Prior to CAR-T: Hold therapy & Bridging therapy

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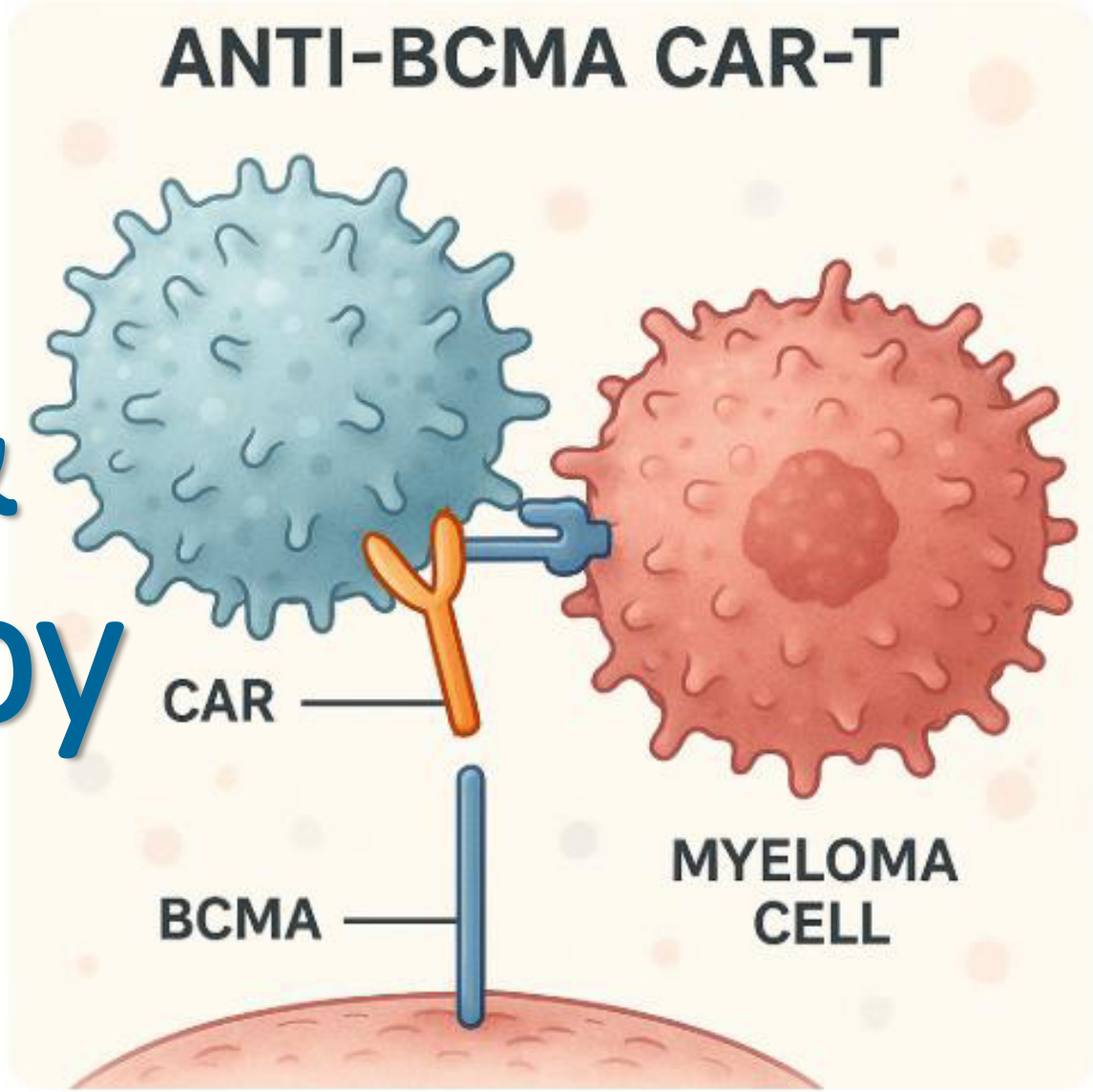


Factors Affecting CART Therapy Eligibility:

- **Bulky/rapidly progressive disease** ⇨ increases risk of clinical deterioration during washout for leukapheresis /CAR T-cell manufacturing
- **Severe cytopenia** ⇨ unsafe apheresis, poor CAR T-cell yield
- **High doses of alkylator** ⇨ reduced lymphocyte counts & T-cell fitness for CAR T-cell manufacturing

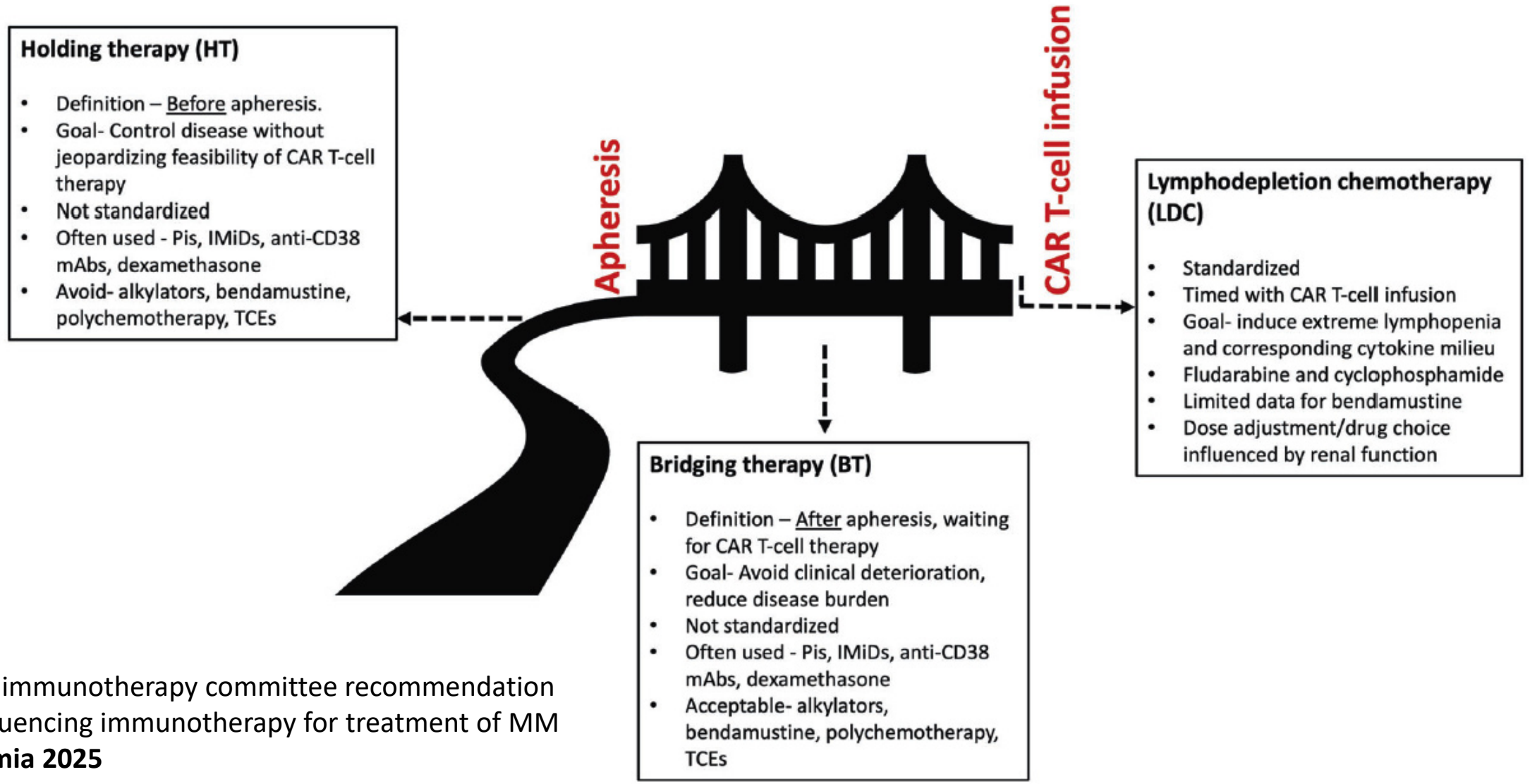
Consensus guidelines and recommendations for the management and response assessment of CAR-t therapy in clinical practice for RRMM: a report from the IMWG Immunotherapy Committee. **Lancet Oncol 2024**

Patients Selection

- The following patients were excluded from KarMMa/CARTITUDE studies, safety of BCMA CART in these situations remains to be defined:
  - Active plasma cell leukaemia
  - Secondary CNS involvement
  - Poor renal function (CCT<30 mL per min)
  - Secondary amyloidosis
- Successful results from case reports are available

Consensus guidelines and recommendations for the management and response assessment of CAR-t therapy in clinical practice for RRMM: a report from the IMWG Immunotherapy Committee. **Lancet Oncol 2024**

Distinction between holding therapy, bridging therapy and LD chemotherapy in the care of patient undergoing CAR-T



IMWG immunotherapy committee recommendation on sequencing immunotherapy for treatment of MM **Leukemia 2025**

Recommendations for myeloma treatment before leukapheresis:

Consider drug half-life, effect on number/fitness of T cells, and clinically feasible washout period to optimize the collected T cells for CAR T manufacturing

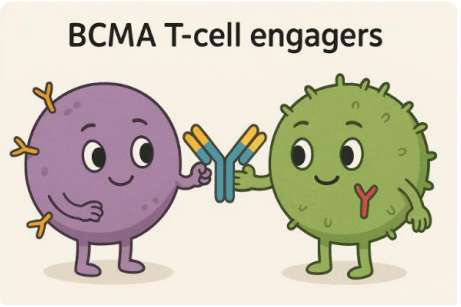
- Avoid lymphotoxic drugs [**Bendamustine, HD cyclophosphamide**, **Melphalan, Fludarabine, HD steroids]** where possible- should be avoided at least in **1–2 months** before leukapheresis, possibly longer

- A **14 days washout** period for **chemotherapy drugs** should be used when possible to allow T-cell count recovery

- **Radiation** <5% of the BM, a washout period might not be needed

- **LD corticosteroids IMIDs, venetoclax** - a short half-life, **7 days** washout period

Recommendations for myeloma treatment before leukapheresis:

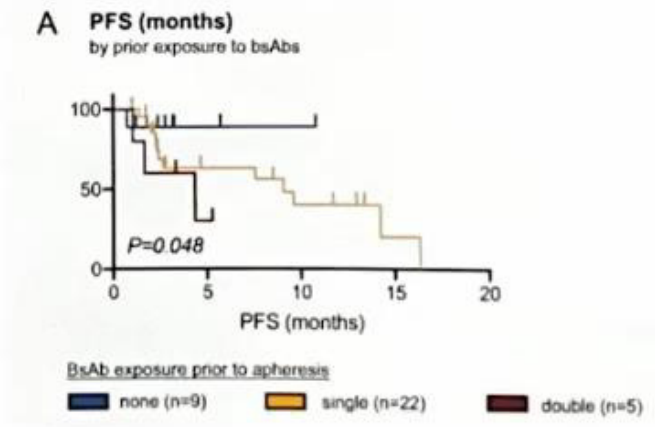


- T-cell exhaustion is reported in patients who are refractory to / relapsed after BCMA T-cell engagers (TCEs)
- Patients proceeding to CAR T immediately after TCE have higher risk of manufacturing failure and less durable responses
- A treatment-free period from bispecific antibodies might help improve T-cell fitness; a 4-week minimum washout period before apheresis is suggested regardless of TCE target
- For patients who could qualify for both TCE and CAR T-cell therapies -considered for CAR T-cell therapy first

Prior therapy can impact CAR T apheresis samples and therefore, manufacturing and patient outcomes

- In RRMM setting : 5% manufacturing failure rate and 10-20% OOS rate. Prior bispecific therapy is a reason for many of these patients[1]

- Prior BCMA BsAb therapy was associated with :
  - reduced T-cell numbers, including CD3 T cells, CD4 T cells and T-regulatory cells, compared with patients without prior BCMA CAR T exposure[2]
  - shorter PFS compared with no prior BsAb[3]



Patients who did not receive anti-BCMA CAR-T[4]

N= 12	
Manufacturing failure	5
Disease progression	5
Patient decision	2
First manufacturing unsuccessful	6 (4 had prior BCMA)
Total deaths	8

Talquetamab in peri-apheresis period

N= 12	
Age, median (range)	61 years (50-75)
Male sex, n (%)	5 (42%)
ECOG ≥2, n (%)	2 (17%)
High-risk disease / Extramedullary disease	7 (58%) / 5 (42%)
Median prior lines	6 (range 4-10)
Median time from Talquetamab to apheresis	94 days (28-174)
Response to Talquetamab	11/12 (92%)
CAR-T infusion	8/12 (67%)
Reasons for no infusion	**Manufacturing failure** (2), PD (1), OOS (1)

1. Sidana S, et al. Blood. 2025;145(1):85-97; 2. Castaneda O, et al. ASH 2024. Abstract #5168; 3. Waldschmidt JM, et al. ASH 2024. Poster #2007; 4. Dhakal B, et al. ASH 2024. Oral #931

BCMA: B Cell Membrane Antigen; BsAb, bispecific Antibody; CAR T, chimeric antigen receptor T; ECOG, Eastern cooperative oncology group; OOS, out of specification; PD, progressing disease; PFS, progression free survival; RRMM, relpasing / remitting Multiple myeloma;

Bridging therapy

After leukapheresis (Bridging therapy):

- Bridging therapy (BT) is essential before CAR-T infusion
- Main aim: tumor de-bulking
- Rapid PD/high tumor burden- associated with:
  - Shortened survival
  - Increased rates of CAR-T–related toxicities (more severe CRS, ICANS, late neurologic symptoms)
- A recent analysis demonstrated an ORR of 12% to BT in patients treated with CAR-T outside of clinical trials in United States

Optimising bridging therapy is important for effective disease control prior to administering cilta-cel[1]

CARTITUDE-1[2]

N=97 received cilta-cel; of these:

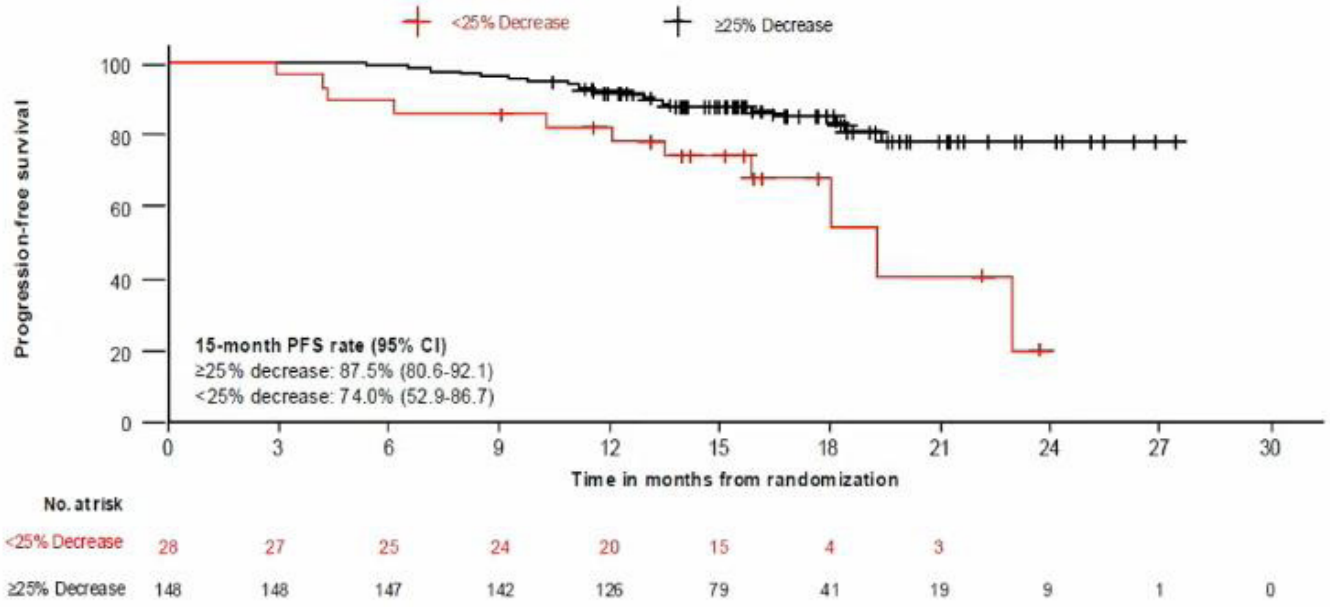
- **n=73** received bridging therapies, including systemic corticosteroids (n=63), antineoplastic agents (n=62) or immunosuppressants (n=26)

CARTITUDE-4[1]

N=176 received cilta-cel; of these:

- **n=158** received D-Pd bridging therapy
- **n=18** received P-Vd bridging therapy

PFS by tumour burden change of ≥25% between baseline and start of lymphodepletion in CARTITUDE-4 (post-hoc analysis)[1]



In CARTITUDE-4, an improved response to bridging therapy correlates with longer PFS, highlighting the importance of optimising bridging therapy for effective disease control prior to administering cilta-cel[1]

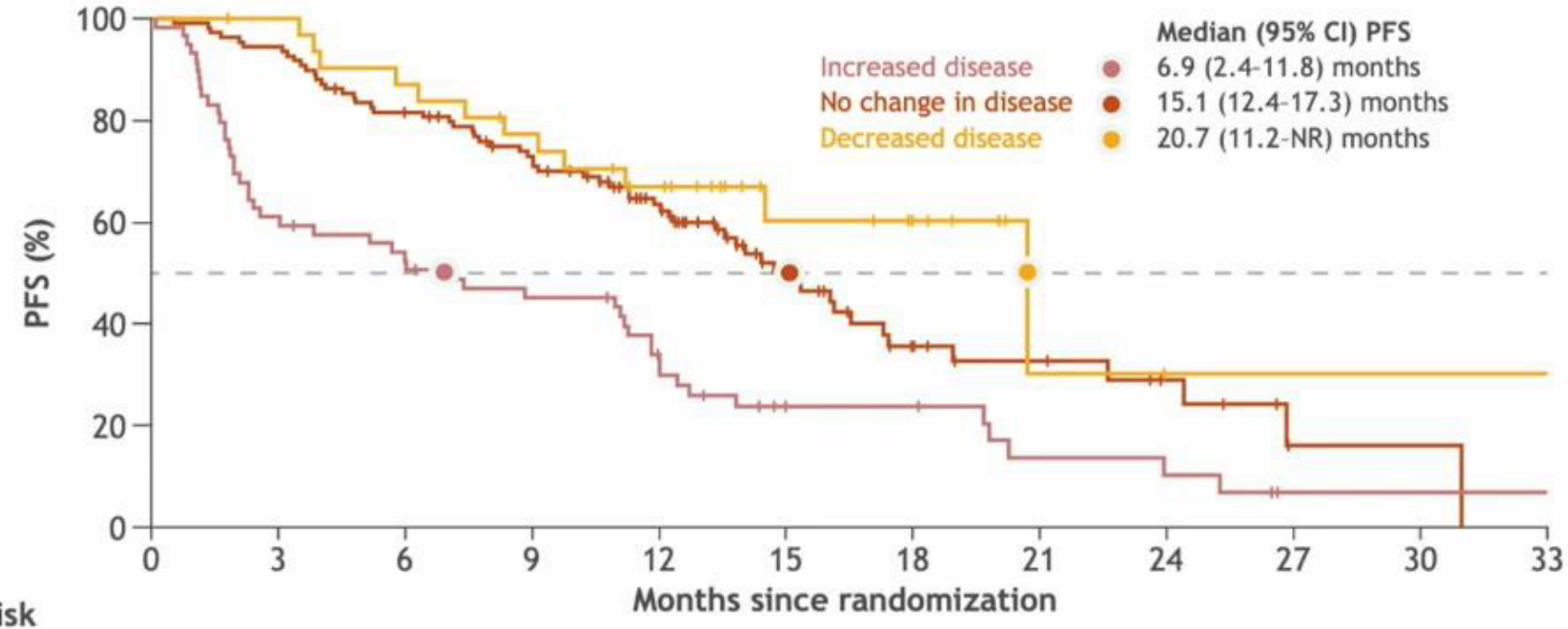
Clinicians must refer to individual local SmPCs to ensure chosen bridging therapy proceeds according to licensed uses. Appearance in this presentation does not signify that the regimen is necessarily approved in this setting.

CI, confidence interval; D, daratumumab; d, dexamethasone; P, pomalidomide; PFS, progression-free survival; V, bortezomib.

1. Anguille S, et al. IMS 2024 (Abstract No. P-005 – poster); 2. Berdeja JG et al. Lancet 2021;398:314–324.

KarMMa-3 – ide-cel: PFS per bridging therapy

Choice of bridging therapy may impact PFS[1]



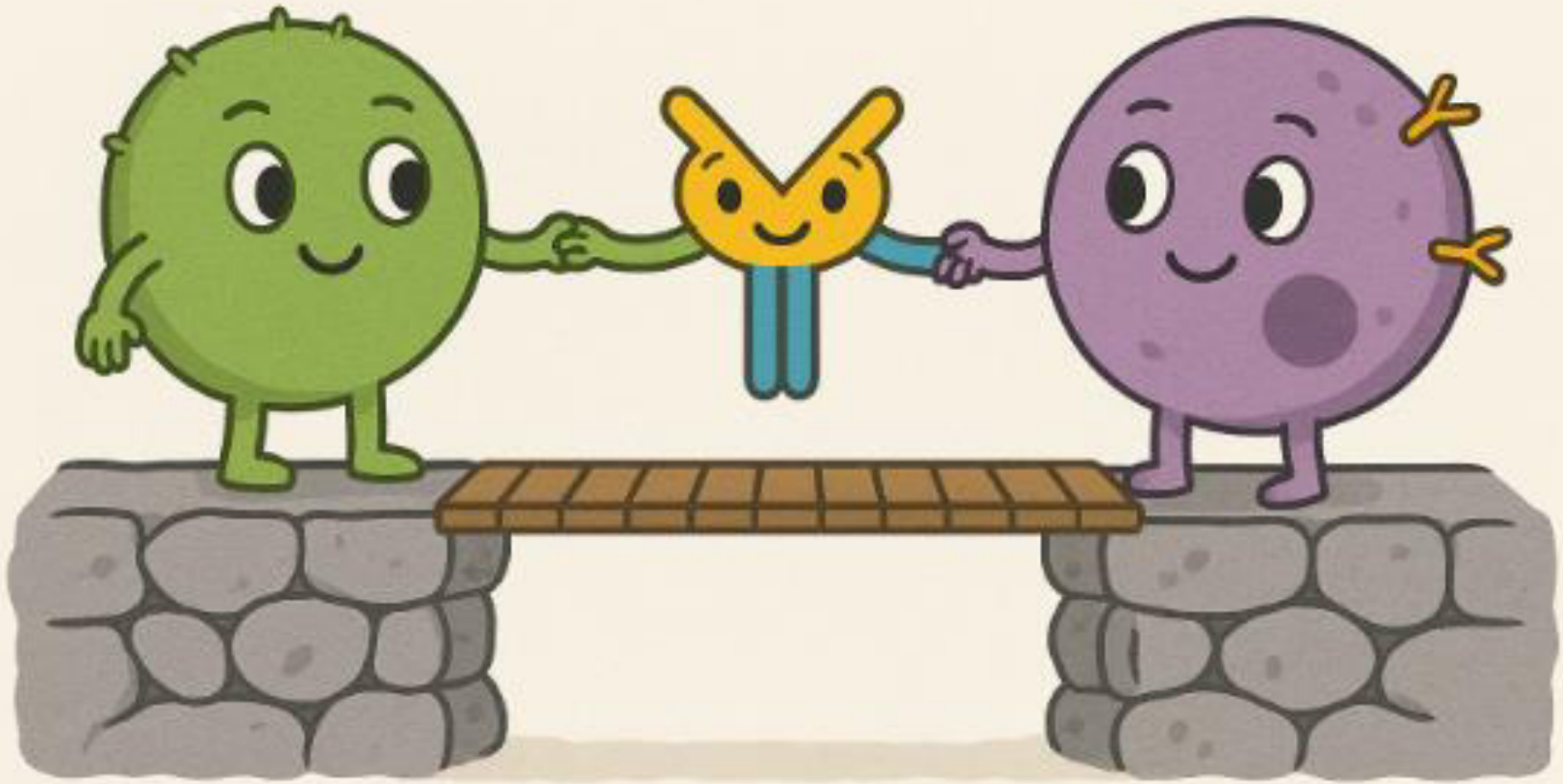
Patients at risk												
Increased disease	59	36	31	25	17	9	8	4	3	0	0	0
No change in disease	109	103	88	74	54	27	15	10	6	1	1	0
Decreased disease	32	31	27	23	18	9	7	1	0	0	0	0

CI, confidence interval; NR, not reached; PFS, progression-free survival.
1. Einsele H, et al. IMS 2023 (Abstract No. P008 – poster presentation).

After leukapheresis (Bridging therapy):

- Disease burden and previous kinetics of disease progression should guide the selection of BT
- Patients with low disease burden that is not rapidly progressing, consider minimum therapy to limit disease progression during CART manufacturing to reduce risk of organ toxicities and serious side-effects that might delay/preclude CART-infusion
- Priority for agents to which a patient's disease has not become refractory
- Preclinical data suggest **IMIDs and anti-CD38 antibodies** might improve T-cell function and CART activities
- Given the risk for CAR T-cell manufacturing failure, **consider avoiding lympho-toxic drugs -** re-collection of T cells might be required
- If bridging therapy is used, consider completing at least 1 cycle prior to LD and a washout period of at least 1 week

T-cell engager as bridging therapy before anti-BCMA CAR-T



After leukapheresis (BT):

- The effect of other BCMA-targeted therapy immediately before CAR T-cell therapy is unknown; therefore, due to potential **concern for down-regulation of antigen expression-**not recommended if alternative therapies are available
- Real-world data suggest that CAR-T after BCMA-targeted T cell–redirecting agent is associated with adverse outcomes. These analyses included patients who progressed upon treatment with a BsAb, with CAR-T cells being the salvage therapy

TCE therapy is reasonable as BT if targeting a different antigen than CART

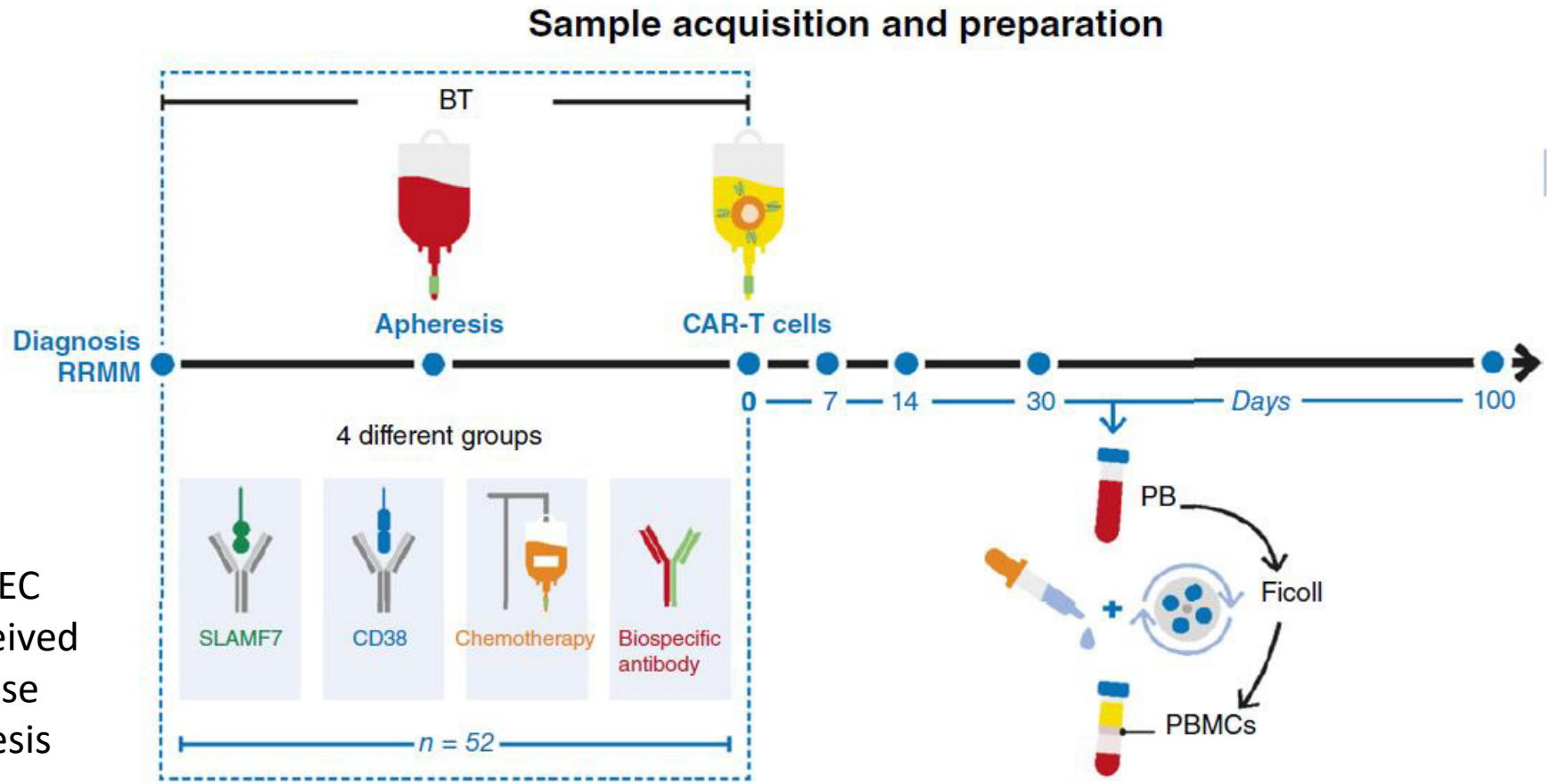
Talquetamab Bridging: Paving the Way to BCMA CAR-T Cell Therapy in RRMM

- An ORR 62%

- 58 patients went on to receive CAR-T following talq bridging (45 cilta-cel; 13 ide-cel)
  - 65% experienced CRS, grade 3 CRS in 2 (3%) pts
  - ICANS occurred in 5 (8.6%) pts, 1 (1.7%) grade 3 ICANS
  - Only 1 pt had delayed NT (facial nerve palsy) at the last follow up

- Response was evaluable in 40 pts - a response at day +30 in 39/40 (97.5%) pts

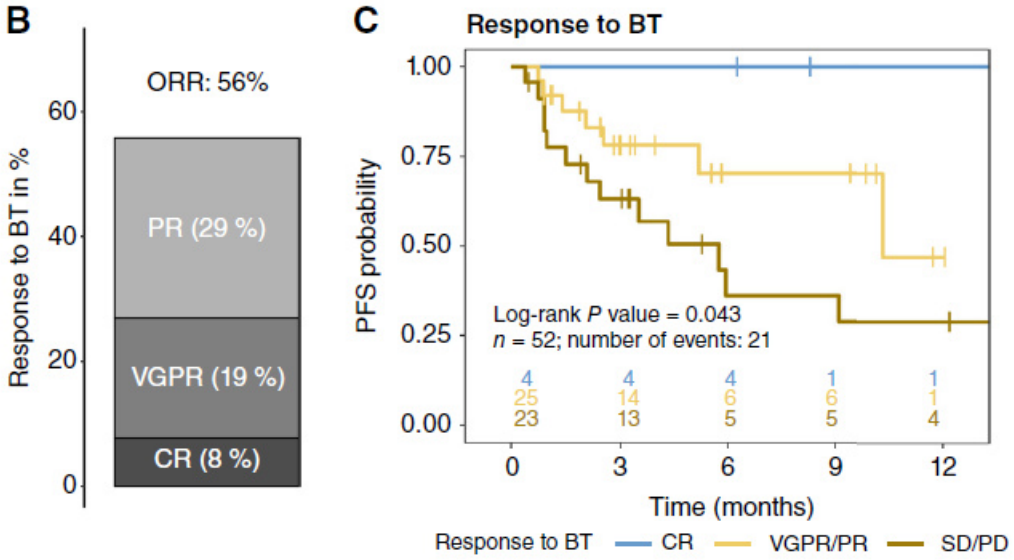
BsAb as Bridging to BCMA CART for RRMM



5 pts- TAL, 5 pts-TEC
9/10 patients received their first BsAb dose before leukapheresis

Fandrei et al **BLOOD CANCER DISCOVERY** Jan 2025

Remission status after BT influences outcome after CAR-T cell therapy



ORR to BT

PFS to CART according to BT RESPONSE

ORR to BT – sub groups

CRS according to BT

When selecting a bridging therapy, IMWG guidelines recommend balancing disease control and potential AEs[1]

IMWG guidelines for selecting bridging therapy[1]

Consider disease burden and prior disease progression

Avoid lymphotoxic drugs* in case more T cells need to be collected

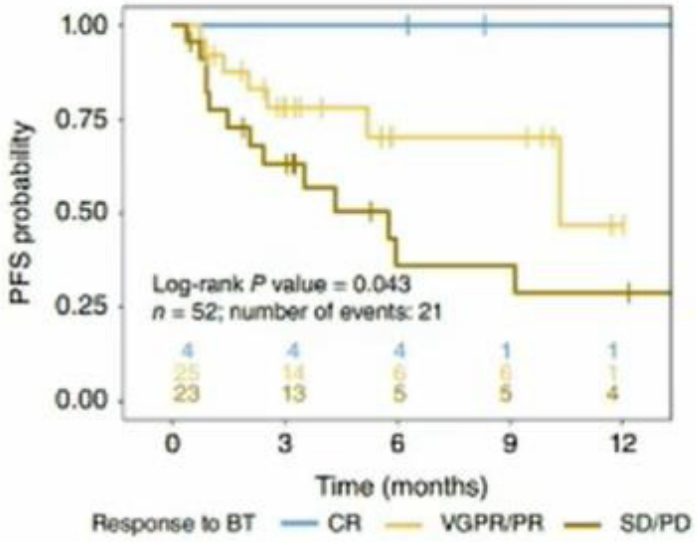
BCMA-targeting agents are not recommended if there are other therapies available

To reduce risk of CRS, IEC-HS, and neurotoxicity in those with high disease burden or rapidly progressing disease, avoid agents that the patient is refractory to

Anti-CD38 mAbs and IMiDs may improve outcomes but consider washout before lymphodepletion

Waiting for the deepest response with bridging therapy is not needed: provided it is safe to do so, **administer CAR-T cells as soon as they have been manufactured and delivered**

Real-world analysis: PFS with ide-cel/ cilta-cel by response to bridging therapy (n=52)[2]



Treatment outcome with CAR-T cell therapy was significantly influenced by depth of response to bridging therapy[2]

endamustine or high-dose cyclophosphamide.[1]
erse event; BCMA, B cell maturation antigen; CAR, chimeric antigen receptor; CR, complete response; CRS, cytokine release syndrome; IEC-HS, immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome; IMiD, immunomodulatory
IWG, International Myeloma Working Group; mAb, monoclonal antibody; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; VGPR, very good partial response.