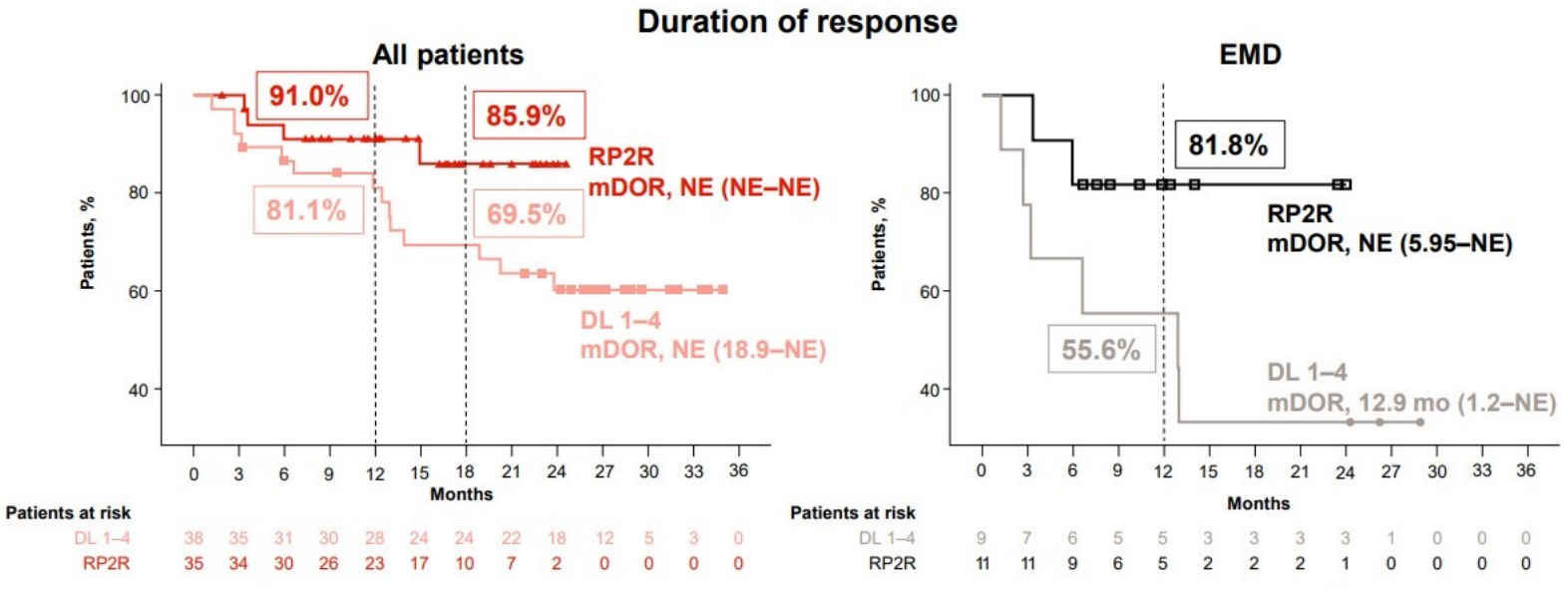

| Characteristic | RP2R (n=44) | All doses (N=94) |
|---|---|---|
| Median age, years (range) | 63.0 (41–80) | 64.5 (39–81) |
| Male, n (%) | 23 (52.3) | 49 (52.1) |
| Race, n (%) | | |
| White | 32 (72.7) | 75 (79.8) |
| Black/African American | 0 (0) | 1 (1.1) |
| Asian | 12 (27.3) | 17 (18.1) |
| Unknown | 0 (0) | 1 (1.1) |
| Extramedullary plasmacytomas ≥1,[a] n (%) | 18 (40.9) | 34 (36.2) |
| High-risk cytogenetics,[b] n (%) | 8 (42.1) | 21 (41.2) |
| ISS stage,[c] n (%) | | |
| I | 19 (46.3) | 38 (44.7) |
| II | 14 (34.1) | 26 (30.6) |
| III | 8 (19.5) | 21 (24.7) |
| Years since diagnosis, median (range) | 5.5 (0.3–12.9) | 6.1 (0.3–14.6) |

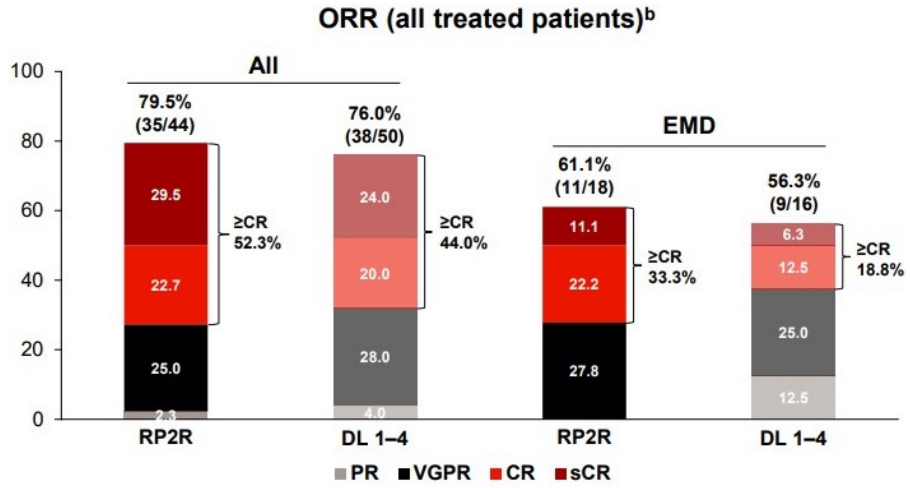
| Characteristic | RP2R (n=44) | All doses (N=94) |
|---|---|---|
| Median prior LOT, n (range) | 4.0 (2–10) | 4.0 (1–11) |
| Exposure status, n (%) | | |
| Belantamab mafodotin | 5 (11.4) | 18 (19.1) |
| CAR-T therapy[d] | 2 (4.5) | 4 (4.3) |
| Bispecific antibody[e] | 2 (4.5) | 7 (7.4) |
| Any BCMA-directed therapy | 9 (20.5) | 27 (28.7) |
| Triple-class | 44 (100.0) | 94 (100.0) |
| Penta-drug | 28 (63.6) | 61 (64.9) |
| Refractory status, n (%) | | |
| Proteasome inhibitor | 41 (93.2) | 85 (90.4) |
| Immunomodulatory drug | 41 (93.2) | 91 (96.8) |
| Anti-CD38 | 43 (97.7) | 93 (98.9) |
| Triple-class | 37 (84.1) | 81 (86.2) |
| Penta-drug | 13 (29.5) | 31 (33.0) |
| To last line of therapy | 39 (88.6) | 87 (92.6) |

Cohen Y et al, IMS 2024

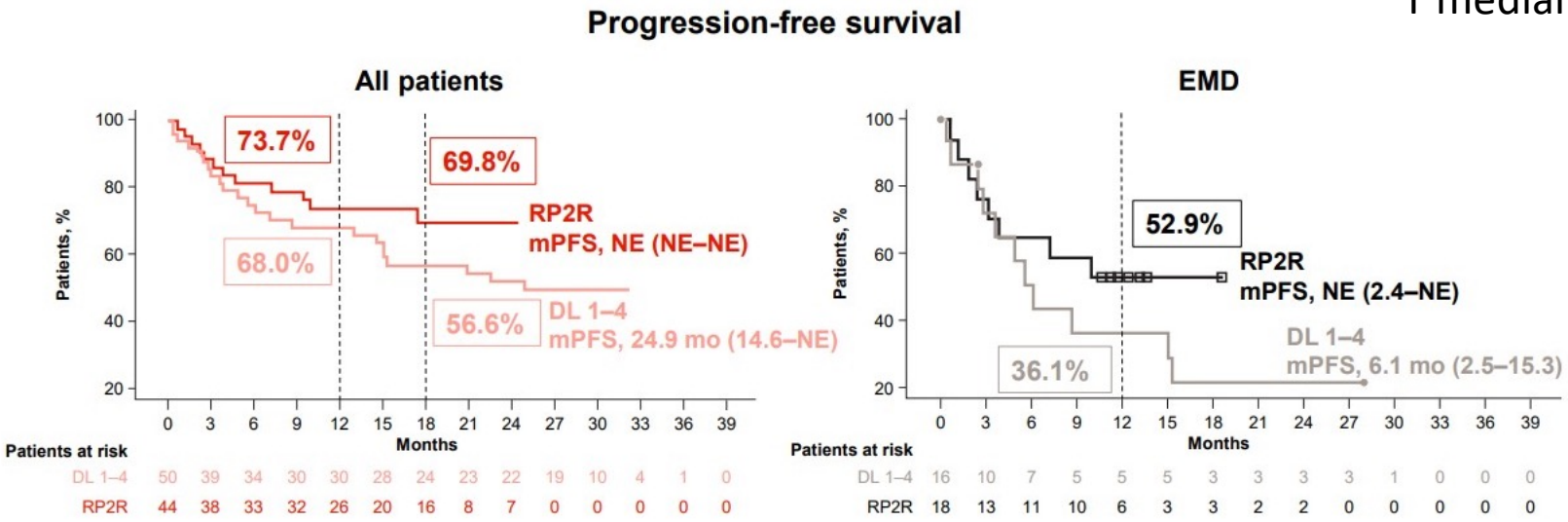
# Tec + Tal: Efficacia

**Talquetamab + Teclistamab in Patients With Relapsed/Refractory Multiple Myeloma: Updated Phase 1b Results From RedirecTT-1 With >1 Year of Follow-Up**




T mediano alla 1° risposta: 1.4 m (All), 3 m (EMD)




Cohen Y et al, IMS 2024

# Tec + Tal: Safety

## Talquetamab + Teclistamab in Patients With Relapsed/Refractory Multiple Myeloma: Updated Phase 1b Results From RedirecTT-1 With >1 Year of Follow-Up

| Most common AEs (≥35% overall),[a] n (%) | RP2R (n=44) | | All doses (N=94) | |
|---|---|---|---|---|
| | Any Grade | Grade 3/4 | Any Grade | Grade 3/4 |
| CRS | 33 (75.0) | 0 (0) | 74 (78.7) | 2 (2.1) |
| Taste changes[b] | 22 (50.0) | NA | 61 (64.9) | NA |
| Non-rash skin AEs[c] | 25 (56.8) | 0 (0) | 57 (60.6) | 0 (0) |
| Nail-related AEs[d] | 21 (47.7) | 0 (0) | 49 (52.1) | 0 (0) |
| Pyrexia | 14 (31.8) | 1 (2.3) | 48 (51.1) | 2 (2.1) |
| Diarrhea | 21 (47.7) | 2 (4.5) | 45 (47.9) | 3 (3.2) |
| Cough | 13 (29.5) | 0 (0) | 42 (44.7) | 1 (1.1) |
| Dry mouth | 18 (40.9) | 0 (0) | 40 (42.6) | 0 (0) |
| COVID-19 | 21 (47.7) | 6 (13.6) | 38 (40.4) | 17 (18.1) |
| Rash AEs[e] | 14 (31.8) | 1 (2.3) | 37 (39.4) | 1 (1.1) |
| Pneumonia | 14 (31.8) | 7 (15.9) | 34 (36.2) | 19 (20.2) |

| Most common AEs (≥40% overall),[a] n (%) | RP2R (n=44) | | All doses (N=94) | |
|---|---|---|---|---|
| | Any Grade | Grade 3/4 | Any Grade | Grade 3/4 |
| Neutropenia | 30 (68.2) | 25 (56.8) | 69 (73.4) | 64 (68.1) |
| Anemia | 18 (40.9) | 11 (25.0) | 53 (56.4) | 36 (38.3) |
| Thrombocytopenia | 12 (27.3) | 9 (20.5) | 40 (42.6) | 28 (29.8) |

| | RP2R (n=44) | All doses (N=94) |
|---|---|---|
| Patients with CRS,[a] n (%) | 33 (75.0) | 74 (78.7) |
| Grade 1 | 23 (52.3) | 50 (53.2) |
| Grade 2 | 10 (22.7) | 22 (23.4) |
| Grade 3 | 0 (0) | 2 (2.1) |
| Days to onset,[b] median (range) | 2 (1–4) | 2 (1–733) |
| Duration, days, median (range) | 2 (1–5) | 2 (1–8) |
| Supportive measures,[c] n (%) | 28 (63.6) | 61 (64.9) |
| Tocilizumab | 10 (22.7) | 24 (25.5) |
| IV fluids | 8 (18.2) | 11 (11.7) |
| Corticosteroids | 1 (2.3) | 3 (3.2) |
| Oxygen | 1 (2.3) | 1 (1.1) |
| Vasopressor | 0 (0) | 1 (1.1) |

**CRS** alla RP2R limitate a G<3

**5 ICANS** in 3 pz (3.2%) (max G3) all doses.

2 ICANS in 1 pz (max G1) alla RP2R

Il profilo di safety è coerente con quello dei BsAbs somministrati singolarmente

**Non evidenza di tossicità additiva**

**Citopenia** compatibile con BsAbs somministrati singolarmente, neutropenia febbrile 12.8%

Gli **AEs correlati a GPRC5D** sono frequenti ma limitati a G<3

AEs G3/4 >5%: polmonite, COVID-19

Rate di discontinuazione correlato a TEAEs: 13.6% all doses, 16.0% RP2D

AEs G5: 11.4% all doses, 14.9% RP2D (11/14 secondari a infezione)

Cohen Y et al, IMS 2024

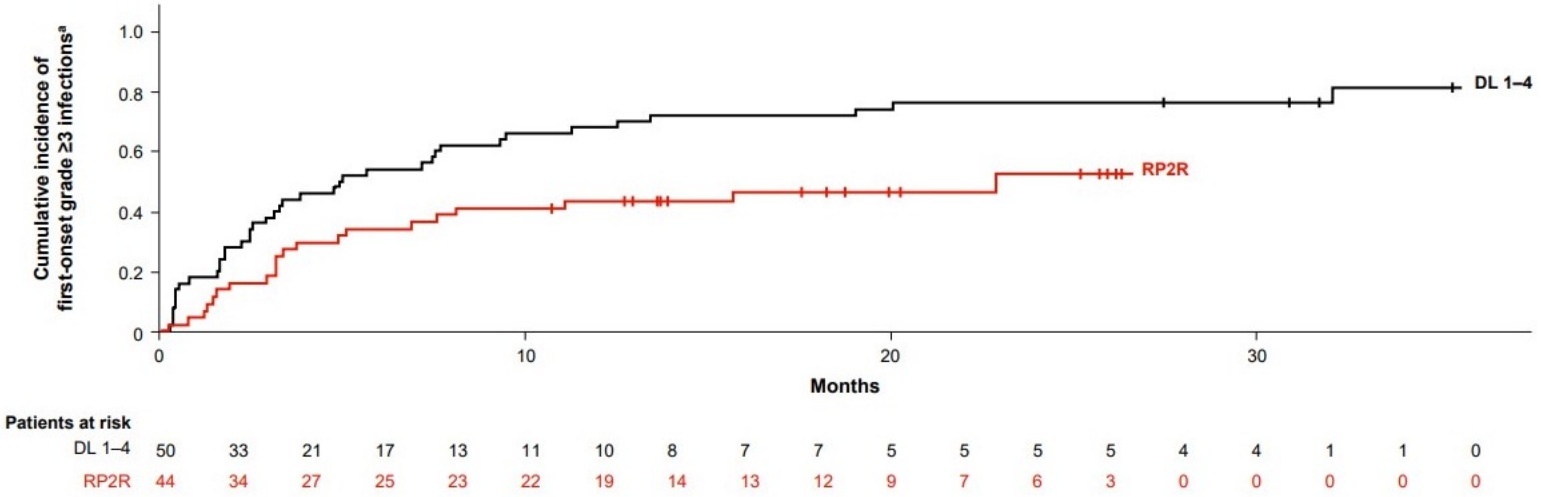
# Tec + Tal: Safety. Infezioni

**Talquetamab + Teclistamab in Patients With Relapsed/Refractory Multiple Myeloma: Updated Phase 1b Results From RedirecTT-1 With >1 Year of Follow-Up**

| Most common AEs (≥5% overall),[a] n (%) | RP2R (n=44) | | All doses (N=94) | |
|---|---|---|---|---|
| | Any Grade | Grade 3/4 | Any Grade | Grade 3/4 |
| **Infections** | 38 (86.4) | 21 (47.7) | 84 (89.4) | 60 (63.8) |
| COVID-19 | 21 (47.7) | 6 (13.6) | 38 (40.4) | 17 (18.1) |
| Pneumonia | 14 (31.8) | 7 (15.9) | 34 (36.2) | 19 (20.2) |
| Upper respiratory tract infection | 11 (25.0) | 0 (0) | 23 (24.5) | 3 (3.2) |
| Nasopharyngitis | 4 (9.1) | 0 (0) | 14 (14.9) | 0 (0) |
| Sinusitis | 4 (9.1) | 0 (0) | 12 (12.8) | 1 (1.1) |
| Rhinovirus infection | 2 (4.5) | 0 (0) | 10 (10.6) | 3 (3.2) |
| Bronchitis | 3 (6.8) | 1 (2.3) | 9 (9.6) | 3 (3.2) |
| Respiratory tract infection | 3 (6.8) | 1 (2.3) | 9 (9.6) | 5 (5.3) |
| Urinary tract infection | 7 (15.9) | 1 (2.3) | 9 (9.6) | 1 (1.1) |
| Oral candidiasis | 2 (4.5) | 0 (0) | 7 (7.4) | 2 (2.1) |
| Sepsis | 4 (9.1) | 4 (9.1) | 7 (7.4) | 7 (7.4) |
| Septic shock | 1 (2.3) | 1 (2.3) | 7 (7.4) | 6 (6.4) |

**Infezioni G3/4** 63.8% all doses, 47.7% RP2R
Tra le infezioni G≥3 >5%: polmonite, infezione da COVID-19, sepsi

L'incidenza cumulativa di infezioni G3/4 ha un plateau a 6 mesi



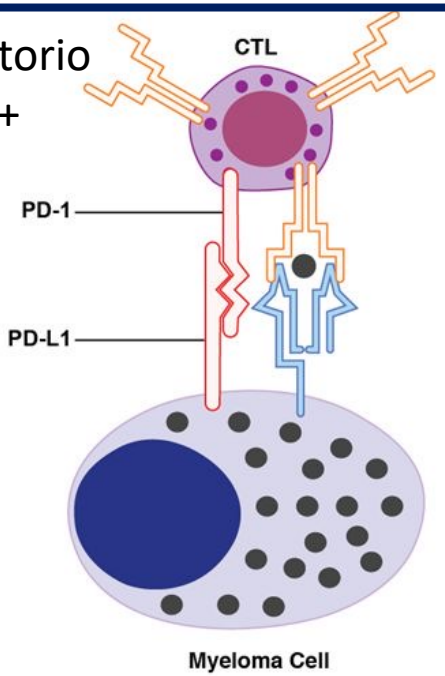

Cohen Y et al, IMS 2024

# Strategie per ottimizzare l'efficacia dei BsAbs

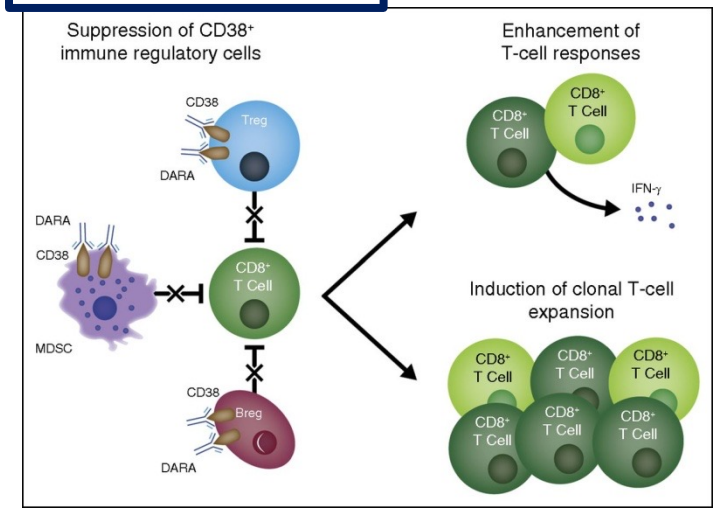
## Combinazione con agenti ad azione immunomodulante

### Check point inhibitors

Abrogazione del segnale inibitorio
→ attivazione delle cell TCD8+



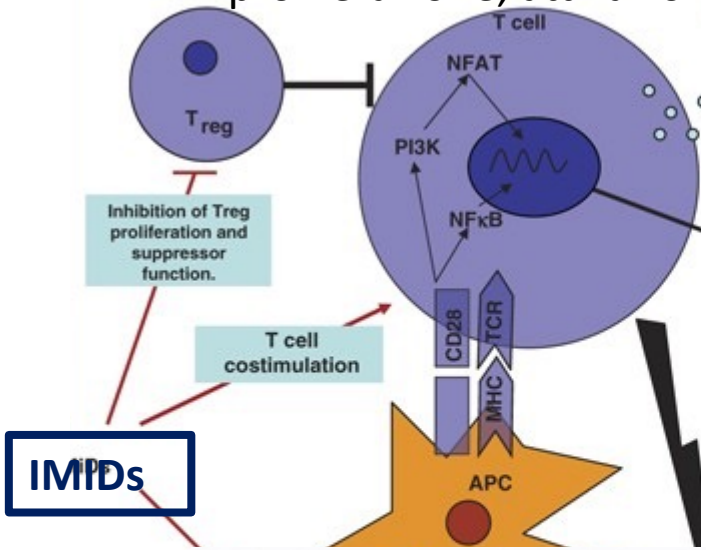

### Daratumumab



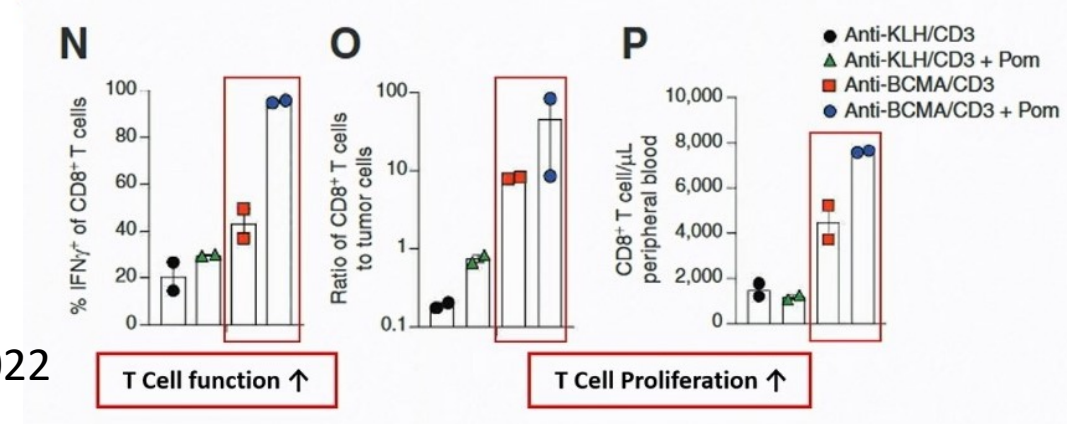

Riduzione delle cell immunoregolatorie CD38+
→ espansione clonale delle cell TCD8+

### IMIDs

Costimolazione delle cell T
Soppressione dei T-regs
→ proliferazione, attivazione delle cellule T CD8+

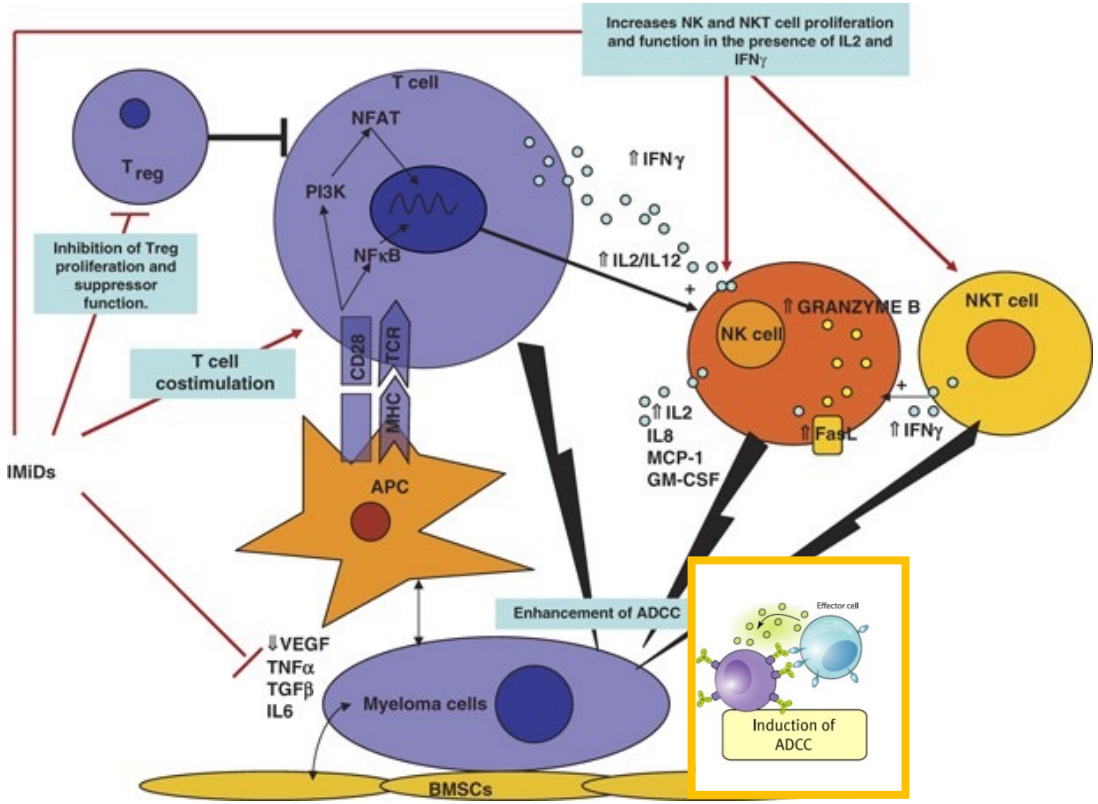



La combinazione BsAbs + IMIDs/CelMODs riduce T cell exhaustion




Meermeier EW et al,
Blood Cancer Discov 2022

# IMIDs + Dara: Effetti sinergici




IMIDs e Dara hanno effetti immunomodulanti parzialmente sovrapponibili:
- Espansione/attivazione cellule effettrici
- Riduzione delle cellule immunoregolatorie

IMIDs hanno effetto priming/induzione di ADCC da parte di Dara attraverso:
- Attivazione delle cellule NK
- Up-regolazione di CD38

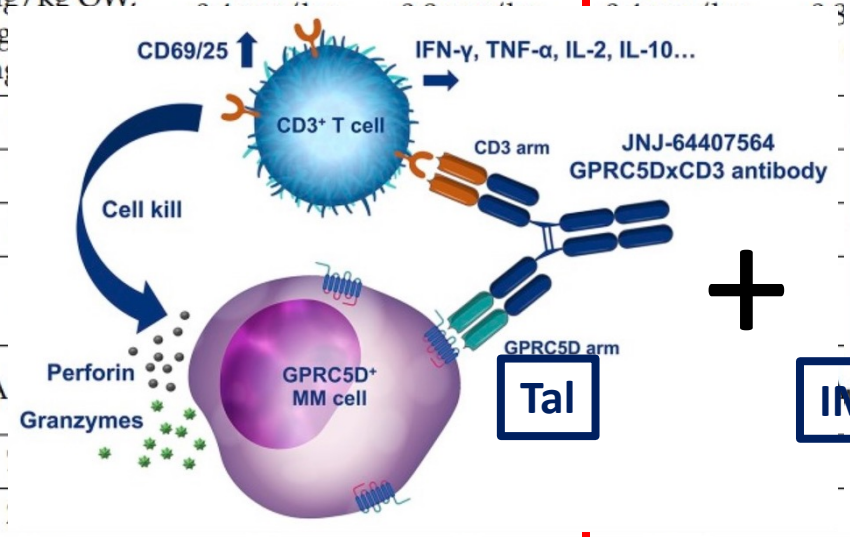
# Combinazioni di BsAbs

| BsAb Combination | Tec-Dara | Tal-Dara | | Tal-Poma | | Tec-Dara-Len | Tal-Tec |
|---|---|---|---|---|---|---|---|
| Clinical trial | Phase 1 trial TRIMM-2 (NCT04108195) | | | Phase 1b trial MonumenTAL-2 (NCT05050097) | | Phase 1b trial MajesTEC-2 (NCT04722146) | Phase 1b trial RedirecTT-1 (NCT04586426) |
| Dosing schedule | Tec SC 1.5 mg/kg QW, 3.0 mg/kg Q2W, 3.0 mg/kg QW | Tal SC 0.4 mg/kg QW | Tal SC 0.8 mg/kg Q2W | Tal SC 0.4 mg/kg QW | Tal SC 0.8 mg/kg Q2W | Tal SC 0.72 or 1.5 mg/kg QW, 3.0 mg/kg from C3 | Tec 3.0 mg/kg Tal 0.8 mg/kg SC Q2W |
| Pts n° | 65 | 14 | 51 | 16 | 19 | 35 | 34 |
| Prior LOT, median n | 5 | 6 | 5 | 3 | 3 | 2 | 4 |
| TCR, % | 75 | 57 | 61 | 31 | 21 | NA | 76.5 |
| Prior BCMA-targeted tp, % | 12 | 57 | 53 | 25 | 0 | NA | NA |
| Prior PI/IMiD/ anti-CD38 mAb, % | NA/97/63 | NA/NA/79 | NA/NA/90 | NA/NA/75 | NA/NA/74 | 100/100/28.5 | NA/NA/NA |
| ORR, % | 76.5 | 71 | 84 | 94 | 84 | 93.5 | 96 |
| ≥CR, % | 21.5 | 43 | 52 | 62.5 | 37 | 55 | 41 |
| DoR | NA | NA | 20 mo | 100% at 9 mo | 84% at 9 mo | NA | NA |
| PFS | NA | 77% at 12 mo | 19 mo | 94% at 9 mo | 75.5% at 9 mo | NA | 77% at 9 mo |
| OS | NA | 92% at 12 mo | 91.5% at 12 mo | NA | NA | NA | NA |

Da Tacchetti P et al, Cancers 2024

# Combinazioni di BsAbs: Tal + Pom

| BsAb Combination | Tec-Dara | Tal-Dara | | Tal-Poma | | Tec-Dara-Len | Tal-Tec |
|---|---|---|---|---|---|---|---|
| Clinical trial | Phase 1 trial TRIMM-2 (NCT04108195) | | | Phase 1b trial MonumenTAL-2 (NCT05050097) | | Phase 1b trial MajesTEC-2 (NCT04722146) | Phase 1b trial RedirecTT-1 (NCT04586426) |
| Dosing schedule | Tec SC 1.5 mg/kg QW. 3.0 mg 3.0 mg | Tal SC | Tal SC | Tal SC | | | |
| Pts n° | | | | | | | |
| Prior LOT, median n | | | | | | | |
| TCR, % | | | | | | | |
| Prior BCMA-targeted tp, % | | | | | | | |
| Prior PI/IMiD/ anti-CD38 mAb, % | NA | | | | | | |
| ORR, % | | | | | | | |
| ≥CR, % | | | | | | | |
| DoR | NA | NA | 20 mo | 100% at 9 mo | 84% at 9 mo | NA | NA |
| PFS | NA | 77% at 12 mo | 19 mo | 94% at 9 mo | 75.5% at 9 mo | NA | 77% at 9 mo |
| OS | NA | 92% at 12 mo | 91.5% at 12 mo | NA | NA | NA | NA |

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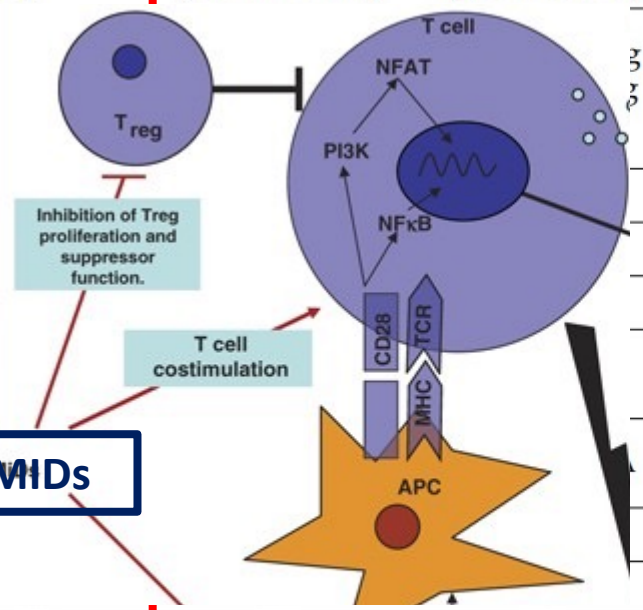



Da Tacchetti P et al, Cancers 2024

# Tal + Pom: MonumenTAL-2 (Phase 1b). Efficacia

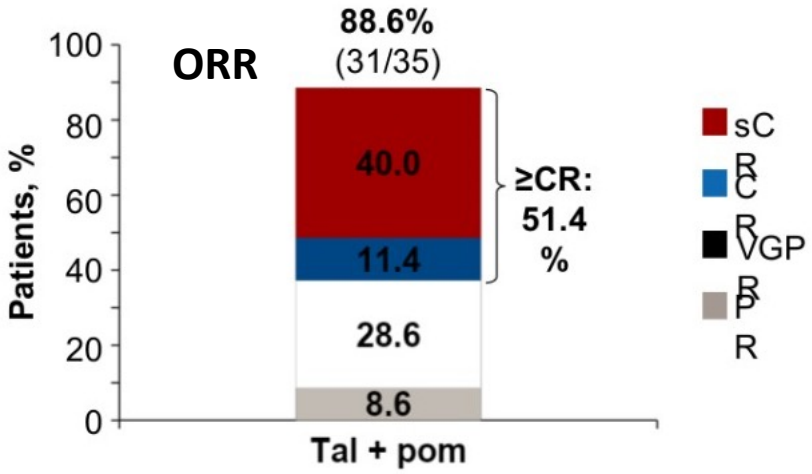
**Talquetamab, a GPRC5D×CD3 Bispecific Antibody, in Combination With Pomalidomide in Patients With Relapsed/Refractory Multiple Myeloma: Safety and Efficacy Results From the Phase 1b MonumenTAL-2 Study**

**Eligibility criteria**
- Measurable multiple myeloma
- ≥2 prior LOT, including a PI and lenalidomide
- ECOG PS of 0 or 1
- Prior pom and TCR (CAR-T and BsAb) permitted
- No prior GPRC5D therapy

**Dosing schedule:**
**Tal**[a]
0.4 mg/kg SC QW or 0.8 mg/kg SC Q2W
+
**Pom**
Starting at cycle 2
2.0 mg PO daily, with dose escalation to 4.0 mg PO daily permitted

**Primary endpoint:**
Safety[b]

**Key secondary endpoints:**
ORR,[c] time to response, DOR, PFS




| | Tal + pom (N=35) |
|---|---|
| Median follow-up (range), months | 16.8 (1.2–25.1) |
| Median time to first response (range), months | 1.1 (0.0–3.3) |
| Median DOR, months (95% CI) | NR (12.0–NE) |
| 12-month DOR rate, % (95% CI) | 74.4 (53.5–86.9) |
| Median PFS, months (95% CI) | NR (12.9–NE) |
| 12-month PFS rate, % (95% CI) | 72.6 (53.9–84.7) |

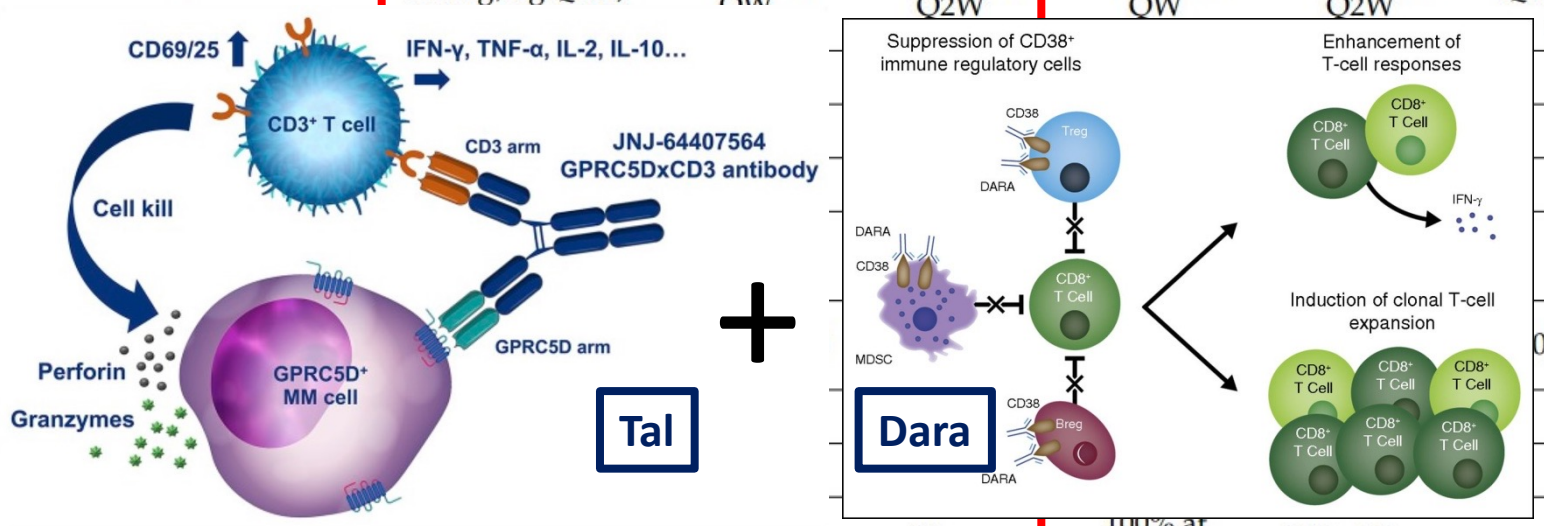
| Depth of response | 12-month DOR rate (95% CI), % |
|---|---|
| PR | 0.0 (NE–NE) n=2 |
| VGPR | 78.8 (38.1–94.3) n=11 |
| CR | 80.4 (50.6–93.2) n=17 |

ORR elevato anche in pz HCR (77.8%), precedente CAR-T (100%) o Pom (100%)
Trend di correlazione di DOR con la profondità della risposta

Searle E et al, EHA 2024. P911

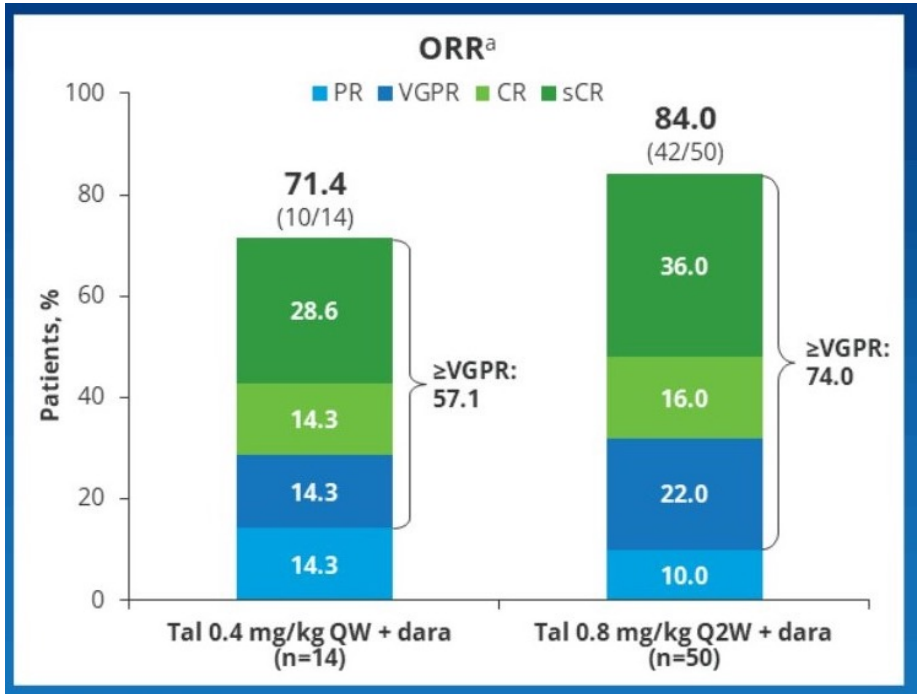
# Combinazioni di BiAbs: Tal + Dara

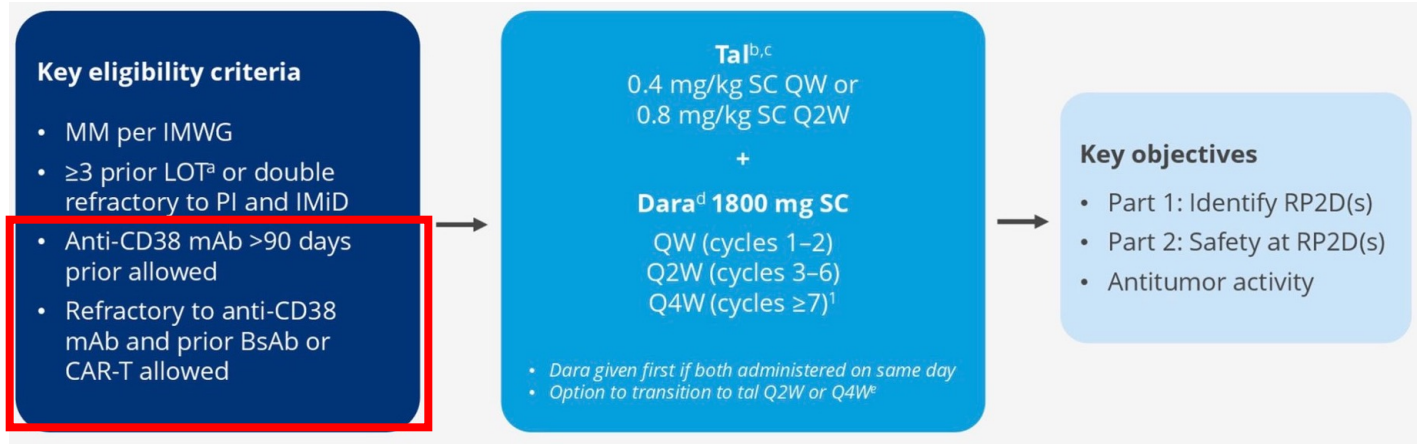
| BsAb Combination | Tec-Dara | Tal-Dara | | Tal-Poma | | Tec-Dara-Len | Tal-Tec |
|---|---|---|---|---|---|---|---|
| Clinical trial | Phase 1 trial TRIMM-2 (NCT04108195) | | | Phase 1b trial MonumenTAL-2 (NCT05050097) | | Phase 1b trial MajesTEC-2 (NCT04722146) | Phase 1b trial RedirecTT-1 (NCT04586426) |
| Dosing schedule | Tec SC 1.5 mg/kg QW, 3.0 mg/kg Q2W, | Tal SC 0.4 mg/kg QW | Tal SC 0.8 mg/kg Q2W | Tal SC 0.4 mg/kg QW | Tal SC 0.8 mg/kg Q2W | Tal SC 0.72 or 1.5 mg/kg QW, 3.0 mg/kg from C3 | Tec 3.0 mg/kg Tal 0.8 mg/kg SC Q2W |
| | | | | | | 35 | 34 |
| | | | | | | 2 | 4 |
| | | | | | | NA | 76.5 |
| | | | | | | NA | NA |
| | | | | | | 00/100/28.5 | NA/NA/NA |
| | | | | | | 93.5 | 96 |
| | | | | | | 55 | 41 |
| DoR | NA | NA | 20 mo | 100% at 9 mo | 84% at 9 mo | NA | NA |
| PFS | NA | 77% at 12 mo | 19 mo | 94% at 9 mo | 75.5% at 9 mo | NA | 77% at 9 mo |
| OS | NA | 92% at 12 mo | 91.5% at 12 mo | NA | NA | NA | NA |




Da Tacchetti P et al, Cancers 2024

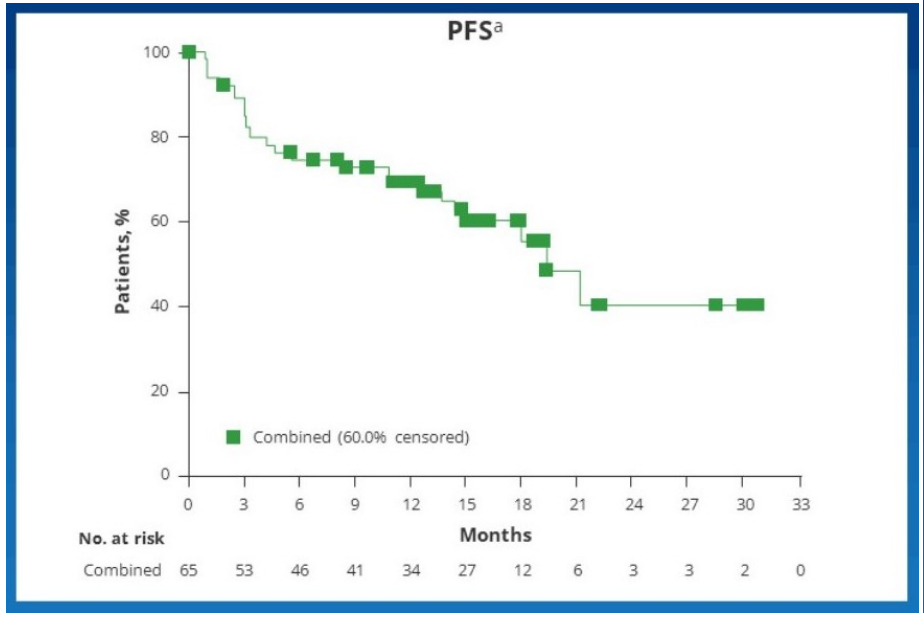
# Tal + Dara: TRIMM-2 (Phase 1). Efficacia




ORR elevato anche in pz
- esposti a anti-CD38 (63.6%, 82.2%)
- refrattari a anti-CD38 (63.6%, 80.0%)

- esposti a TCR (CAR-T, BsAbs, inclusa BCMA-TT) (66.7%, 78.9%)

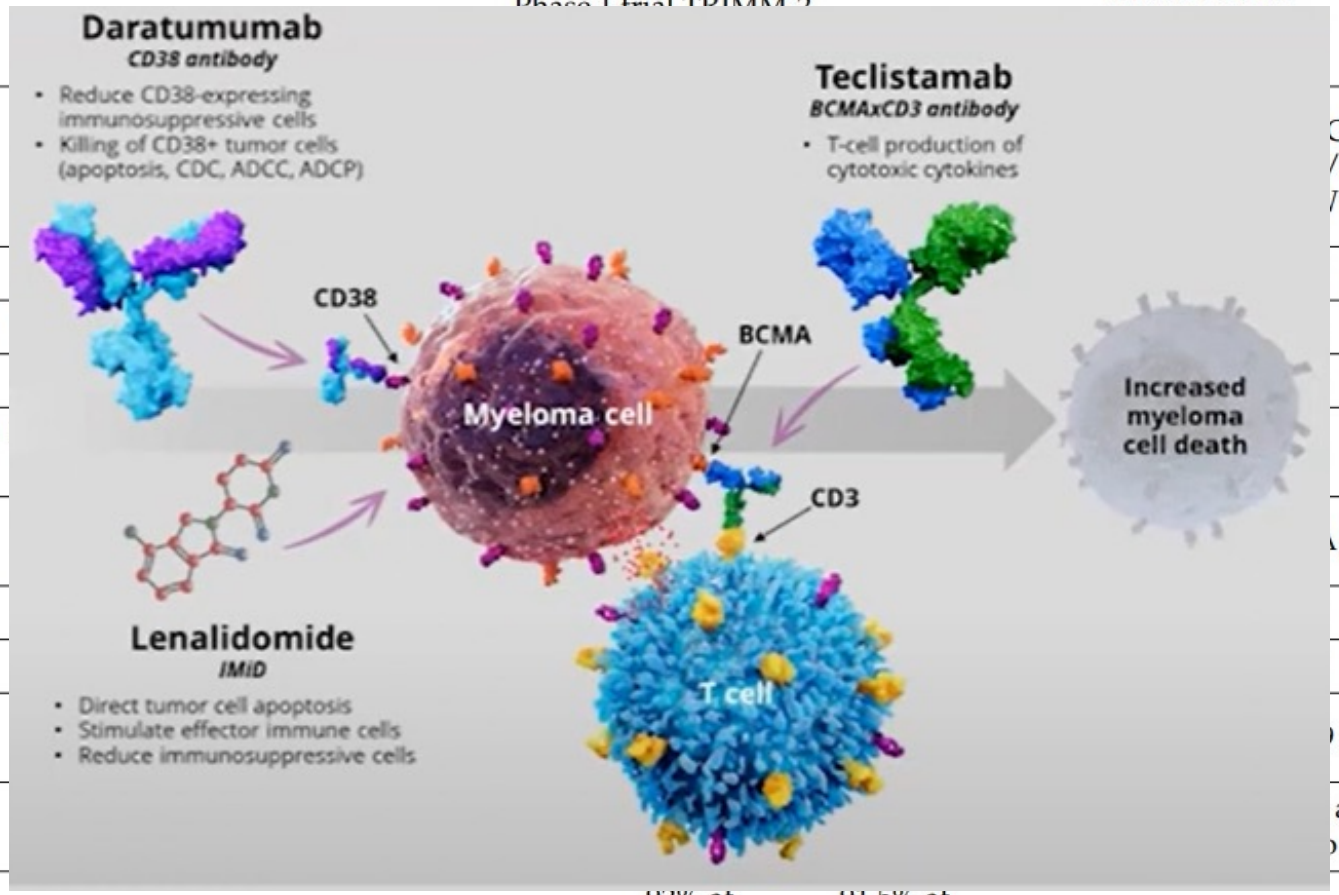



| Parameter | Tal 0.4 mg/kg QW + dara (n=14) | Tal 0.8 mg/kg Q2W + dara (n=51) |
|---|---|---|
| Median PFS, mo (range) | NR (2.73–NE) | 19.4 (12.5–NE) |
| 12-mo PFS, % (95% CI) | 77.4 (44.9–92.1) | 67.4 (52.3–78.6) |
| Median OS, mo (range) | NR (NE–NE) | NR (NE–NE) |
| 12-mo OS, % (95% CI) | 92.3 (56.6–98.9) | 91.5 (78.8–96.7) |

Bhagirathbhai R et al, ASCO 2023. P 8003

# Combinazioni di BiAbs: Tec-Dara-Len

| BsAb Combination | Tec-Dara | Tal-Dara | Tal-Poma | Tec-Dara-Len | Tal-Tec |
|---|---|---|---|---|---|
| | | Phase 1 trial TRIMM-2 | Phase 1b trial | Phase 1b trial MajesTEC-2 (NCT04722146) | Phase 1b trial RedirecTT-1 (NCT04586426) |
| | | | | Tal SC 0.72 or 1.5 mg/kg QW, 3.0 mg/kg from C3 | Tec 3.0 mg/kg Tal 0.8 mg/kg SC Q2W |
| | | | | 35 | 34 |
| | | | | 2 | 4 |
| | | | | NA | 76.5 |
| | | | | NA | NA |
| | | | | 100/100/28.5 | NA/NA/NA |
| | | | | 93.5 | 96 |
| | | | | 55 | 41 |
| | | | | NA | NA |
| | | | | NA | 77% at 9 mo |
| OS | NA | 92% at 12 mo | 91.5% at 12 mo | NA | NA | NA | NA |




Da Tacchetti P et al, Cancers 2024

# Tec-Dara-Len: MajesTEC-2 (Phase 1b). Efficacia

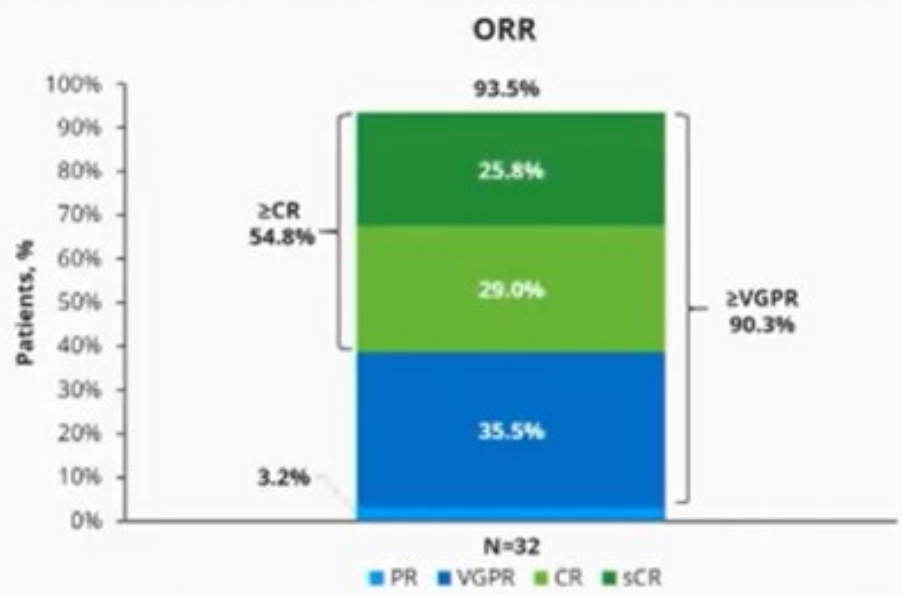
**Key eligibility criteria**
- Measurable MM
- 1–3 prior lines of therapy, including an IMiD and a PI

**Primary endpoints**
- Safety[a]
- Dose-limiting toxicities

**Key secondary endpoints**
- ORR[b]
- Rate of ≥VGPR and ≥CR[b]
- Duration of response
- Time to response

**Tec-Dara-Len Dosing Schedule:**

| Tec | Dara | Len |
|---|---|---|
| Following step-up dosing<br>0.72 mg/kg or 1.5 mg/kg SC QW, with transition to 3 mg/kg SC Q2W starting at cycle 3 | 1800 mg SC (per approved schedule)<br>Cycles 1–2: QW<br>Cycles 3–6: Q2W<br>Cycles 7+: Q4W | 25 mg PO daily for 21 days of a 28-day cycle, starting at cycle 2<br>Cycles 2–4: dexamethasone 40 mg PO given QW |




| Variable | Median (range) |
|---|---|
| Follow-up, months | 8.4 (1.1–12.9) |
| Time to first response, months | 1.0 (0.7–3.3) |
| Time to ≥CR, months | 3.0 (1.0–10.4) |

**mediana pLOT 2 (1-3 pLOT)**
HCR 25.0/46.7%

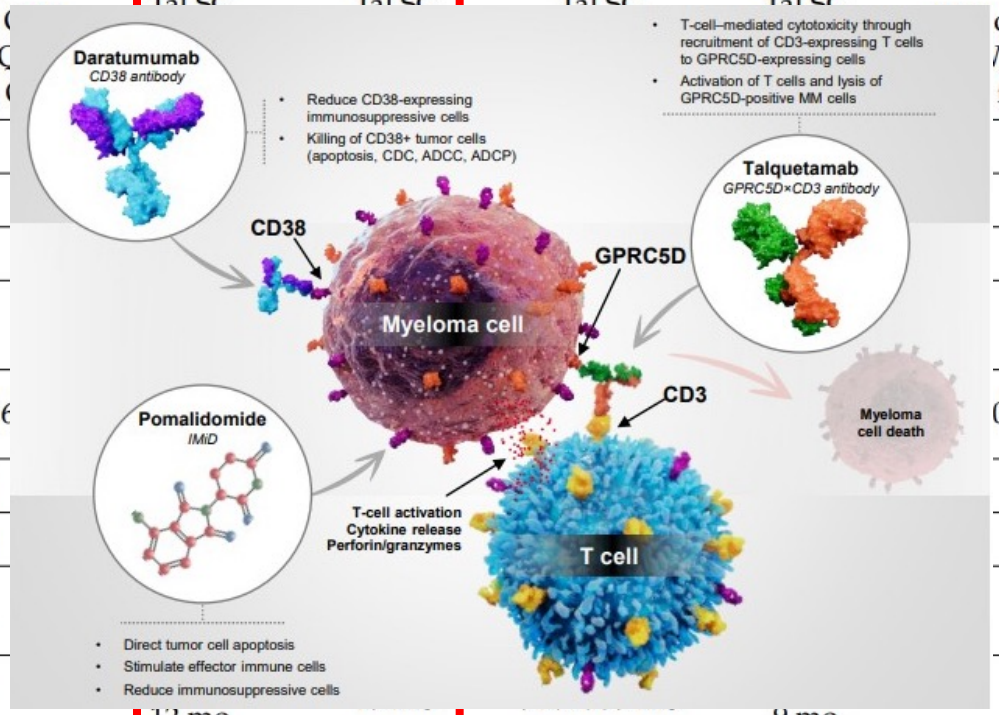
Efficacia in pz refrattari a anti-CD38 (23.1/15.8%) e/o a Len (46.2/15.8%)

Al data cut off (follow-up mediano 8.4 m) 80.6% dei pz rimanevano liberi da progressione e in trattamento

Searle E et al, EHA 2023. P 30

# Combinazioni di BiAbs: Tal-Dara-Pom

| BsAb Combination | Tec-Dara | Tal-Dara | | Tal-Poma | | Tec-Dara-Len | Tal-Tec |
|---|---|---|---|---|---|---|---|
| Clinical trial | Phase 1 trial TRIMM-2 (NCT04108195) | | | Phase 1b trial MonumenTAL-2 (NCT05050097) | | Phase 1b trial MajesTEC-2 (NCT04722146) | Phase 1b trial RedirecTT-1 (NCT04586426) |
| Dosing schedule | Tec SC 1.5 mg/kg Q 3.0 mg/kg Q 3.0 mg/kg | Tal SC | Tal SC | Tal SC | Tal SC | Tal SC or 1.5 mg/kg /, 3.0 mg/kg from C3 | Tec 3.0 mg/kg Tal 0.8 mg/kg SC Q2W |
| Pts n° | 65 | | | | | 35 | 34 |
| Prior LOT, median n | 5 | | | | | 2 | 4 |
| TCR, % | 75 | | | | | NA | 76.5 |
| Prior BCMA-targeted tp, % | 12 | | | | | NA | NA |
| Prior PI/IMiD/ anti-CD38 mAb, % | NA/97/6 | | | | | 0/100/28.5 | NA/NA/NA |
| ORR, % | 76.5 | | | | | 93.5 | 96 |
| ≥CR, % | 21.5 | | | | | 55 | 41 |
| DoR | NA | | | | | NA | NA |
| PFS | NA | 12 mo | | | 9 mo | NA | 77% at 9 mo |
| OS | NA | 92% at 12 mo | 91.5% at 12 mo | NA | NA | NA | NA |




Da Tacchetti P et al, Cancers 2024

# Tal + Dara + Pom: TRIMM-2 (Phase 1). Caratteristiche dei pazienti

**Key eligibility criteria**

- MM per IMWG
- ≥3 prior LOT[a] or double refractory to PI and IMiD
- Permitted:
  - Anti-CD38 mAb >90 days and IMiD >7 days prior
  - Refractory to anti-CD38 mAb
  - Prior bispecific antibody or CAR-T exposure

→ **Tal[b]** 0.4 mg/kg SC QW or 0.8 mg/kg SC Q2W + **Dara[c]** 1800 mg SC QW cycles 1–2, Q2W cycles 3–6, Q4W cycles ≥7 + **Pom** 2 mg PO starting cycle 2

*Tal: May change schedule from QW to Q2W after cycle 4 if in PR and from Q2W to Q4W after cycle 8 if in VGPR*

*Pom: May be reduced in response to hematologic AEs*

**Key objectives**

- Safety and antitumor activity

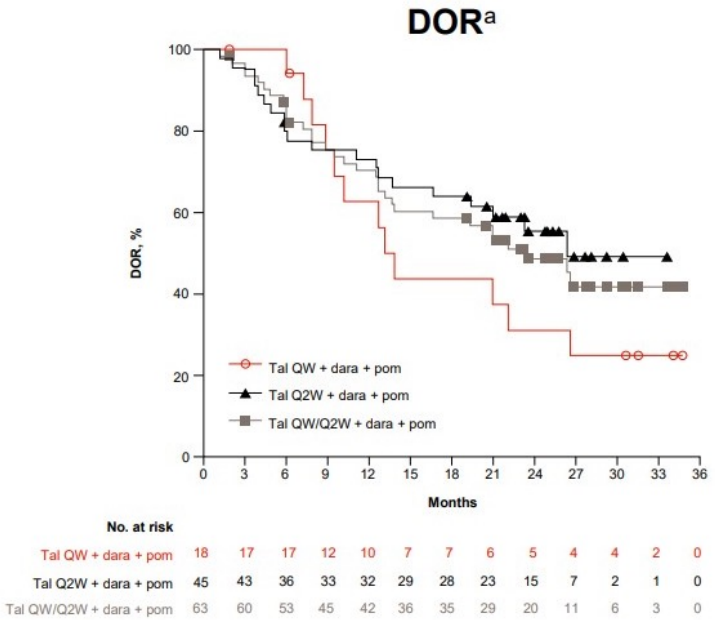
| Characteristic | Tal 0.4 mg/kg QW + dara + pom (n=18) | Tal 0.8 mg/kg Q2W + dara + pom (n=59) |
|---|---|---|
| Age (years), median (range) | 62 (42–75) | 64 (33–81) |
| Male, n (%) | 12 (66.7) | 31 (52.5) |
| Race, n (%) | | |
| White | 12 (66.7) | 51 (86.4) |
| Black/African American | 4 (22.2) | 4 (6.8) |
| Asian | 1 (5.6) | 1 (1.7) |
| American Indian/Alaska Native | 0 (0) | 1 (1.7) |
| Not reported | 1 (5.6) | 2 (3.4) |
| Soft tissue plasmacytoma(s),[a] n (%) | 4 (22.2) | 14 (23.7) |
| High cytogenetic risk,[b] n (%) | 4 (22.2) | 13 (27.7) |
| ISS stage,[c] n (%) | | |
| I | 8 (50.0) | 29 (52.7) |
| II | 3 (18.8) | 15 (27.3) |
| III | 5 (31.3) | 11 (20.0) |
| Time since diagnosis (years), median (range) | 5.7 (0.3–18.3) | 7.2 (0.7–17.5) |

| Characteristic | Tal 0.4 mg/kg QW + dara + pom (n=18) | Tal 0.8 mg/kg Q2W + dara + pom (n=59) |
|---|---|---|
| Prior LOT (n), median (range) | 6 (3–11) | 6 (1–17) |
| Prior stem cell transplantation, n (%) | 16 (88.9) | 50 (84.7) |
| Prior therapies, n (%) | | |
| Anti-CD38 | 17 (94.4) | 55 (93.2) |
| IMiD | 18 (100.0) | 59 (100.0) |
| Triple class[d] | 17 (94.4) | 55 (93.2) |
| Penta drug[e] | 12 (66.7) | 41 (69.5) |
| BCMA-targeted therapy | 13 (72.2) | 40 (67.8) |
| CAR-T | 5 (27.8) | 19 (32.2) |
| Bispecific antibody[f] | 6 (33.3) | 17 (28.8) |
| ADC | 3 (16.7) | 12 (20.3) |
| Refractory status, n (%) | | |
| Anti-CD38[g] | 15 (83.3) | 49 (83.1) |
| Pom | 13 (72.2) | 45 (76.3) |
| Triple class[d] | 15 (83.3) | 45 (76.3) |
| Penta drug[e] | 4 (22.2) | 20 (33.9) |
| Any prior bispecific antibody | 7 (38.9) | 22 (37.3) |
| To last line of therapy | 17 (94.4) | 53 (89.8) |

Bahlis N et al, IMS 2024

# Tal + Dara + Pom. Efficacia

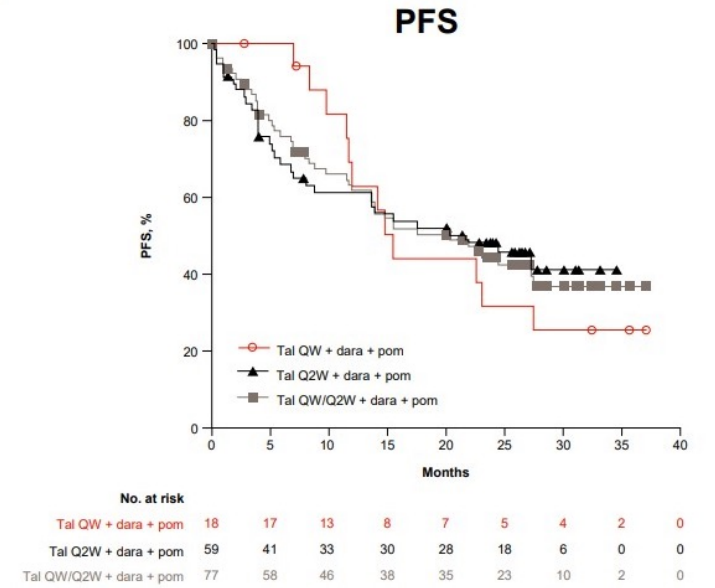
## Talquetamab + Daratumumab + Pomalidomide in Patients With Relapsed/Refractory Multiple Myeloma: Results From the Phase 1b TRIMM-2 Study




| Parameter | Tal 0.4 mg/kg QW + dara + pom (n=18) | Tal 0.8 mg/kg Q2W + dara + pom (n=45) |
|---|---|---|
| Median (range) follow-up, months | 15.8 (3.2–37.9) | 17.5 (0.2–37.7) |
| Median DOR, months (95% CI) | 13.8 (8.8–26.6) | 26.4 (16.7–NE) |
| 12-month DOR, % (95% CI) | 62.7 (35.1–81.3) | 73.1 (57.5–83.7) |

**12-month DOR (QW + Q2W tal)**

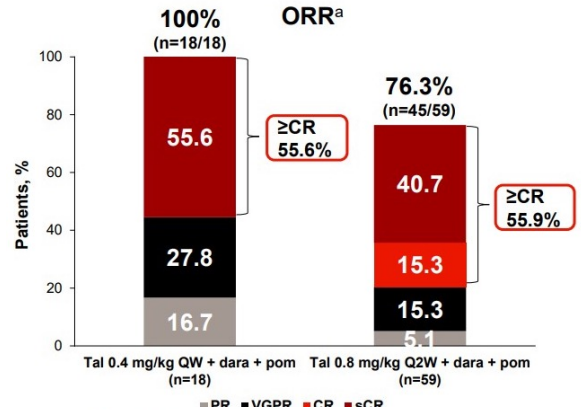
- Anti-CD38 naïve/sensitive (n=13): 83.9%
- Pom naïve/sensitive (n=16): 80.8%
- Anti-CD38 refractory (n=50): 67.0%
- Pom refractory (n=47): 67.0%
- Bispecific antibody refractory (n=24): 70.2%
- Prior CAR-T (n=20): 84.4%

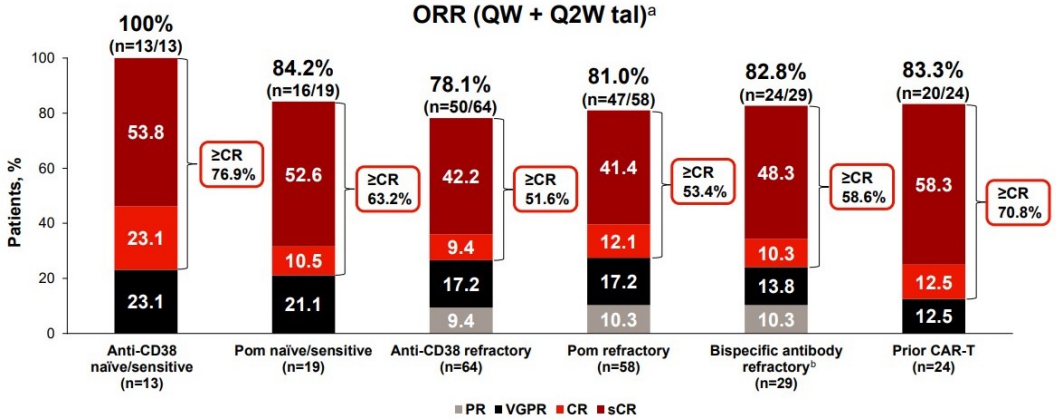



| Parameter | Tal 0.4 mg/kg QW + dara + pom (n=18) | Tal 0.8 mg/kg Q2W + dara + pom (n=59) |
|---|---|---|
| Median (range) follow-up, months | 15.8 (3.2–37.9) | 17.5 (0.2–37.7) |
| Median PFS, months (95% CI) | 15.4 (11.5–27.5) | 20.3 (7.9–NE) |
| 12-month PFS, % (95% CI) | 62.7 (35.1–81.3) | 61.1 (47.1–72.4) |

**12-month PFS (QW + Q2W tal)**

- Anti-CD38 naïve/sensitive (n=13): 84.6%
- Pom naïve/sensitive (n=19): 68.4%
- Anti-CD38 refractory (n=64): 56.9%
- Pom refractory (n=58): 59.4%
- Bispecific antibody refractory (n=29): 69.2%
- Prior CAR-T (n=24): 73.9%



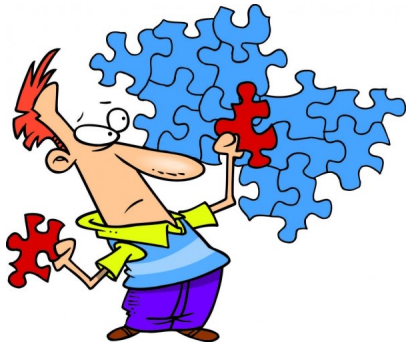

T mediano alla 1° risposta: 1 m

ORR 81.8%, ≥CR 55.8% (dati combinati)

ORR, DOR e PFS favorevoli anche in pz refrattari a Dara, Pom, BsAbs e precedente CAR-T

Bahlis N et al, IMS 2024

# BsAbs in combinazione. In sintesi:



Le combinazioni di BsAbs (Tec, Tal) con altri agenti ad azione immunomodulante (IMIDs e/o anti-CD38) e la combinazione  Tec + Tal si associano a aumento ORR e rate di risposte profonde vs BsAbs in monoterapia
Le risposte sono rapide e durature

Le combinazioni di BsAbs (Tec, Tal) con altri farmaci ad azione immunomodulante (IMIDs e/o anti-CD38) superano la refrattarietà agli agenti somministrati singolarmente

Le combinazioni di Tal sono efficaci anche in pz esposti a terapie T cell redirecting (CAR-T, BsAbs, inclusa BCMA-TT)

Le combinazioni di BsAbs (i.e. Tec + Tal) si associano a outcome favorevoli in alcune categorie di rischio (EMD)

Le combinazioni di BsAbs (Tec, Tal) con altri agenti ad azione immunomodulante (IMIDs e/o anti-CD38) e la combinazione Tec + Tal non si associano a tossicità extraematologica additiva, in particolare ad aumento dell'incidenza di infezioni G3/4, rispetto ai BsAbs in monoterapia
Le combinazioni di BsAbs (Tec, Tal) e di Tec + Tal si associano a elevato rate di CRS, gli eventi sono tuttavia limitati a G <3.

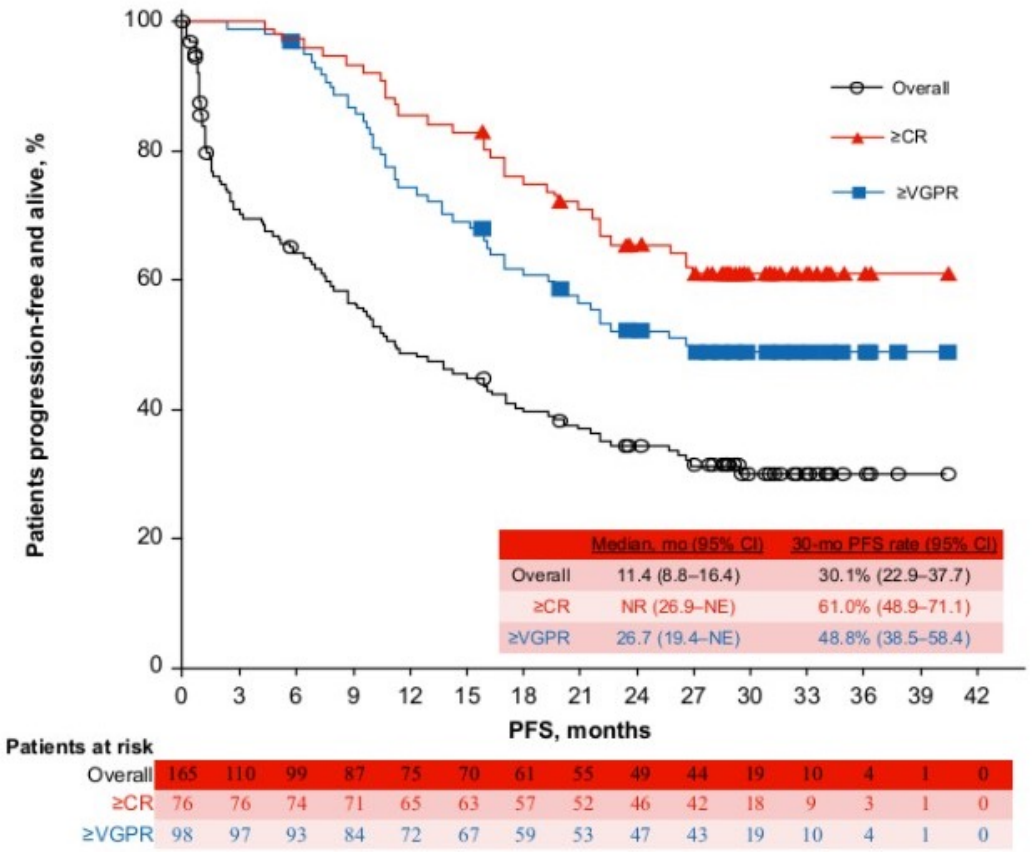
Follow-up più prolungati sono necessari a definire gli outcome a lungo termine

# Strategie per ottimizzare l'efficacia dei BsAbs

## Timing di utilizzo precoce

-

**Figure 4: PFS**




Garfall AL et al, ASCO 2024. P7540

**Long-Term Follow-Up From MajesTEC-1 of Teclistamab, a BCMA×CD3 Bispecific Antibody, in Patients With Relapsed/Refractory Multiple Myeloma**

mPFS nei pz con **≤3 precedenti LOT:** 18.1 m
mPFS nei pz con **>3 precedenti LOT:** 9.7 m

van de Donk WCJ et al, ASCO 2023. Poster 8011

# Strategie per ottimizzare l'efficacia dei BsAbs

## Timing di utilizzo precoce

**MajesTEC-3**[1]
NCT05083169
1–3 prior lines (estimated N=560)
1:1
- Tec + Dara
- Dara-Pd / Dara-Vd

**MagnetisMM-5**[2]
NCT05020236
Relapsed MM after R and a PI (estimated N=854)
1:1:1
- Elra
- Elra + Dara
- Dara-Pd

**MajesTEC-9**[3]
NCT05572515
1–3 prior lines (estimated N=590)
1:1
- Tec monotherapy
- PVd / Kd

**MonumenTAL-6 study design**

**Key eligibility criteria**
- 1–4 prior LOT, including anti-CD38 mAb and Len
- ECOG PS ≤2
- Naive to Tec, Pom, GPRC5D-directed therapy
- Naive to Elo (EPd arm)

1:1:1 randomization
- Tal + Tec
- Tal + Pom
- Investigator's choice: EPd or PVd

**Primary endpoint**
- PFS

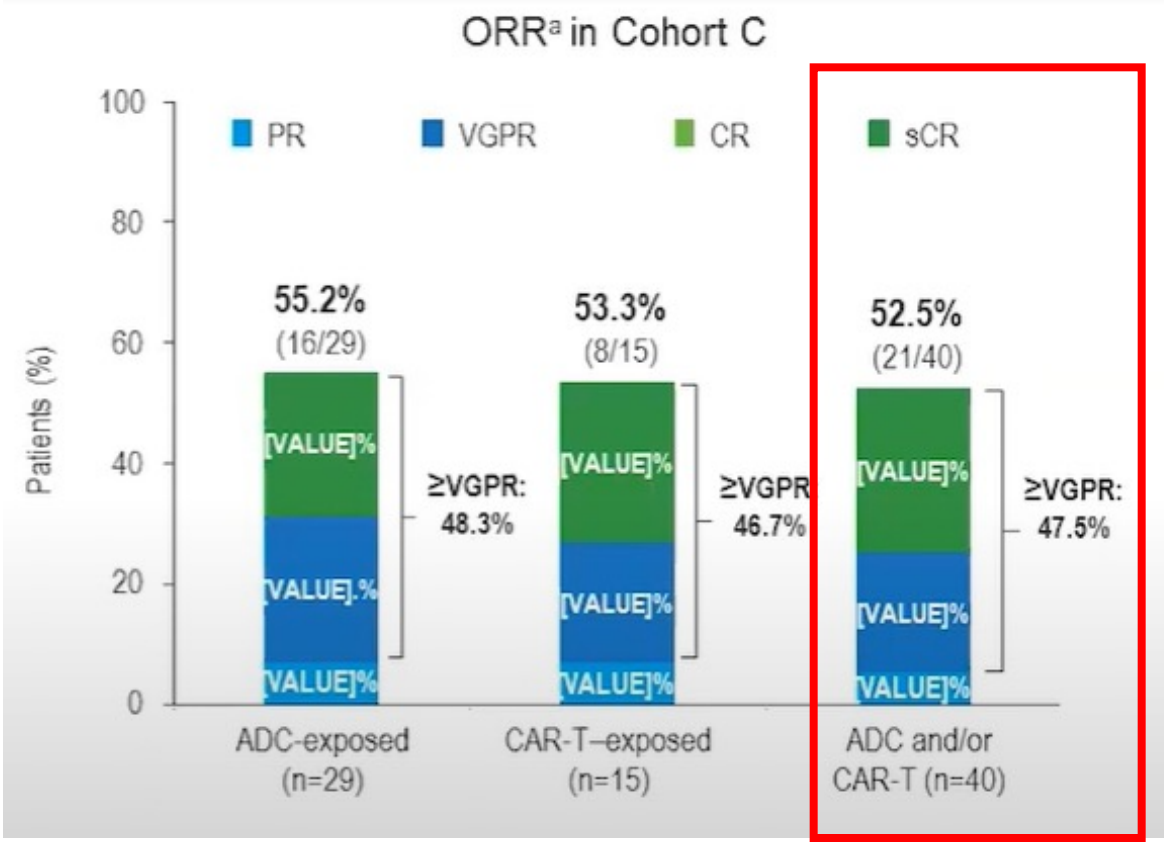
**Key secondary endpoints**
- ORR
- MRD-negativity rate
- OS
- PROs

**MonumenTAL-3**[1,2]
GPRC5D; NCT05455320
RRMM ≥1 prior lines, including a PI and Len (estimated N=810)
1:1:1
- Tal + Dara-P
- Dara-Pd
- Tal + Dara

**CAMMA-1**[3,4]
FcRH5; NCT04910568
RRMM Arms B and C: ≥2 prior lines, including a PI and IMiD* (estimated N=184)
1:1:1
- Cevo monotherapy
- Cevo + Pd
- Cevo + Dara-d

**Forimtamig**[5,6]
GPRC5D; NCT04557150
RRMM Prior PI and IMiD (estimated N=480)
- Forimtamig (dose escalation + dose expansion cohorts)

# Sequencing: Teclistamab dopo precedente BCMA-TT (CAR-T, ADC): MajesTEC-1, Cohort C




ORR 52.5% in pz con precedente esposizione BCMA-TT (CAR-T e/o ADC) vs 63% nella popolazione generale

3 di 4 pz trattati con ADC e CAR-T hanno ottenuto una risposta

mDOR NR
Con follow-up mediano di 11.8 m, il 71.4% dei pz responsivi ha mantenutola risposta

Profilo di safety sovrapponibile ai pz BCMA-TT-naive

Touzeau C et al, EHA 2022

# Sequencing: Talquetamab dopo precedente BCMA-TT (CAR-T, BsAbs, ADC): MonumenTAL-1

**Updated Results of Talquetamab, a GPRC5D×CD3 Bispecific Antibody, in Patients with Relapsed/Refractory Multiple Myeloma with Prior Exposure to T-Cell Redirecting Therapies: Results of the Phase 1/2 MonumenTAL-1 Study**

| | Overall (N=70) | Prior BCMA CAR-T (n=48[a]) | Prior BCMA BsAb (n=23[a]) | Prior BCMA ADC and prior TCR (n=8) |
|---|---|---|---|---|
| ORR, n (%) | 46 (65.7) | 35 (72.9) | 12 (52.2) | 6 (75.0) |

[a]One patient received both BCMA CAR-T and BCMA BsAb.

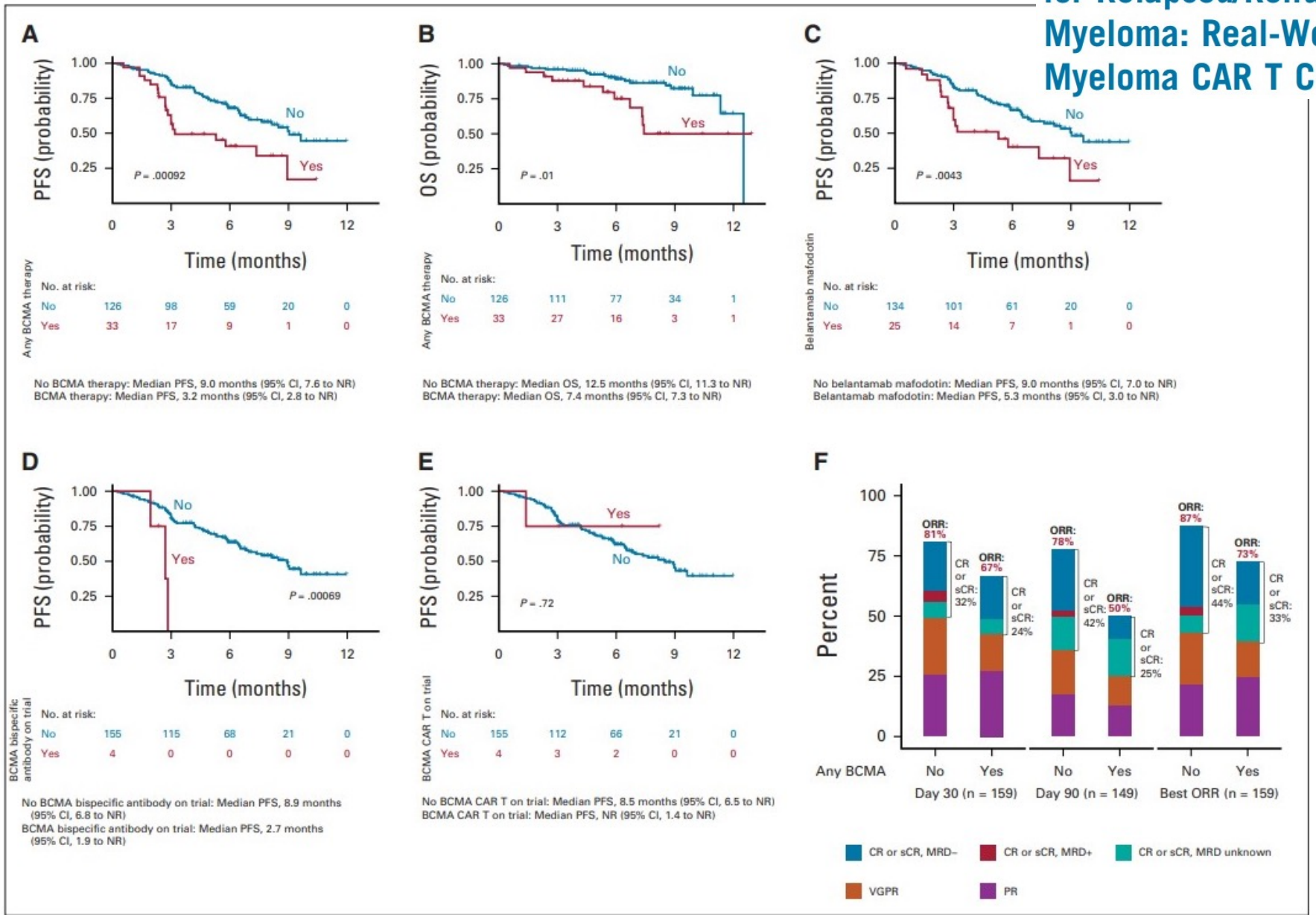
ORR 65.7% nei pz con precedente BCMA-TT (CAR-T, BsAbs, ADC), simile a popolazione complessiva e nei pz con precedente CAR-T e ADC

**ORR inferiore (52.2%) nei pz con precedente BsAbs anti-BCMA** in particolare quando somministrati in linea immediatamente precedente (28.6%) vs qualsiasi linea (61.1%)

Jakubowiak AJ, ASH 2023

# Sequencing. CAR-T dopo precedente BCMA-TT. Studi di Real World

## Idecabtagene Vicleucel for Relapsed/Refractory Multiple Myeloma: Real-World Experience From the Myeloma CAR T Consortium




In analisi multivariata, i pz con precedente BCMA-TT, HCR, ECOG PS ≥2 al momento della linfodeplezione, e età inferiore si associano a PFS inferiore

I pz con precedente qualsiasi BCMA-TT, precedente Belamaf, BCMA-BsAbs, ma non quelli con precedente BCMA-CAR-T, hanno PFS significativamente inferiore vs i pz non esposti

Hansen DK et al, JCO 2023

# Sequencing. CAR-T dopo precedente BCMA-TT: Studi di Real World

## Efficacy Outcomes: Timing of Prior BCMA-TT

| Timing Characteristic | Responders (n=36) | Non-responders (n=13) | |
|---|---|---|---|
| Duration of prior BCMA-TT in days, median (range) | 23 (1-208) | 63 (1-370) | p = 0.025* |
| Time from last BCMA-TT to apheresis in days, median (range) | 169.5 (30-1066) | 84 (1-286) | p = 0.017* |
| Time from last BCMA-TT to ide-cel infusion in days, median (range) | 209 (16-1118) | 128 (32-362) | p = 0.052* |

*P values by Wilcoxon rank sum test

| Timing Characteristic | Prior BCMA-TT > 6 months (n=29) | Prior BCMA-TT < 6 months (n=20) | |
|---|---|---|---|
| Overall Response Rate, n (%) | 24 (83%) | 12 (60%) | p = 0.076 by Chi-square |
| ≥ CR | 10 (35%) | 4 (20%) | |

Ferreri JC et al, Blood Canc J 2023

ide-cel

Nei pz responsivi a CAR-T vs non responsivi:
- minore durata della precedente BCMA-TT
- tempo più prolungato dalla precedente BCMA-TT alla aferesi e alla infusione di Ide-cel

- ORR e ≥CR rate superiori in pz trattati con ide-cel con BCMA-TT >6 m vs <6 m

**Il timing della somministrazione di CAR-T rispetto alla più recente esposizione a BCMA-TT e la durata delle precedente BCMA-TT potrebbero rappresentare fattori predittivi di risposta**

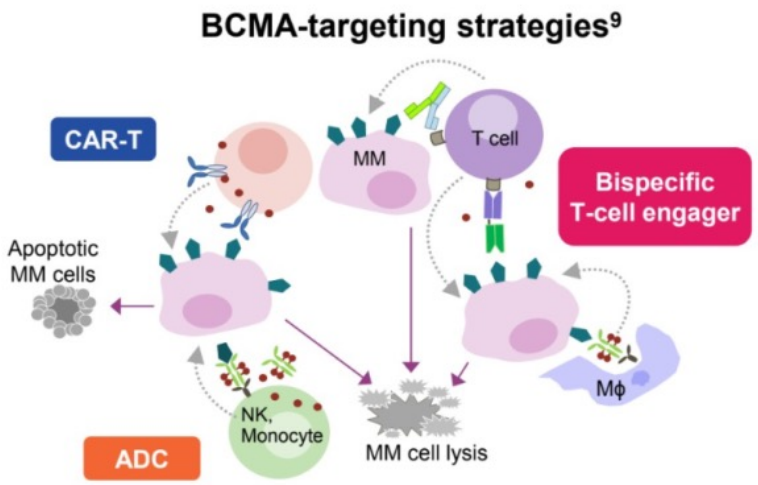
**Table 2. Timing of B-cell maturation antigen (BCMA)-targeting treatment**

| Treatments | Total cilta-cel N = 18* | |
|---|---|---|
| | Responders n = 12 | Nonresponders n = 6 |
| Duration of last anti-BCMA treatment, days | | |
| Median | 29.5 | 63.5 |
| Range | 1-277 | 22-527 |
| Time from last anti-BCMA treatment to apheresis, days | | |
| Median | 161.0 | 56.5 |
| Range | 26-695 | 40-895 |
| Time from last anti-BCMA treatment and cilta-cel infusion, days | | |
| Median | 235.0 | 117.5 |
| Range | 62-749 | 95-944 |

Cohen AD et al, Blood 2023

cilta-cel

# E’ possibile un ritrattamento/trattamento sequenziale con agenti anti-BCMA? In sintesi:




Il ritrattamento/trattamento sequenziale con agenti anti-BCMA è proponibile.
I dati emersi dagli studi clinici di fase 1/2 e di Real World suggeriscono:

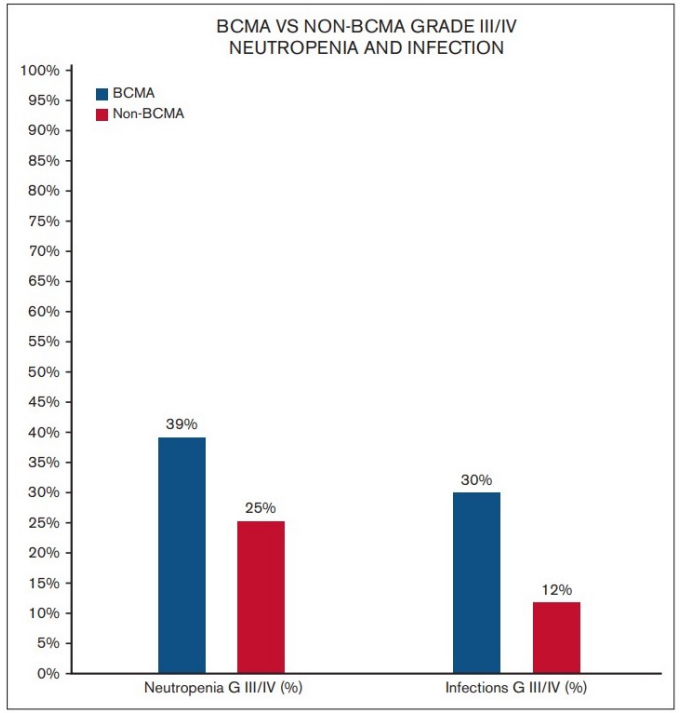
- Impatto negativo di precedente BsAbs su CAR-T (maggior probabilità di antigen escape e di T cell exhaustion correlate alla stimolazione antigenica continua)
- Modesto impatto di precedente CAR-T su BsAbs
- La perdita dell’Ag BCMA (antigen loss) potrebbe non rappresentare un meccanismo di resistenza comune, dal momento che BCMA è essenziale per la sopravvivenza delle PC

Nello studio KarMMa (ide-cel) solo il 4% dei pz responsivi ha presentato una perdita dell’Ag BCMA alla progressione

L’individuazione e il monitoraggio dei meccanismi di resistenza primaria o acquisita a potrebbero contribuire a guidare le decisioni rispetto alla possibilità e alle modalità di un ritrattamento/trattamento sequenziale con BCMA-TT (meccanismi di resistenza correlati al microambiente, alla cellula T, alla cellula tumorale)

Necessità di dati prospettici al fine di definire il timing e le modalità di sequencing

# Rischio infettivo nei pazienti trattati con BsAbs




Risk of infections associated with the use of bispecific antibodies in multiple myeloma: a pooled analysis

1185 pz trattati con BsAbs (71.6 % anti-BCMA) in monoterapia, senza precedente esposizione ad altri BsAbs

| | |
|---|---|
| Neutropenia: di ogni grado | 38.6%, G3/4 34.8% |
| Infezioni di ogni grado | 50%, G3/4 24.5% |
| 25% dei decessi correlati a infezione | |
| Ipogammaglobulinemia (riportata in 4 studi): | 75.3% |

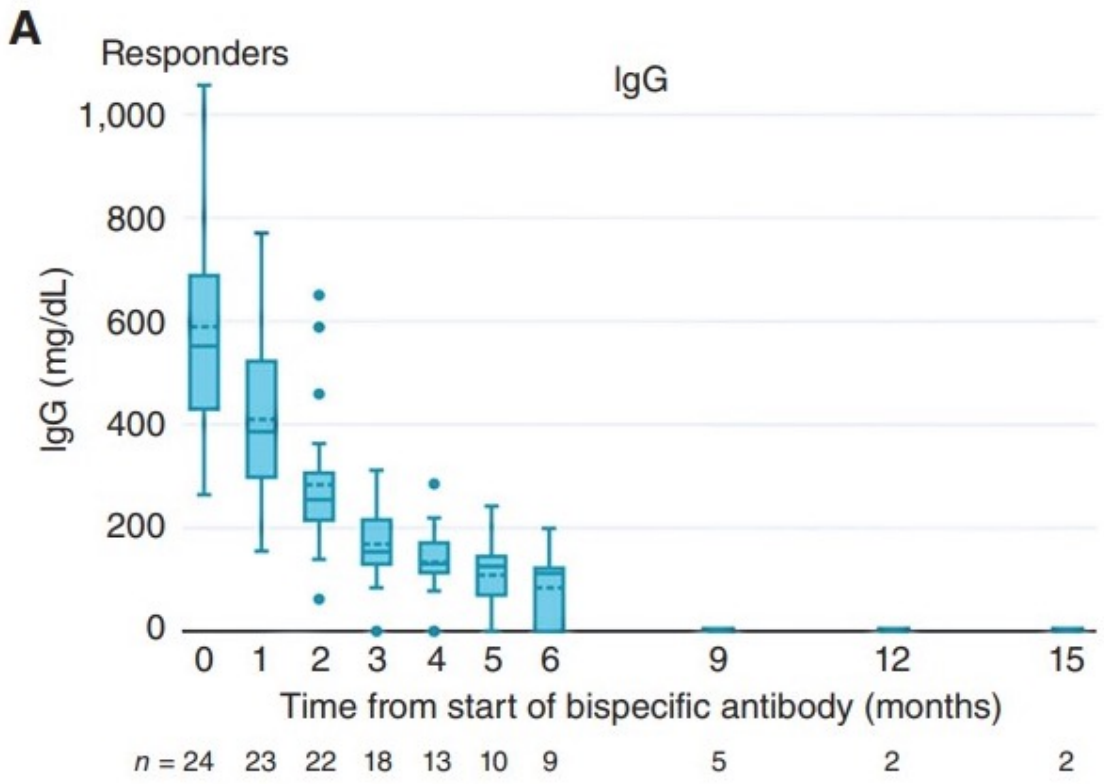
**BsAbs non-anti-BCMA vs anti-BCMA**:

| | |
|---|---|
| Neutropenia G3/4 | 25.3% vs 39.2% |
| Infezioni G3/4 | 11.9% vs 30% |

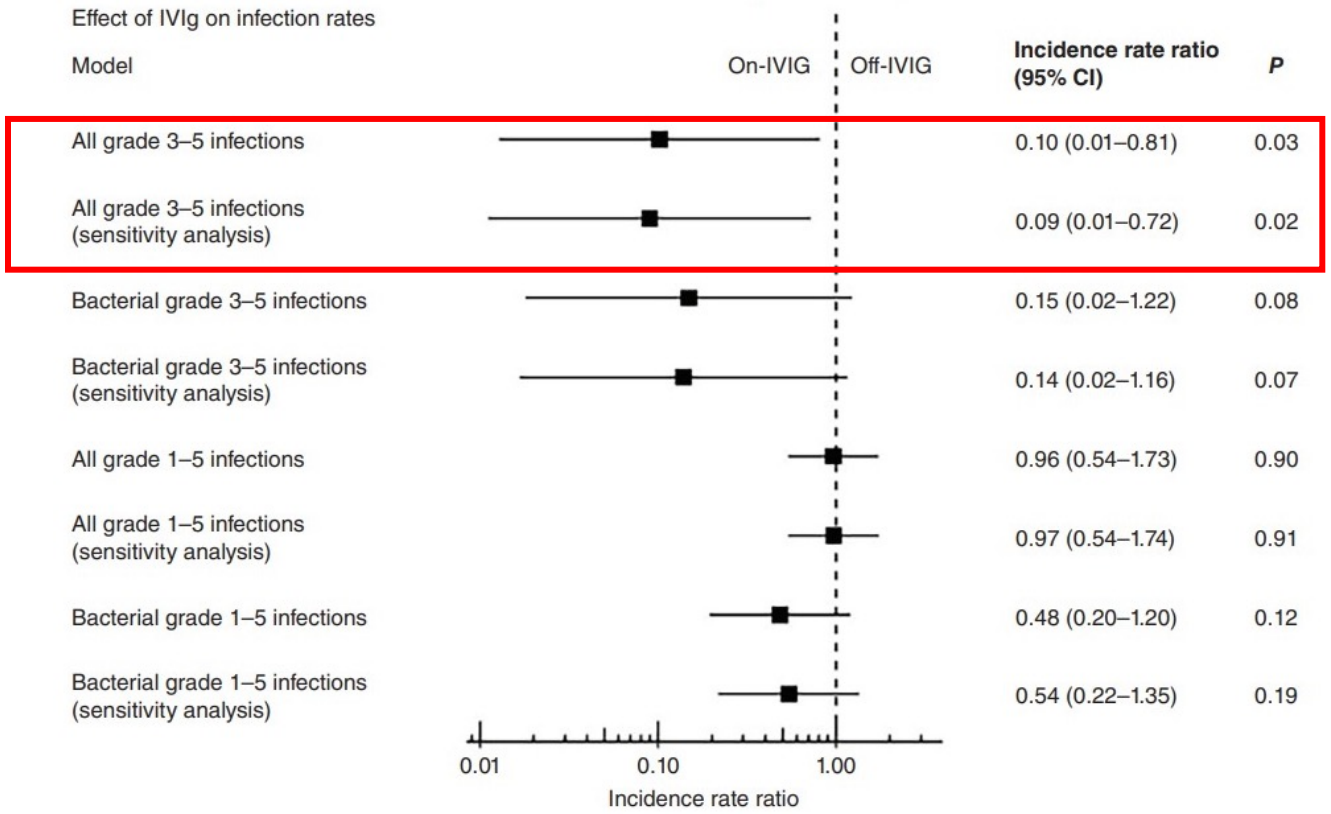
**Strategie per ridurre il rischio infettivo:**
- Utilizzo precoce (pz meno pretrattati)
- Riduzione della frequenza di somministrazione, terapia a tempo definito (?)
- Profilassi con immunoglobuline
- Profilassi antinfettiva e monitoraggio

Mazahreh F et al, Blood Adv 2023

# Strategie per migliorare il profilo di safety nei pazienti trattati con BsAbs. Profilassi con immunoglobuline




Ipogammaglobulinemia severa si sviluppa nel 100% dei pz responsivi e si mantiene per l'intera durata del trattamento




In corso di somministrazione di **IVIg, l'incidenza di infezioni G≥3 era ridotta del 90%** rispetto all'osservazione (incidence rate ratio 0.10; 95% CI, 0.01–0.80; P = 0.03)

Lancman G et al, Blood Canc Disc 2023

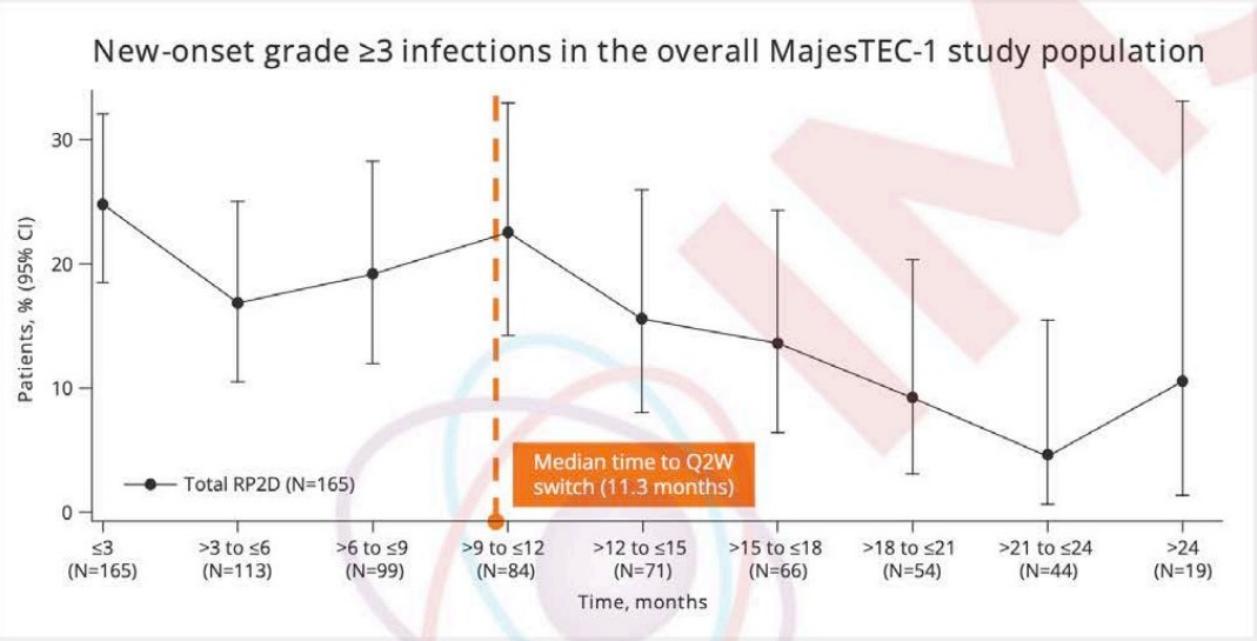
# Strategie per migliorare il profilo di safety nei pazienti trattati con BsAbs. Profilassi antinfettiva

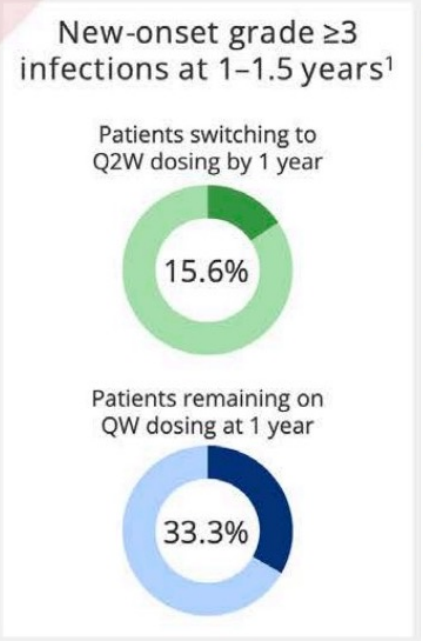
**TABLE 3** Summary of recommendations to prevent infectious complications in MM patients treated with CAR-T cell therapy or bispecific antibodies.

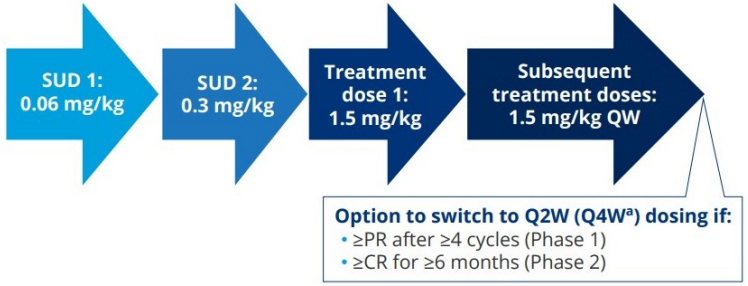
| Pathogen | Intervention | Indication/duration |
|---|---|---|
| Bacterial | Levofloxacin 500 mg PO daily. Consider alternate agents such as cefdinir 300 mg PO twice a day, or augmentin 875 mg PO twice a day in the event of allergy or intolerance to fluoroquinolone | CAR-T cell therapy—Start when ANC < 500 or per MD discretion and continue until neutrophil recovery<br>BsAb—Start with onset of therapy and administer during the first month |
| Bacterial | Immunoglobulin replacement: suggested 400 mg/kg once every 4 weeks | CAR T-cell: Day +30 through 1 year. After 1 year continue until serum IgG >400 mg/dL[a]<br>BsAb: Start at second month of therapy and continue until end of therapy or serum IgG >400 mg/dL[a] (whichever is longer) |
| Bacterial | Pneumococcus conjugated vaccine (PCV) | Revaccination can begin 3–6 months after CAR T-cell therapy. CDC reccomends administration of 1 dose of PCV20 or 1 dose of PCV15 followed by 1 dose of PPSV23 atleast 1 year later. Update vaccination status prior to starting BsAb |
| Herpes Simplex Virus/ Varicella Zoster Virus | Acyclovir 400–800 mg PO twice a day or valacyclovir 500 mg PO once or twice a day | Universal and indefinite prophylaxis, irrespective of vaccination status |
| Cytomegalovirus (CMV) | Pharmacological prophylaxis not recommended | Routine monitoring not recommended. Monitoring of viral load by PCR and CMV-directed therapy recommended in patients with suspected CMV-related disease (colitis, pneumonitis, hepatitis) or otherwise unexplained fever and/or cytopenias or in high-risk patients[b] |
| COVID19 | Immunization | Follow health authorities recommendations for immunosuppressed patients. Revaccination 3–6 months after CAR-T therapy |
| Influenza | Immunization | Seasonal |
| Hepatitis B virus | Entecavir or tenofovir | CAR T-cell or BsAb: patients HBs Ag-positive or HBs Ag-negative, HBc Ab- IgG positive |
| Yeast and mould | Fluconazole 400 mg PO daily | Start when ANC <500 and continue until neutrophil recovery, consider ongoing prophylaxis with anti-mould azole in high-risk patients[b] |
| *Pneumocystis jirovecii* | Trimethoprim 80 mg/sulfamethoxazole 400 mg daily or 160/800 mg 3 times a week (preferred) or dapsone 100 mg PO daily, or atovaquone suspension 750 mg/5 mL—1500 mg = 10 mL PO daily, or pentamidine 300 mg by inhalation via nebulizer every 4 weeks | CAR T-cell: Start on Day +30 through 6 months, or until CD4 ≥ 200/mm$^3$ (whichever is longer)<br>BsAb: Start with therapy and continue for its duration or until CD4 ≥ 200/μL (whichever is longer) |

Meera Mohan et al,
Br J Haematol 2023

# Strategie per migliorare il profilo di safety nei pazienti trattati con BsAbs. Riduzione della frequenza di somministrazione



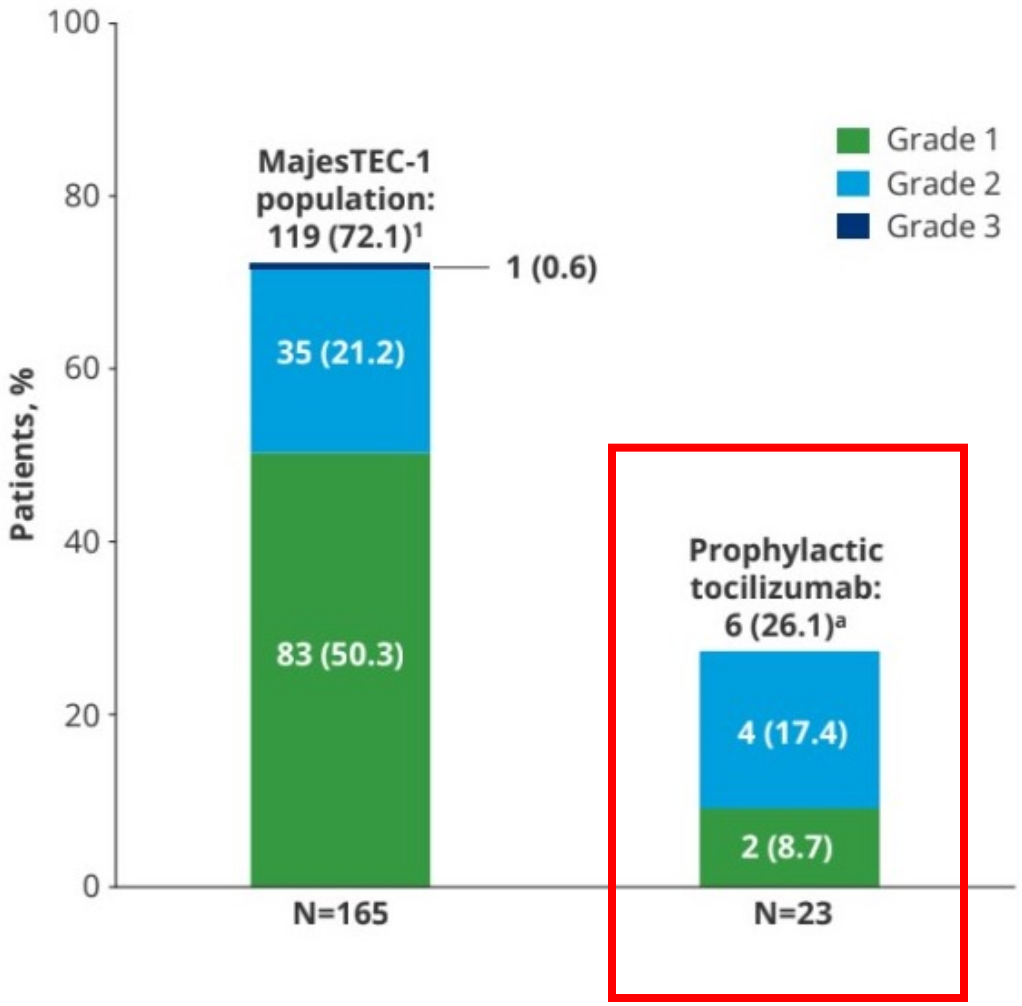




Al data cut-off (follow-up mediano 30.4 m):
165 pz avevano ricevuto Tec alla RP2D (1.5 mg/kg QW)
65 pz erano passati a 1.5 mg/kg Q2W
38 pz rimanevano in trattamento (di cui 37 Q2W)
L'incidenza di infezioni G ≥3 tende a ridursi nel tempo, in particolare dopo i primi 9-12 mesi di trattamento (switch a Q2W; incremento dell'uso di Ig)
**E' stata approvata la somministrazione di Tec 1.5 mg/kg s.c. Q2W nei pz con di ≥RC sostenuta per ≥6 mesi**

Garfall AL et al, ASCO 2024, P7540

Usmani SZ et al, JCO 2023

# Strategie per migliorare il profilo di safety nei pazienti trattati con BsAbs. Profilassi della CRS




Una dose singola di Toci in profilassi precedente la 1a dose di step-up di Tec si associa a riduzione dell'incidenza di CRS al 26.1% (G1/2), corrispondente a una riduzione del 64% rispetto alla popolazione complessiva in MajesTEC-1

La somministrazione di una dose singola di Toci in profilassi potrebbe consentire la somministrazione di Tec in regime ambulatoriale

van de Donk N et al, ASCO 2023. Abs 8033

# Ruolo dei BsAbs nell'era della immunoterapia
## Considerazioni conclusive

La modulazione immunologica è cruciale nell'ottenimento e persistenza della risposta a terapie T cell-dipendenti (BsAbs, CAR-T)

Il concetto di "refrattarietà" in ambito di immunoterapia deve essere rivisto alla luce di:
- Possibilità di modulare farmacologicamente il microambiente immunitario e quindi la risposta terapeutica
- Potenzialità sinergiche degli approcci immunoterapici
- Ruolo del "resting" dei linfociti T nel miglioramento della T cell exhaustion (somministrazione dilazionata/intermittente)

Possibile *rechallenge, utilizzo sequenziale* di approcci immunoterapici (i.e. BCMA-TT) anche in associazione ad agenti potenzialmente in grado di modulare l'assetto immunitario, la fitness delle cellule T e/o l'espressione dell'Ag target, e quindi la risposta

Potenzialità degli agenti immunomodulanti (IMIDs, anti-CD38) quali *backbone* da riproporre attraverso più linee terapeutiche al fine di modulare il microambiente immunitario e sfruttare i meccanismi sinergici

E' auspicabile l'impiego dell'immunoterapia, incluse le terapie T-cell dipendenti, in/dalla fase precoce (limitata esposizione a terapie immunosoppressive, *fitness* delle cellule effettrici)


Grazie per l’attenzione