The Next Generation of Therapy for Relapsed/Refractory Myeloma: CART and Bispecific T-Cell Engagers

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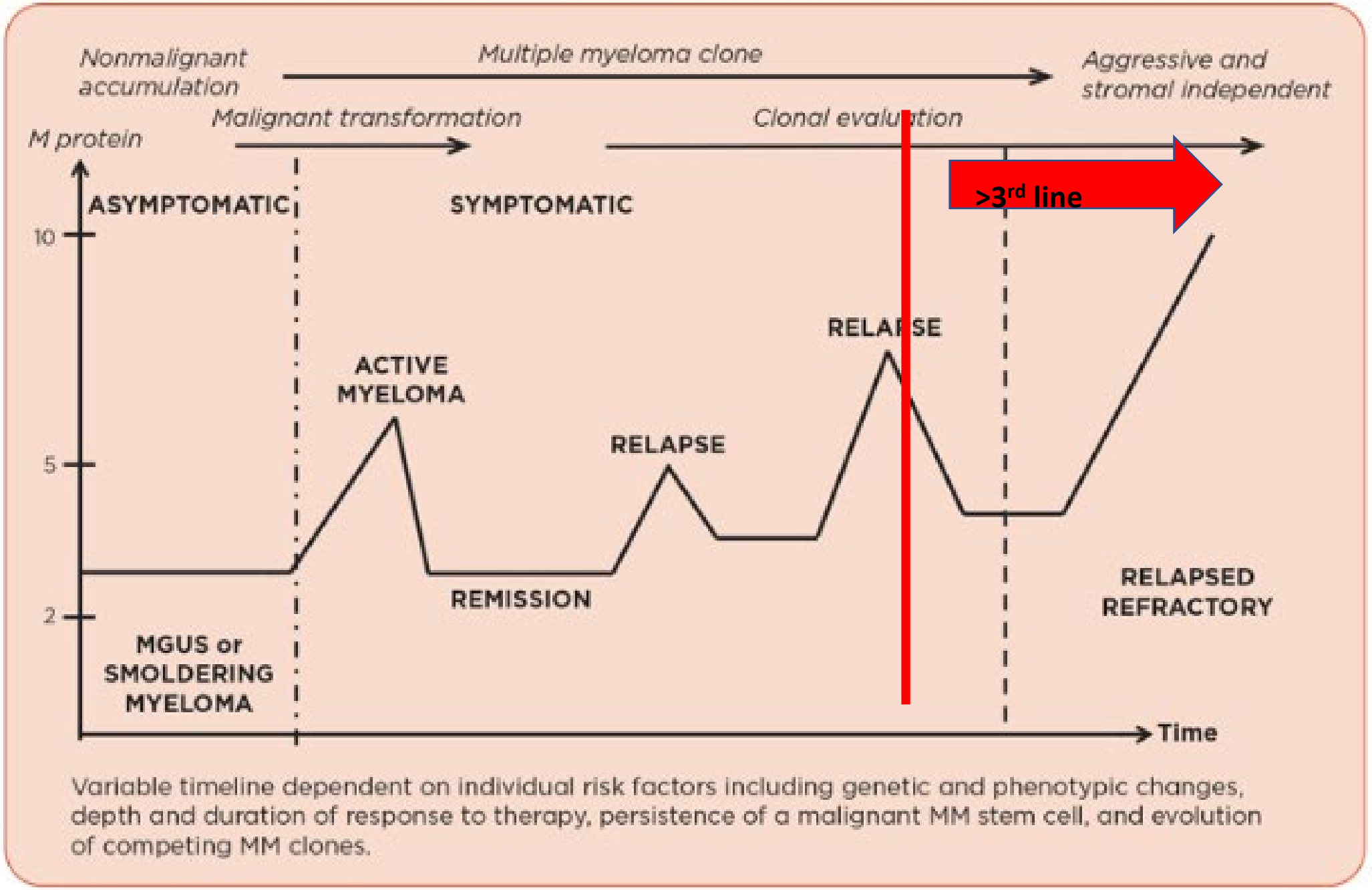
Objectives

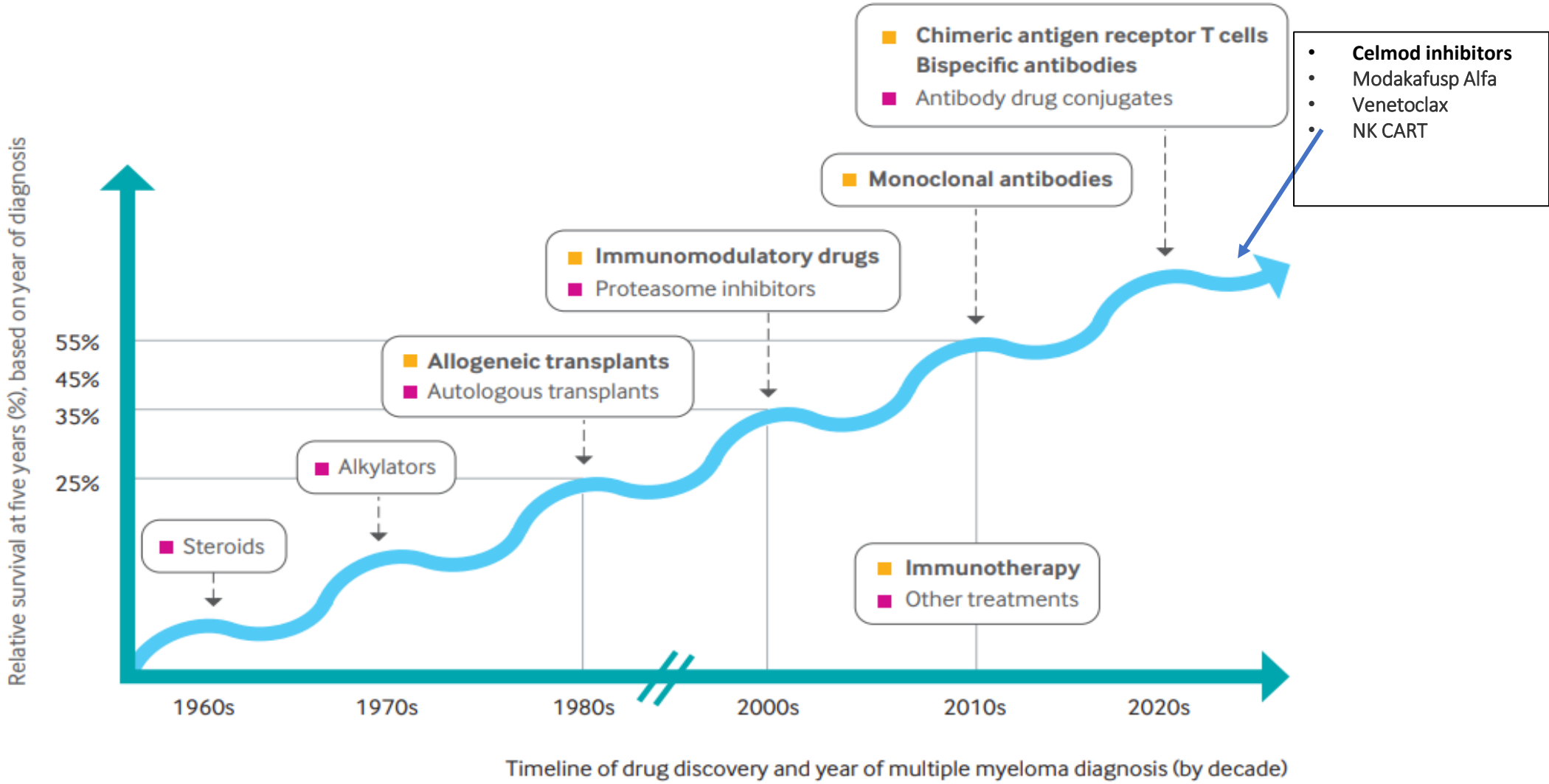
- Therapeutic Historical Perspective
- Historical Outcomes in multiply Relapsed/Refractory Disease
- Brief review Chimeric Antigen Receptor T Cells (“CAR-T”):
  - Idecabtagene vicleucel
  - Ciltacabtagene autoleucel
- **Bispecific T-Cell Engagers (“BiTEs”):**
  - **Teclistamab**
  - **Elrananatmab**
  - **Talquetamab**
  - **Cevostamab**
- **BiTE Toxicity Management**
  - **Cytokine Release Syndrome (CRS)**
  - **Immune effector cell-associated neurotoxicity syndrome (ICANS)**
  - **Infections**



Variable timeline dependent on individual risk factors including genetic and phenotypic changes, depth and duration of response to therapy, persistence of a malignant MM stem cell, and evolution of competing MM clones.

1840s

- Steel and quinine
- Rhubarb and orange peel



- **Celmod inhibitors**
- Modakafusp Alfa
- Venetoclax
- NK CART

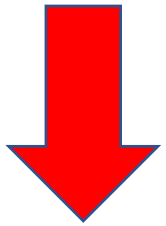
Fig 1 | Multiple myeloma treatments—timeline of drug discovery and five year relative survival (using data from the Surveillance, Epidemiology, and Ends Results program).[6] Data for year of diagnosis and relative survival are: 1975, 26.5% (observed); 1980, 26.0% (observed); 1985, 27.4% (observed); 1990, 29.9% (observed); 1995, 33.5% (observed); 2000, 34.6% (observed); 2005, 47.1% (observed); 2010, 53.6% (observed); 2015,

doi: 10.1136/bmj.m3176 | BMJ 2020;370:m3176

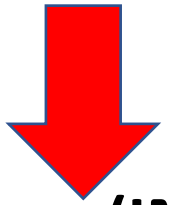
The “Typical” Standard Risk Transplant Eligible Myeloma Story…First Line therapy

- Arguable current standard of care:

- **3 or 4 drug induction -antiCD38 MoAB + PI + ImiD + dexamethasone (eg., D-VRD or D-KRd)**

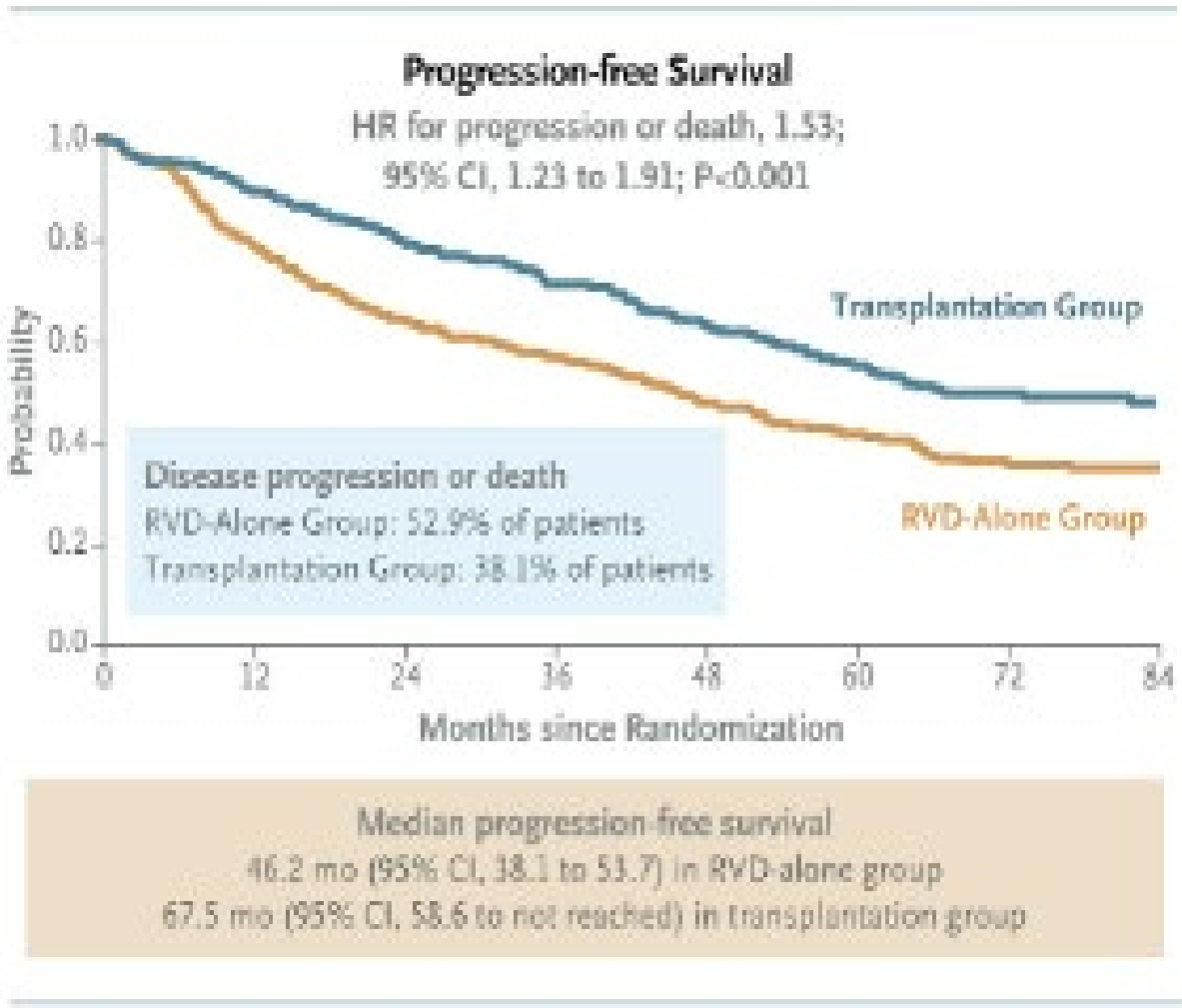


- **autologous SCT with melphalan conditioning**

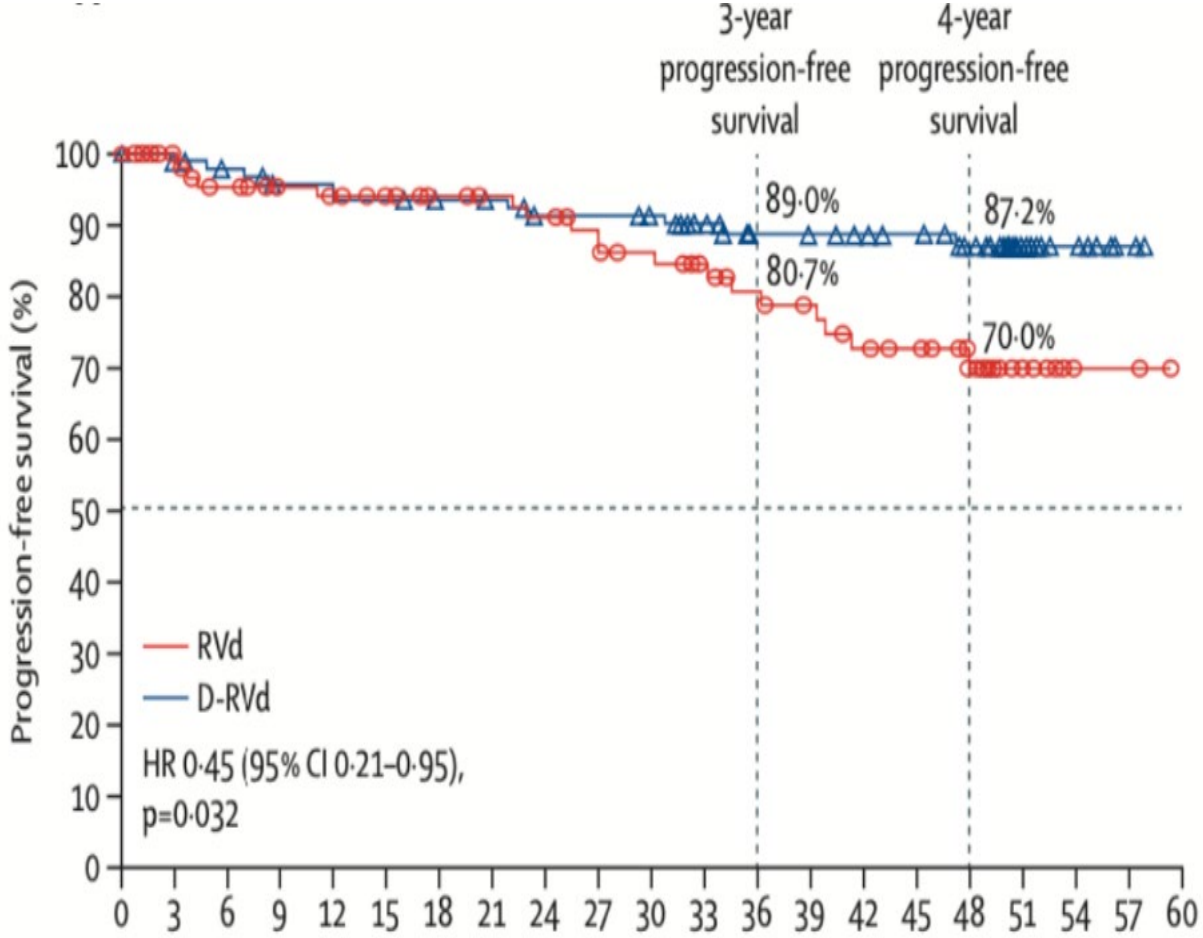


- **maintenance with monotherapy (IMiD) or doublet (ImID+PI vs ImID + antiCD38 MoAB) - until intolerance or progression**

Determination Trial –VRD>SCT>indef maintenance rev



Griffin Trial – DVRd>SCT>DVRd>DR



mPFS – standard risk disease - 6 yrs 8 months
Progression Free at 4 years- 70%

Sept 2023 update - 87% progression free at 4 years

N Engl J Med 2022; 387:132-147.; Lancet Hematology, September 11, 2023

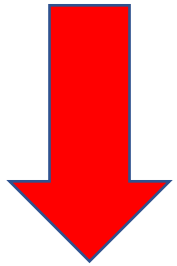
The “Typical” 2nd line therapy at first relapse post transplant...

- antiCD38 MoAB +/-2nd generation ImID +/- 2nd Generation PI until intolerance or progression

Isatuximab or Daratumumab + Carlfilzomib + Dexamethasone

or

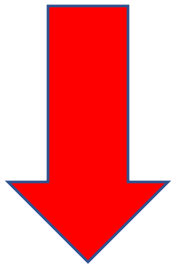
Isatuximab or Daratumumab + Pomalidomide + Dexamethasone



Median PFS – 2- 4 years

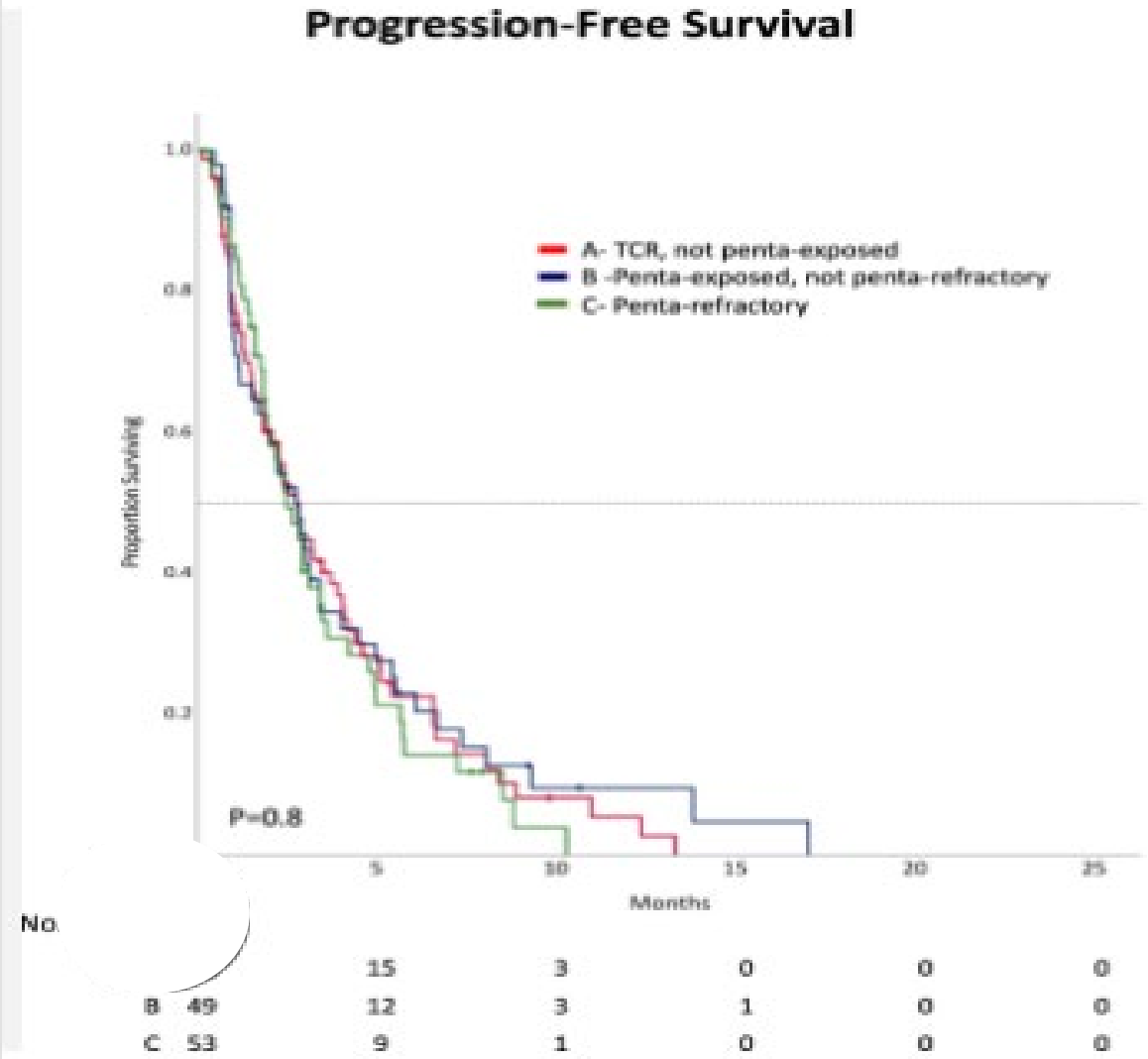
The “Typical” 3rd and 4th line therapy…ie the triple class exposed/refractory (TCE/TCR) population…

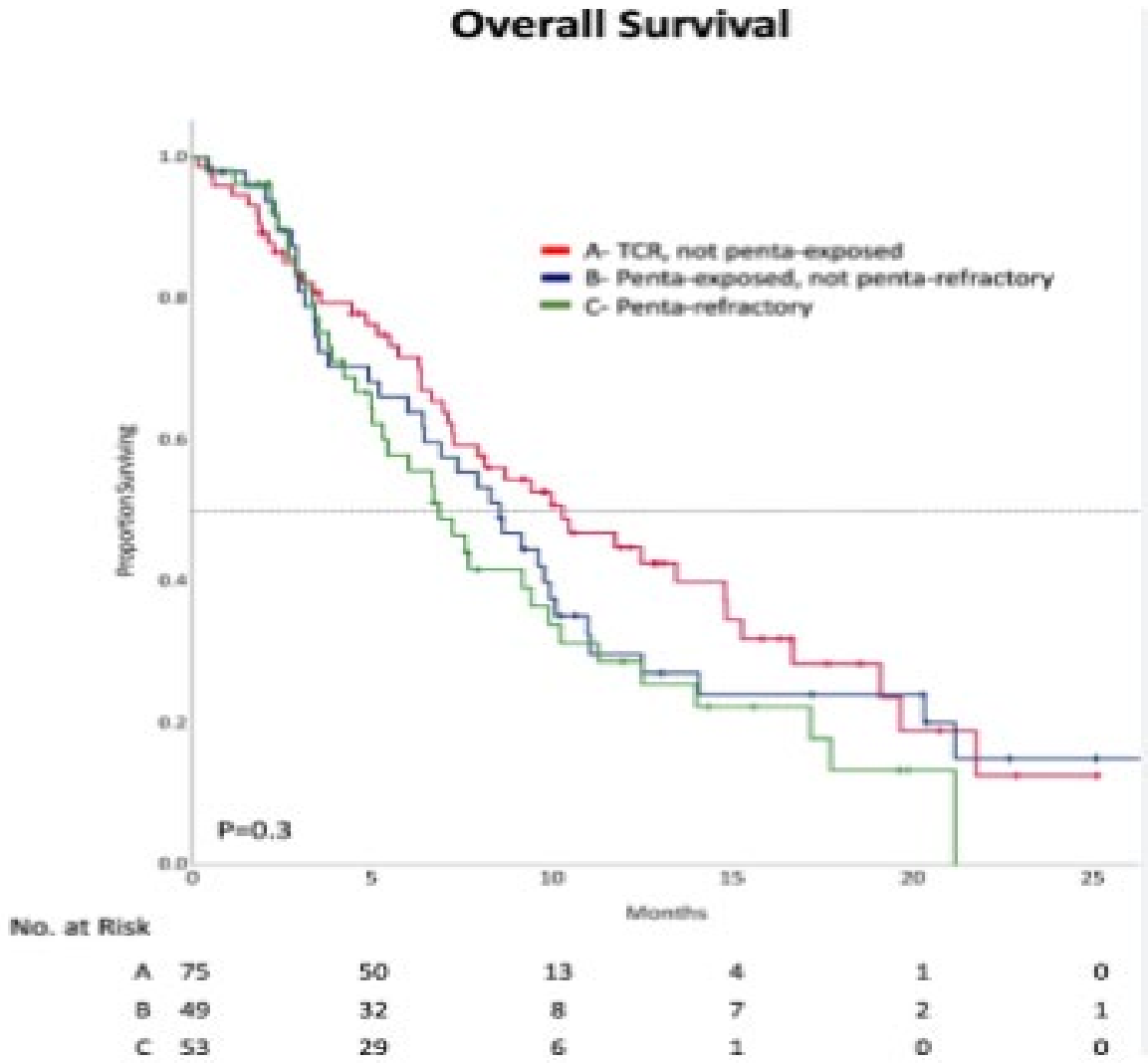
- Options now:
  - Elotuzumab based (EPd, ERd, EVd)
  - Selinexor based (SVd, Sd)
  - Ixazomib Based
  - Cytoxic Chemotherapy (eg: pulse Cytoxan, VDPACE, DCEP, VAD, Bendamustine)
  - Off label therapies - venetoclax in t(11;14) MM
  - Removed from market – Melflufen, Belantamab Mafodotin



Low ORR, Median PFS 3-12 months

Historical Outcomes in TCE/TCR patients…





mPFS <5 months

mOS < 12 months

Leukemia volume 36, pages877–880 (2022)

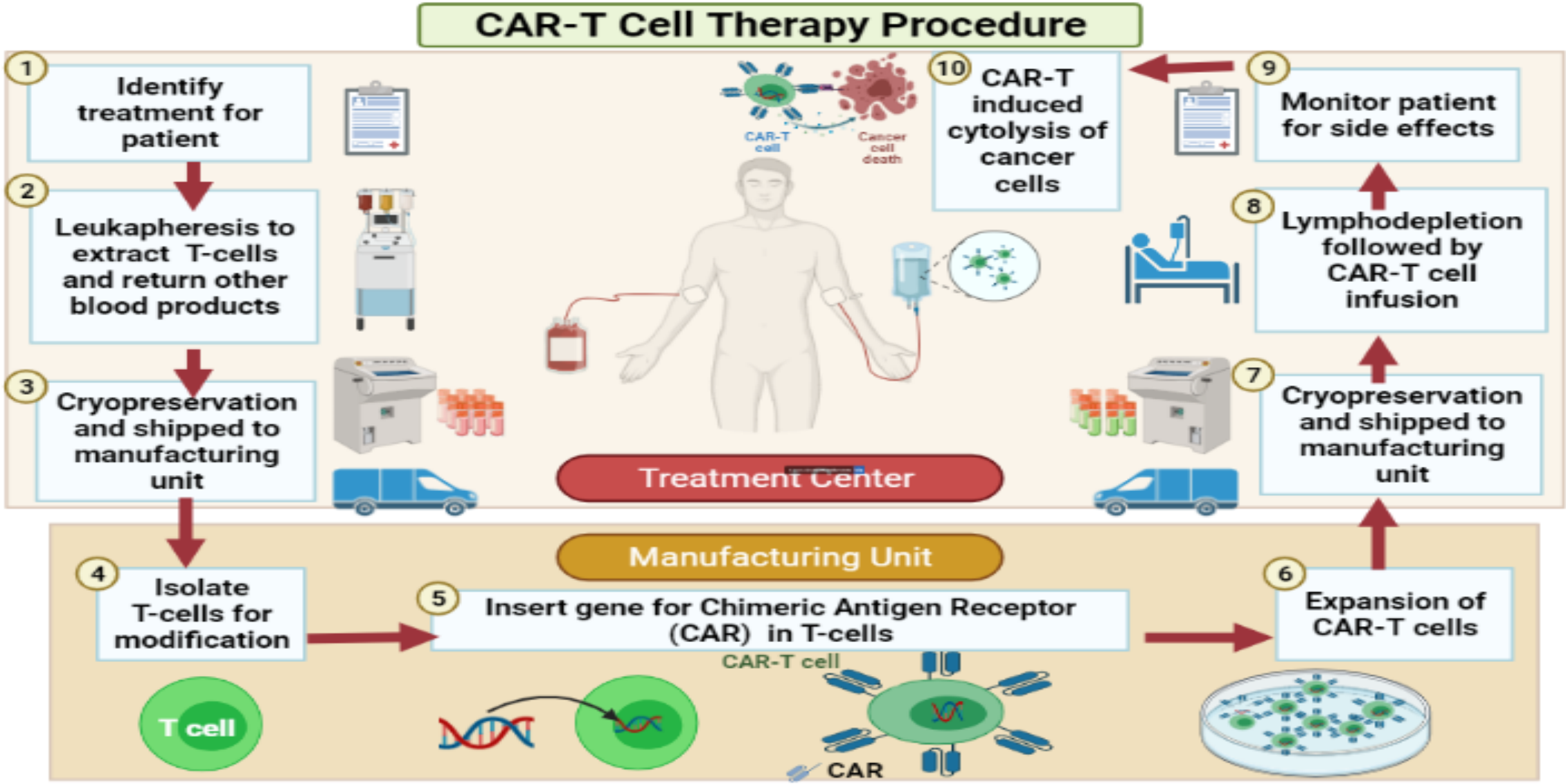
Enter the new kids on the block…2021-2023

- Chimeric Antigen Receptor T Cells ("CAR-T"):
  - Idecabtagene vicleucel – *Abecma* - *BMS* - FDA approved March 2021 -BCMA
  - Ciltacabtagene autoleucel –*Carvykti* - *Janssen* – FDA approved February 2022-BCMA

- **Bispecific T-Cell Engagers ("BiTEs"):**
  - **Teclistamab – *Tecvayli –Janssen* - FDA approved October 2022* -BCMA**
  - **Elrananatmab –*Elrexfio – Pfizer* - FDA approved August 2023* -BCMA**
  - **Talquetamab –*Talvay - Janssen* - FDA approved August 2023* -GPRC5D**
  - **Cevostamab – *Genentech* – Trials ongoing - Likely FDA approval Coming – FcRH5**

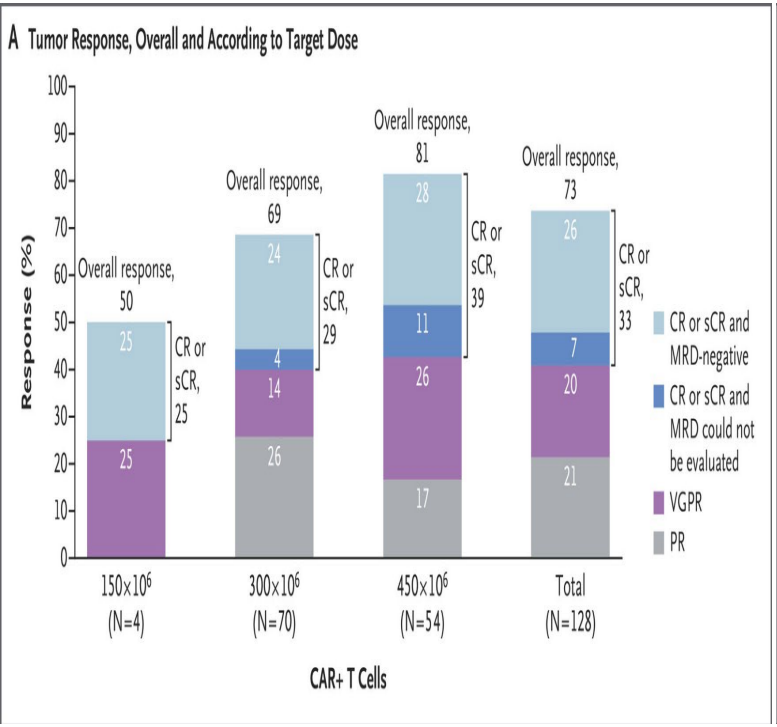
***All FDA Approved for > 4 prior lines of therapy AND Triple Class Refractory**

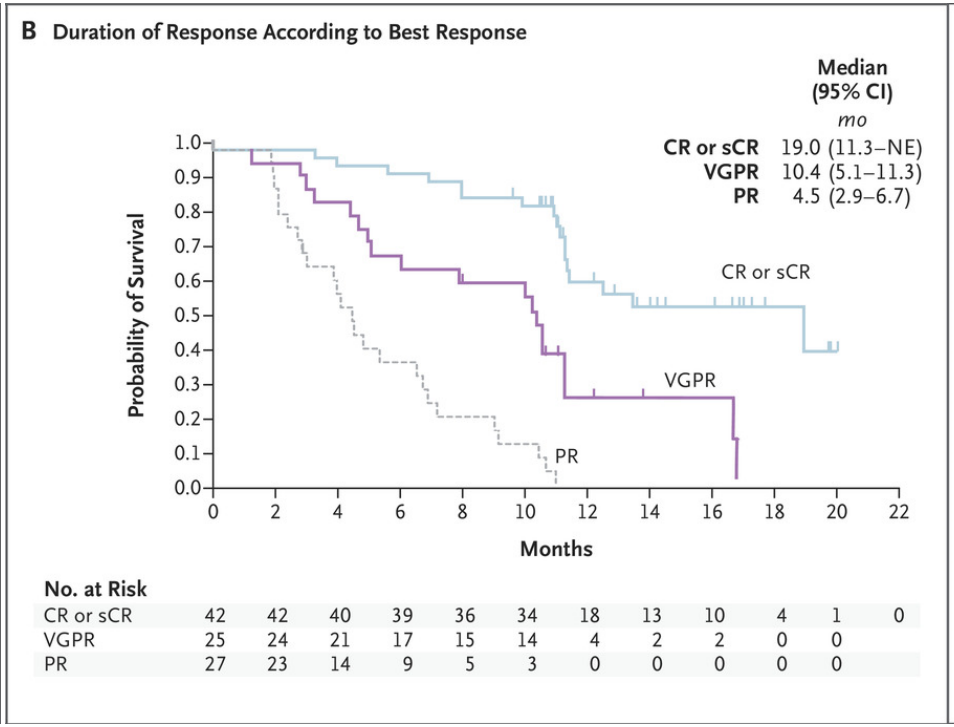
CART in Relapsed Myeloma

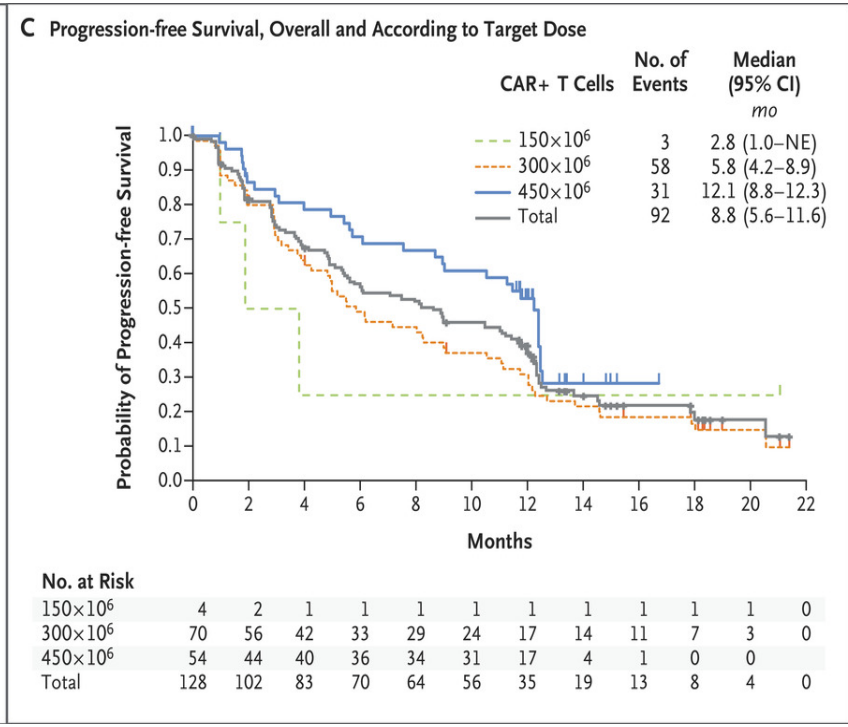


CART in Relapsed Myeloma – Late Relapse

- KARMMA1 – "Ide-Cel" –P2-non RCT ; ≥3 prior lines of therapy; 123 pts; jan 2021 NEJM data led to FDA approval for late relapse only







N Engl J Med 2021; 384:705-716

CART in Relapsed Myeloma – Late Relapse

- CARTITUDE 1 – "Cilta-Cel"-phase 1/2 non RCT - 97 pts; ≥3 prior lines of therapy
- Initial Lancet data from June 2022 led to FDA approval for late relapse only
- Most recent 2023 update data:

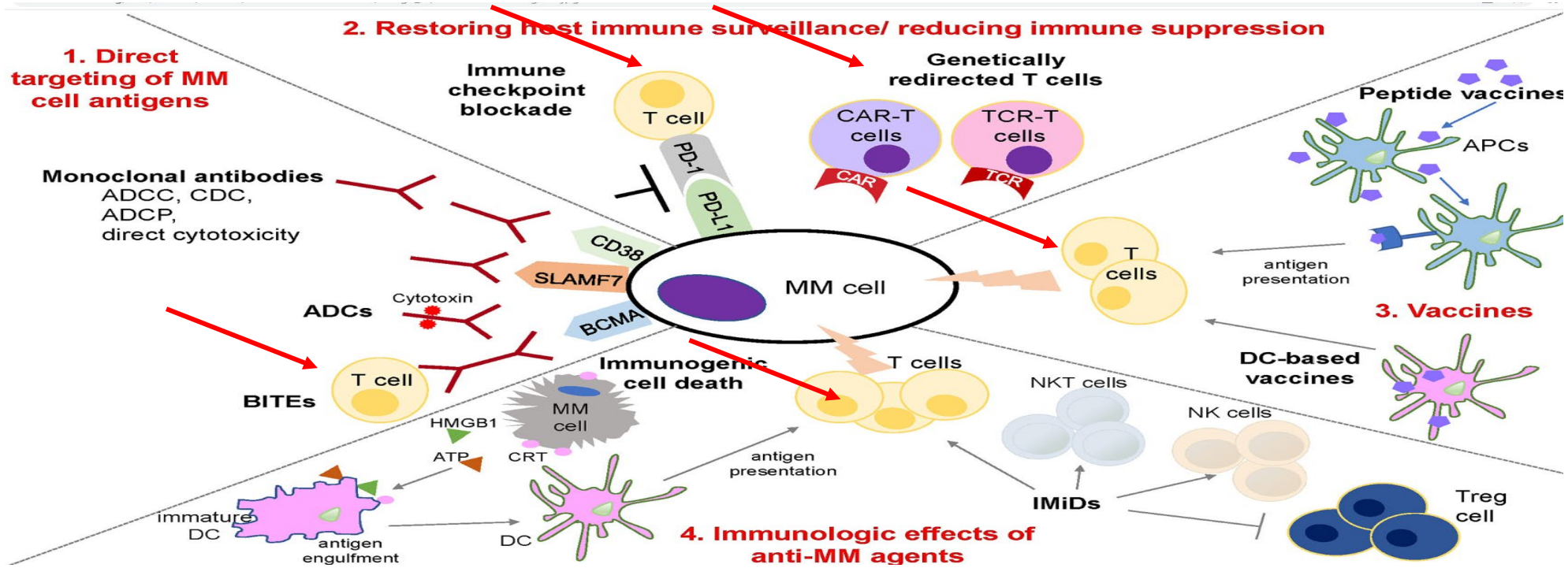
Subgroup	n	mPFS (95% CI), mo	30-mo PFS rate	36-mo PFS rate
All pts	97	34.9 (25.2–NE)	54.2%	47.5%
≥CR	76	38.2 (34.9–NE)	66.8%	59.8%
6-mo sustained MRD negativity[a]	34	32.2 (25.1–NE)	68.6%	45.7%
12-mo sustained MRD negativity[a]	26	NR (NE–NE)	74.9%	NE
12-mo sustained MRD-negative CR[a]	20	NR (NE–NE)	78.5%	NE

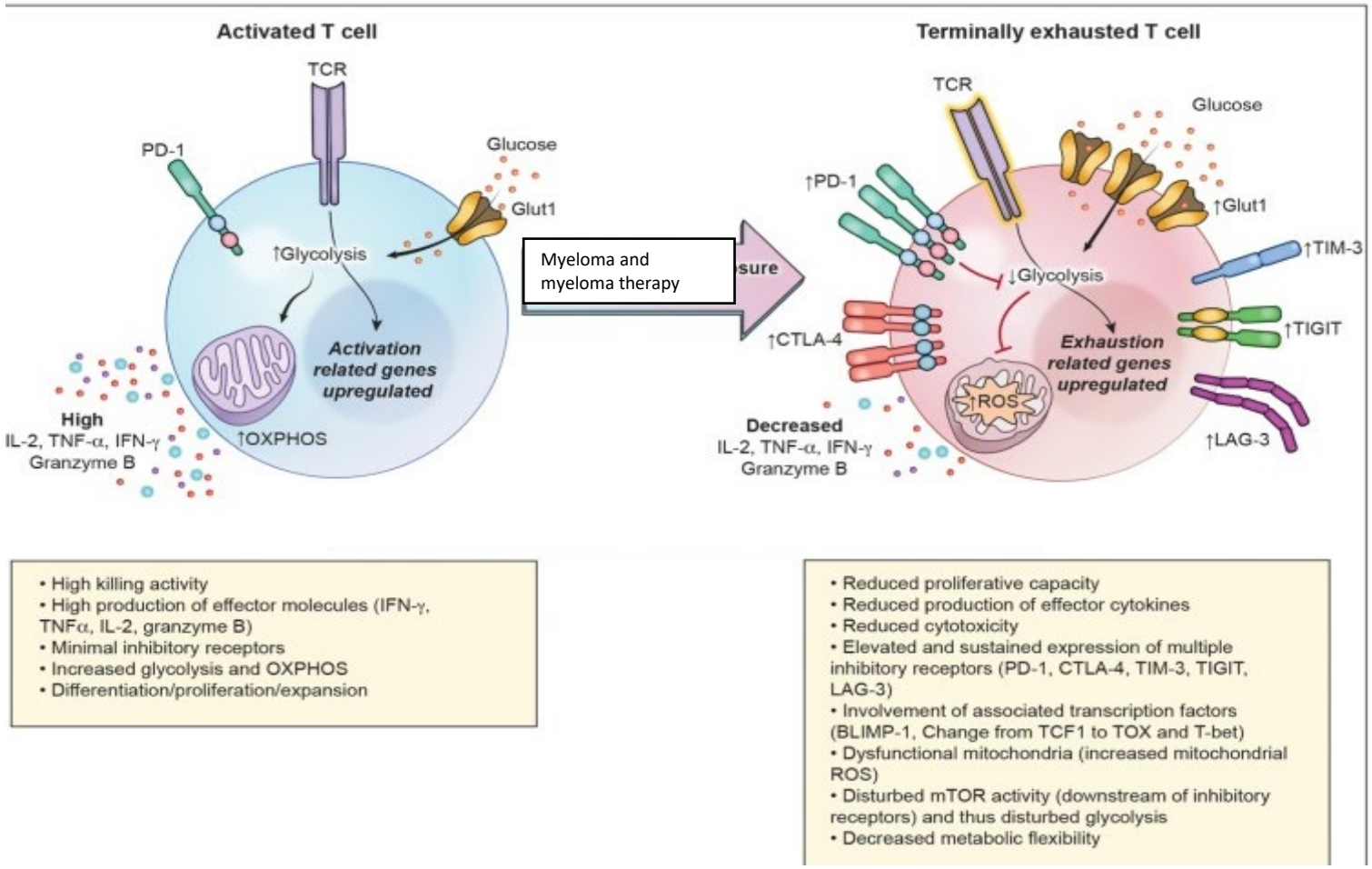
[a]≥2 MRD-negative assessments, 6 or 12 mo apart, with no MRD-positive samples in that interval.

Abstract 8009. ASCO 2023 Annual Meeting.

Immune Exhaustion in Myeloma

- Most of our successful therapeutic strategies to date have been aimed at activating the host immune system to fight myeloma
  - established therapies: IMiDs, PIs, MoABs
  - new therapies : CART and BiTE



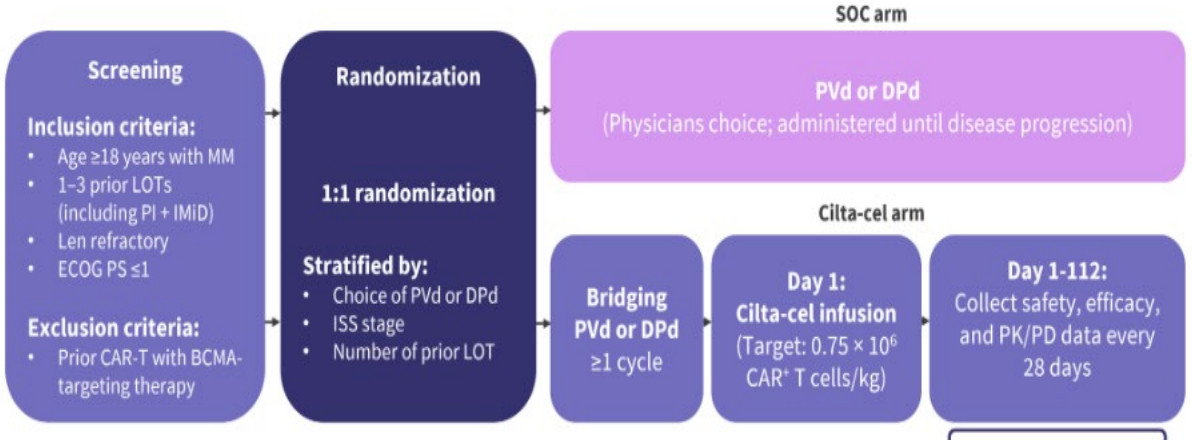


- Through proliferation and therapy we get increasing innate and adaptive immune system dysfunction, notably in the T-cell repertoire
- If drugs show efficacy with “exhausted” t-cells in RRMM then efficacy should be even better with “activated” or “fresh” t cells

Trends in Cancer Journal; published January 19, 2023

CART in Relapsed Myeloma –Early Relapse

CARTITUDE-4: 1-3 prior lines



KARMMA- 3: 2-4 prior lines

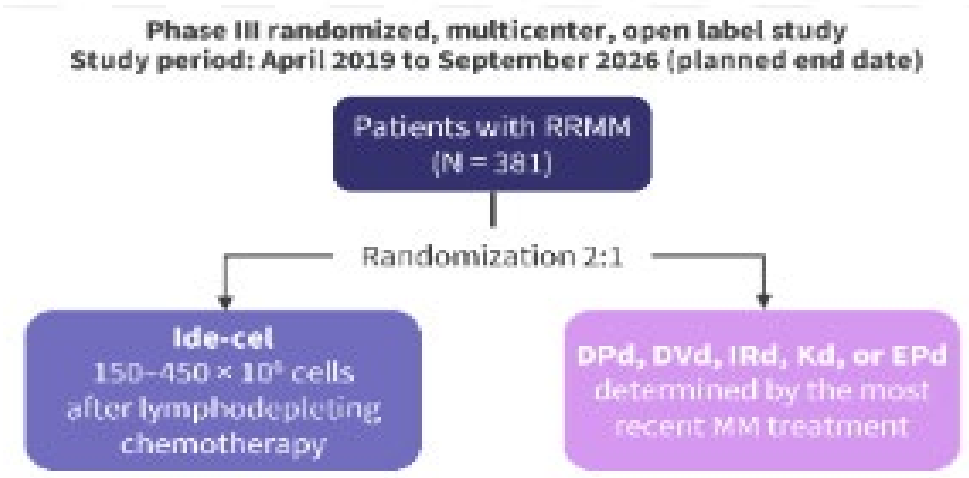


Table 9 Summary of Phase III Trials of CAR-T Cell Therapy in Multiple Myeloma

Variable	KarMMa-3	CARTITUDE-4
Number of patients	386	419
Median age (years)	63	61.5
Prior lines of therapy (median)	3	2
Triple class refractory	65%	14%
Refractory to anti-CD38	95%	24%
Median follow up (months)	18.6	15.9
ORR	71%	84.6%
PFS (median)	13.3 months	NR
12-months PFS	55%	75.9%

Anticipated Cilta-Cel early relapse approval – early-mid 2024

Ide-Cel vs Cilta-Cel

- No RCT between the 2 and likely never will be
- Matching-adjusted indirect comparison (“MAIC”) data and CTC previous PFS data - Cilta-Cel looks like the Winner?

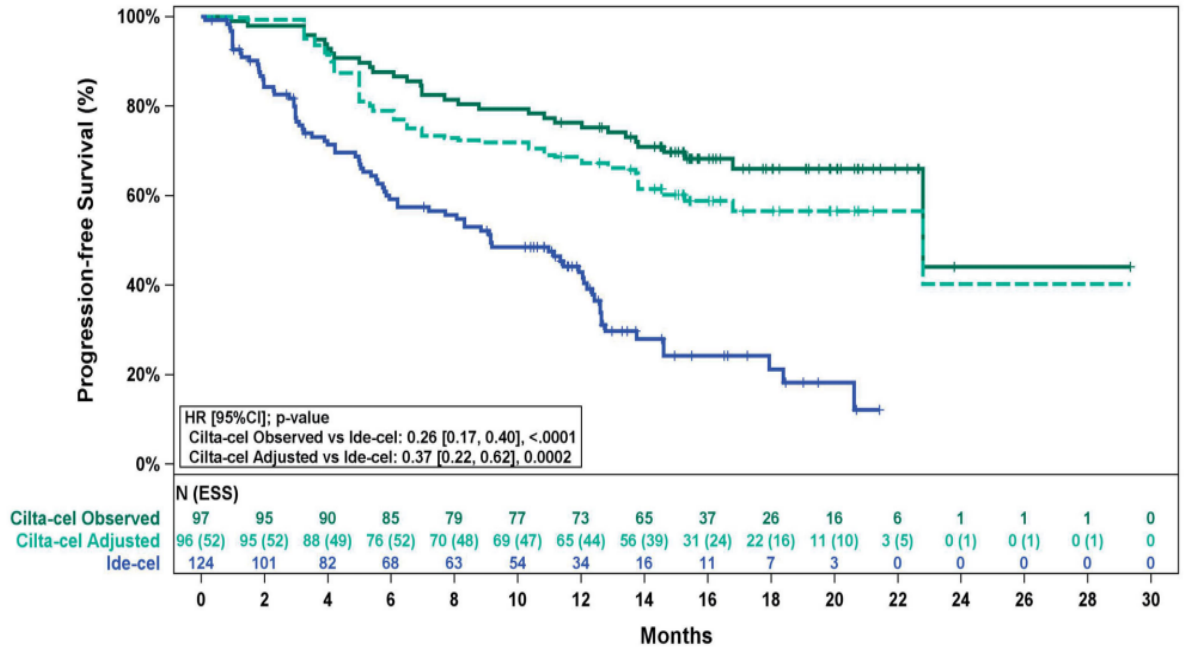


Figure 2. Observed (unadjusted) and adjusted (base case) Kaplan–Meier plots of progression-free survival. *Note.* Base case results adjusted for refractory sta cytogenetic profile, revised International Staging System stage, and all plasmacytomas. Abbreviations: ESS, effective sample size.

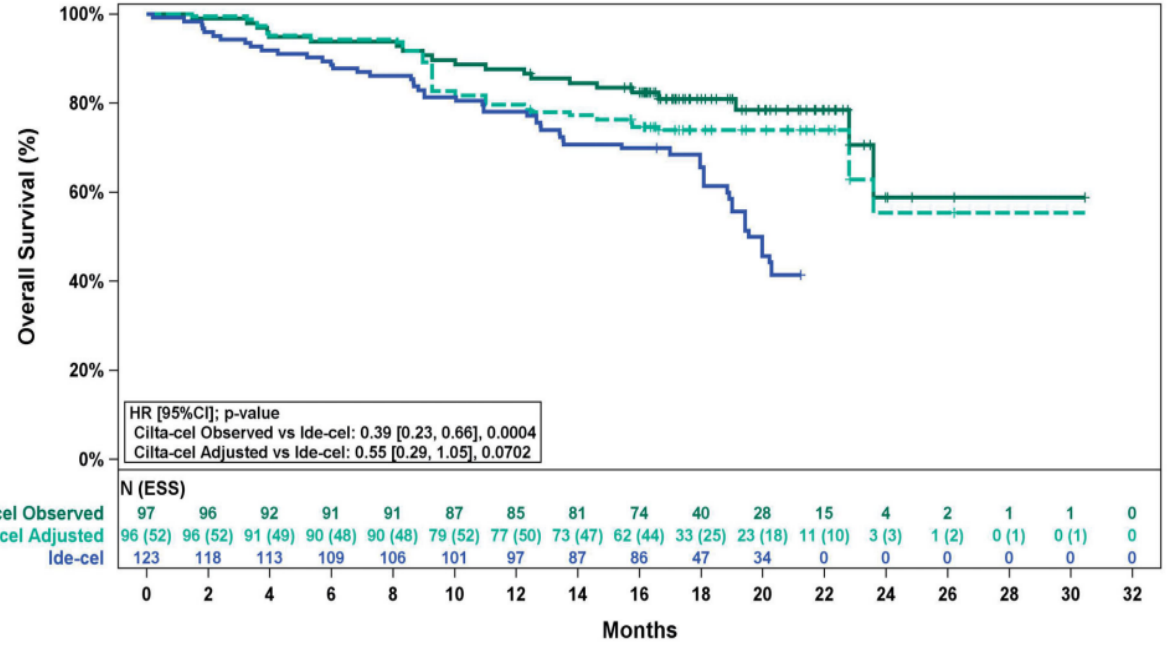


Figure 3. Observed (unadjusted) and adjusted (base case) Kaplan–Meier plots of overall survival. *Note.* Base case results adjusted for refractory status, cytogenet profile, revised International Staging System stage, and all plasmacytomas. Abbreviations: ESS, effective sample size.

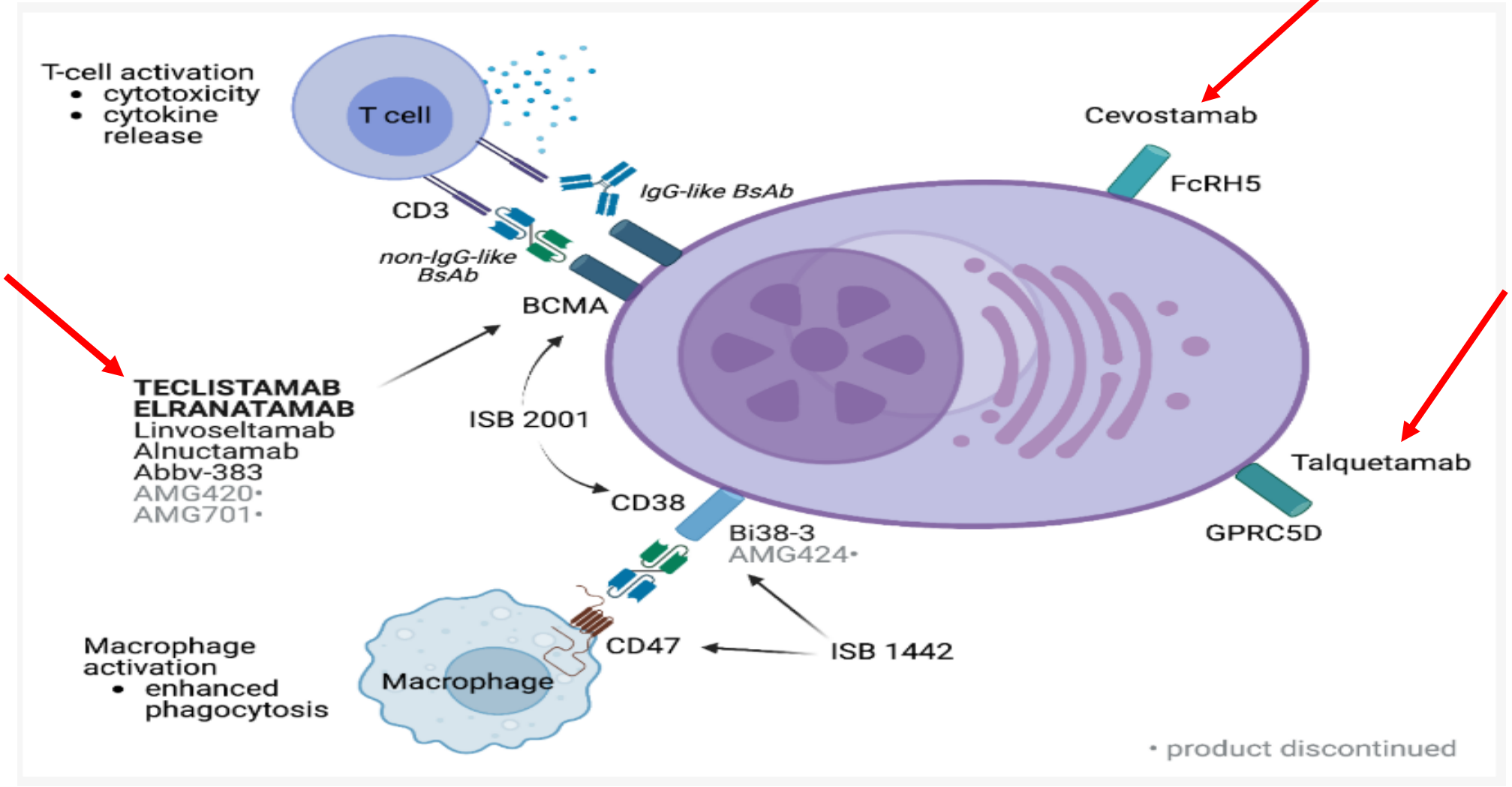
CMRO: 2021, VOL. 37, NO. 10, 1779–1788

CART is great , but not if you can’t get it…

- Extremely limited slots due to cell processing limitations even at academic/transplant centers
- Requires FACT certification to administer
- Insurance and reimbursement obstacles - Cost - $400-500k
- Possible 30-60 day processing time for cells requires effective bridging therapy in already refractory patient population
- Progress being made in all of these areas, but suspect will be years before these are fully addressed
- So until then we need off the shelf, accessible therapy…

BiTEs

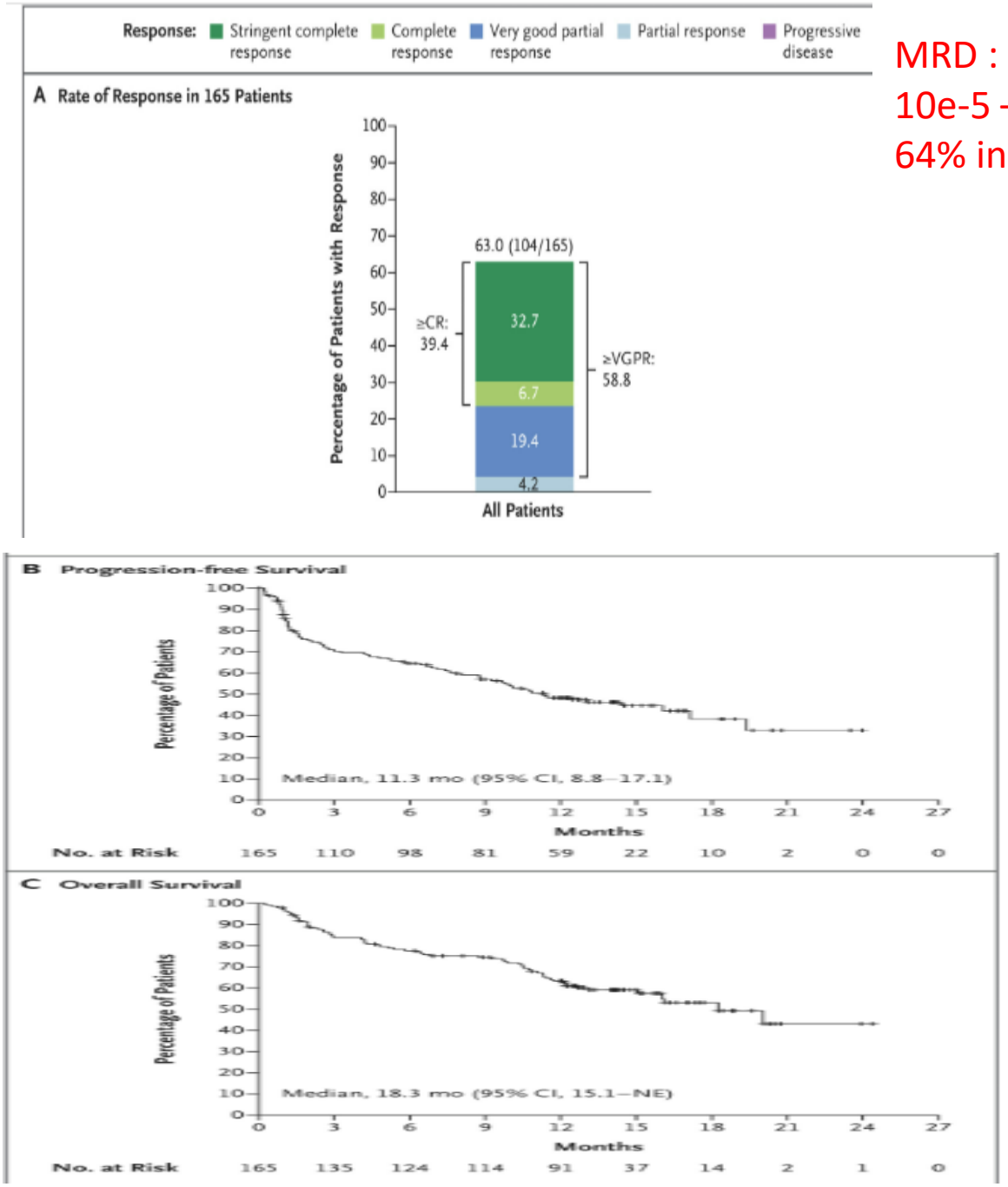
BiTEs Mechanism of Action



Cancers 2023, 15(6), 1819;

Teclistamab – MajesTEC-BCMA

- N=165 ; Phase I
- Primary end point -ORR
- Secondary end points - DOR, IMWG response, TNT, MRD, PFS, pharmacokinetics, safety
- At least 3 prior therapy lines, including triple-class exposure to an ImID, a PI, and an anti-CD38 antibody
- Relative even distribution by age, sex, R-ISS stage, cytogenetic risk, prior therapy
- Q week subcutaneousm at a dose of 1.5 mg/kg
- 0.06>0.3>1.5mg/kg step-up doses were separated by 2 to 4 days and were completed 2 to 4 days before the administration of the first full teclistamab dose and administered inpatient
- Premedications: dexamethasone acetaminophen, and diphenhydramine for each step-up dose and for the first full dose of teclistamab
- Weekly Treatment until intolerance or progression



MRD :
10e-5 – 17%
64% in ≥CR

N Engl J Med 2022; 387:495-505

Teclistimab – MajesTEC-1 – AE's

Table 2. Adverse Events in 165 Patients (Safety Population).*

Event	Any Grade	Grade 3 or 4
	no. of patients (%)	
Any adverse event	165 (100)	156 (94.5)
Hematologic		
Neutropenia	117 (70.9)	106 (64.2)
Anemia	86 (52.1)	61 (37.0)
Thrombocytopenia	66 (40.0)	35 (21.2)
Lymphopenia	57 (34.5)	54 (32.7)
Leukopenia	29 (17.6)	12 (7.3)
Nonhematologic		
Diarrhea	47 (28.5)	6 (3.6)
Fatigue	46 (27.9)	4 (2.4)
Nausea	45 (27.3)	1 (0.6)
Injection-site erythema	43 (26.1)	0
Pyrexia	45 (27.3)	1 (0.6)
Headache	39 (23.6)	1 (0.6)
Arthralgia	36 (21.8)	1 (0.6)
Constipation	34 (20.6)	0
Cough	33 (20.0)	0
Pneumonia	30 (18.2)	21 (12.7)
Covid-19	29 (17.6)	20 (12.1)
Bone pain	29 (17.6)	6 (3.6)
Back pain	27 (16.4)	4 (2.4)
Cytokine release syndrome†	119 (72.1)	1 (0.6)
Neurotoxic event	24 (14.5)	1 (0.6)

* Listed are adverse events of any grade that were reported in at least 15% of the patients, as well as neurotoxic events. Covid-19 denotes coronavirus disease 2019.
† In this analysis, events associated with cytokine release syndrome were graded according to the criteria of the American Society for Transplantation and Cellular Therapy.

N Engl J Med 2022; 387:495-505

Long-term follow-up from MajesTEC-1 of teclistamab, a B-cell maturation antigen (BCMA) x CD3 bispecific antibody, in patients with relapsed/refractory multiple myeloma (RRMM).

Niels W.C.J. van de Donk, Philippe Moreau, Alfred L. Garfall, Manisha Bhutani, Albert Oriol, Ajay K. Nooka, Thomas G. Martin, Laura Rosiñol, Maria-Victoria Mateos, Nizar J. Bahlis, Rakesh Popat, Britta Besemer, Joaquin Martinez-Lopez, Amrita Y. Krishnan, Michel Delforge, Danielle Trancucci, Raluca Verona, Tara Stephenson, Katherine Chastain, Surbhi Sidana; Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, Netherlands; Hematology Clinic, University Hospital Hôtel-Dieu, Nantes, France; Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; Levine Cancer Institute/Atrium Health, Charlotte, NC; Institut Català d'Oncologia and Institut Josep Carreras, Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain; Winship Cancer Center of Emory University, Atlanta, GA; University of California, San Francisco, San Francisco, CA; Hospital Clínic de Barcelona, IDIBAPS, Barcelona, Spain; University Hospital of Salamanca/IBSAL/CIC/CIBERONC, Salamanca, Spain; Arnie Charbonneau Cancer Institute, University of Calgary, Calgary, AB, Canada; University College London Hospitals NHS Foundation Trust, London, United Kingdom; University of Tuebingen, Tuebingen, Germany; Hematología Hospital 12 de Octubre, Madrid, Spain; City of Hope Comprehensive Cancer Center, Duarte, CA; University of Leuven, Leuven, Belgium; Janssen Research & Development, Raritan, NJ; Janssen Research & Development, Spring House, PA; Stanford University School of Medicine, Stanford, CA

Background: Teclistamab is the first approved off-the-shelf BCMA×CD3 bispecific antibody for the treatment of patients (pts) with RRMM based on data from the pivotal phase 1/2 MajesTEC-1 study (NCT03145181/NCT04557098). Moreau et al (*NEJM* 2022) reported rapid, deep, and durable responses: overall response rate (ORR) was 63% (39% ≥complete response [CR] rate), with a median duration of response (mDOR) of 18.4 mo, and median progression-free survival (mPFS) of 11.3 mo after a median follow-up (mFU) of 14.1 mo. Here, we present updated results with extended follow-up of ~2 y (22 mo). **Methods:** Eligible pts were aged ≥18 y, had documented MM (per IMWG 2016 criteria), and had received ≥3 prior lines of therapy (LOT), including a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 antibody. Prior BCMA-targeted therapy was not allowed in this cohort. Pts received teclistamab 1.5 mg/kg QW (the recommended phase 2 dose [RP2D]), with the option to switch to Q2W dosing if they achieved ≥partial response after ≥4 cycles of therapy in phase 1 or ≥CR for ≥6 months in phase 2. The primary endpoint was ORR (assessed per IMWG 2016 criteria by computerized algorithm). AEs were graded per CTCAE v4.03. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded per ASTCT guidelines. **Results:** As of Dec 9, 2022, 165 pts had received teclistamab at the RP2D (median age, 64 y; 58% male; 26% high-risk cytogenetics; 12% International Staging System stage III). Pts had a median of 5 prior LOT (range, 2–14): 92% daratumumab exposed; 78% triple-class refractory; 81% daratumumab-refractory; and 90% refractory to last LOT. At 22 mo mFU, 43% of pts achieved ≥CR, mDOR was 24 mo (95% CI, 16.2–not estimable [NE]), mDOR in pts achieving ≥CR was not reached (95% CI, 24.0–NE), mPFS was 12.5 mo (95% CI, 8.8–17.2), and median overall survival was 21.9 mo (95% CI, 16.0–NE). Hematologic AEs (any grade [gr]/gr 3/4) included neutropenia (72%/65%), anemia (54%/38%), thrombocytopenia (42%/22%), and lymphopenia (35%/33%). Infections occurred in 78% of pts (52% gr 3/4); key infections included respiratory (56%), COVID-19 (27%), other viral (10%), GI (8%), fungal (5%), PJP (4%), and hepatitis B (0.6%). CRS occurred in 72% of pts (0.6% gr 3; no gr 4/5); 5 (3%) pts reported 9 ICANS events (all gr 1/2; all resolved). 1 pt in phase 1 required a teclistamab dose reduction due to neutropenia. 6 treatment-related deaths have occurred (3 due to COVID-19). Of the 49 pts who remain on study, ~90% have received Q2W dosing. **Conclusions:** After ~2 y mFU, pts receiving teclistamab demonstrated deep and durable responses regardless of refractory status, with mPFS of 12.5 mo and mDOR of 24 mo (not reached in those achieving ≥CR). These long-term follow-up data support teclistamab as a safe and effective off-the-shelf BCMA bispecific therapy for pts with RRMM. Clinical trial information: NCT03145181, NCT04557098. Research Sponsor: Janssen Research & Development.

ASCO 2023 MajesTEC – 1 Update:

"After ~2 y mFU, pts receiving teclistamab demonstrated deep and durable responses regardless of refractory status, with mPFS of 12.5 mo and mDOR of 24 mo (not reached in those achieving ≥CR)."

Abstract 8011, ASCO 2023 Annual Meeting.

Alternate Teclistamab Schedule

8034 **Poster Session**

Durability of responses with biweekly dosing of teclistamab in patients with relapsed/refractory multiple myeloma achieving a clinical response in the majesTEC-1 study.

Saad Zafar Usmani, Lionel Karlin, Lotfi Benboubker, Hareth Nahi, Jesús San-Miguel, Danielle Trancucci, Keqin Qi, Tara Stephenson, Alfredo Perales-Puchalt, Katherine Chastain, Ajai Chari; Memorial Sloan Kettering Cancer Center, New York, NY; Centre Hospitalier Lyon Sud, Lyon, France; Hopital Bretonneau, Centre Hospitalier Régional Universitaire, Tours, France; Karolinska University Hospital at Huddinge, Stockholm, Sweden; University of Navarra, Pamplona, Spain; Janssen Research & Development, Raritan, NJ; Janssen Research & Development, Titusville, NJ; Janssen Research & Development, Spring House, PA; Mount Sinai School of Medicine, New York, NY

Background: Teclistamab is the first B-cell maturation antigen (BCMA) bispecific antibody approved for the treatment of relapsed/refractory multiple myeloma (RRMM) at a dose of 1.5 mg/kg weekly (QW) given subcutaneously. A less frequent dosing schedule offers added convenience and flexibility to patients, physicians, and caregivers. We evaluated the ability of patients to maintain their responses after transitioning from QW to every other week (Q2W) dosing schedules in the pivotal phase 1/2 MajesTEC-1 trial (NCT03145181/NCT04557098). **Methods:** Eligible patients had RRMM and received ≥3 prior lines of therapy including a proteasome inhibitor, immunomodulatory drug, and anti-CD38 antibody. Prior BCMA-targeted therapy was not allowed in this cohort. Patients received the recommended phase 2 dose (RP2D) of 1.5 mg/kg teclistamab QW, with the option to switch to Q2W dosing if patients achieved a confirmed partial response or better after ≥4 cycles of treatment (phase 1) or a confirmed complete response (CR) or better for ≥6 months (phase 2). Response was assessed per IMWG 2016 criteria. **Results:** As of Dec 9, 2022, 165 patients in the pivotal cohort had received teclistamab at the RP2D. Of 104 responders, 60 patients switched to Q2W dosing; 50 met the protocol-defined criteria for switching, and 10 switched who did not meet the criteria (4 due to adverse events [AEs]; 6 due to other reasons). Patients who switched had a median age of 64 years, 58% were male, 25% had high-risk cytogenetics, 7% had extramedullary plasmacytomas, and 3% had International Staging System stage III disease at baseline. Patients received a median of 4 prior lines of therapy, and 75% were triple-class refractory. At the time of switch, 49 (82%) patients achieved ≥CR, and 11 (18%) had a very good partial response. Median time to switch from QW to Q2W dosing was 11.1 months (range, 3–20). At median 11.1-month (range, 2–24) follow-up since switching, the median duration of response from the date of switch was 20.5 months (range, 1–23), with 40/60 patients still in response and ongoing treatment. Of the remaining patients, 13/60 have progressed (median time from switch to progression not estimable), 2 discontinued due to AEs, 1 discontinued for other reason, and 4 died. Additional results will be presented. **Conclusions:** Overall, patients from the MajesTEC-1 study who transitioned from QW to less frequent Q2W dosing of teclistamab had sustained remission, with a median duration of response of 20.5 months from the date of switch. Clinical trial information: NCT03145181, NCT04557098. Research Sponsor: Janssen Research & Development.

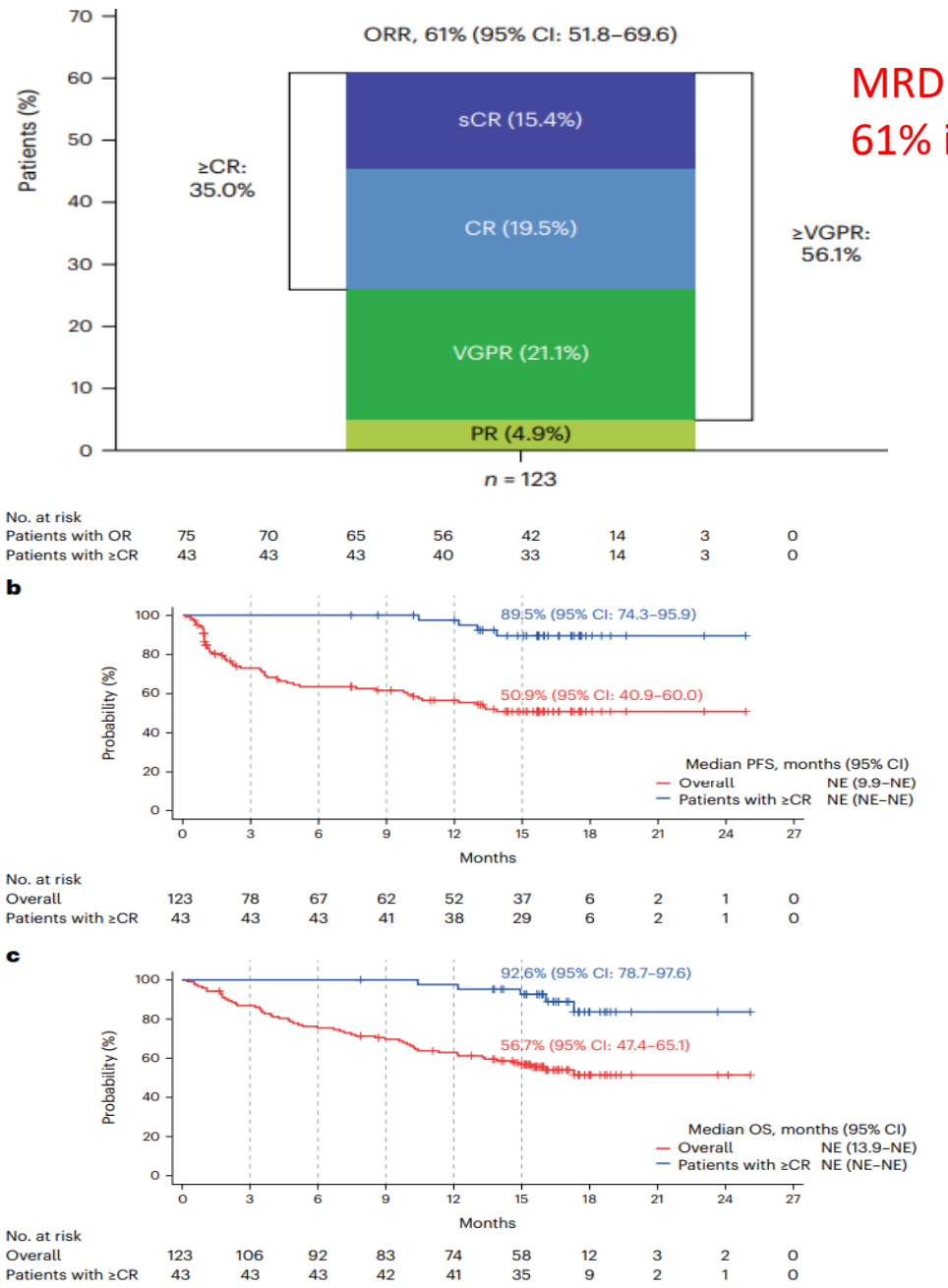
- **If CR or better for sustained for 6 months could transition to every other week dosing**
- **Remission was sustained with median DOR of 20.5 months**
- **Needs further study and FDA label remains weekly dosing**
- **Anecdotally, many myeloma physicians transitioning to EOW dosing in responders even before 6 months**

Abstract 8034, ASCO 2023 Annual Meeting

Elranatamab -MagnetisMM-3 BCMA

- **123 RR Myeloma patients; no prior BCMA directed therapy ; Phase II**
- **primary endpoint –ORR per IMWG criteria**
- **Secondary endpoints- CR, TTR, DOR, duration of CR, MRD negativity rate, PFS, OS**
- **refractory to at least one PI, one ImID and one anti-CD38 antibody, and disease relapsed or refractory to their last antimyeloma regimen**
- **Relative even distribution by age, sex, R-ISS stage, cytogenetic risk, prior therapy**
- **step-up dose 1 of 12 mg on Day 1, step-up dose 2 of 32 mg on Day 4, followed by the first treatment dose of 76 mg on Day 8, and then 76 mg weekly thereafter through week 24**
- **After six cycles, if PR or better or better lasting at least 2 months switched to a Q2W dosing**

MRD rates: 61% in ≥CR



Nature Medicine volume 29, pages2259–2267 (2023)

Elranatamab- MagnetisMM -3 –AEs

Table 2 | Treatment-emergent adverse events occurring in ≥20% of patients receiving elranatamab

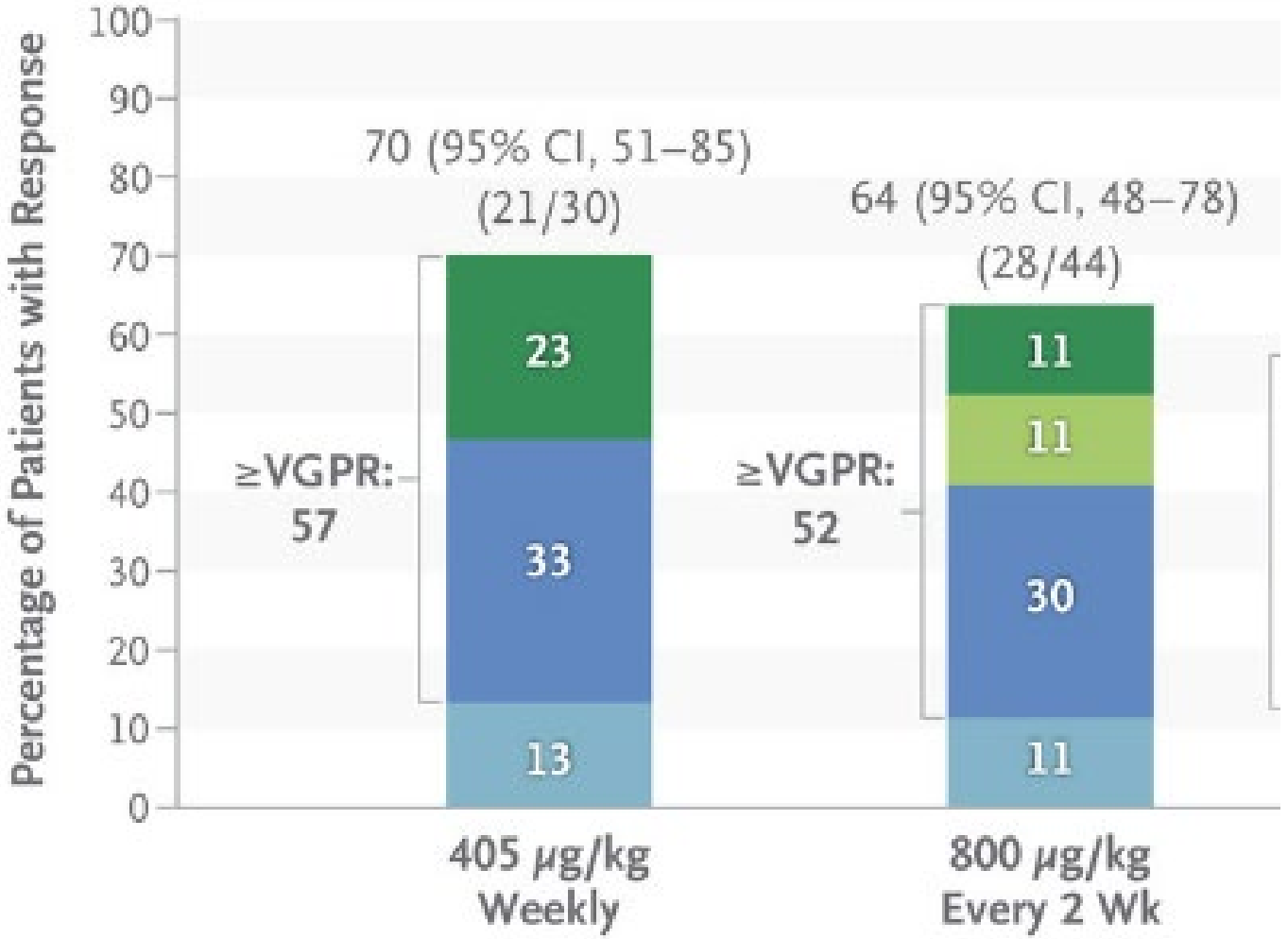
Treatment-emergent adverse events, *n* (%)	*n*=123	
	Any grade	Grade 3 or 4
Any treatment-emergent adverse event	123 (100)	87 (70.7)
Hematologic[a]		
Anemia	60 (48.8)	46 (37.4)
Neutropenia	60 (48.8)	60 (48.8)
Thrombocytopenia	38 (30.9)	29 (23.6)
Lymphopenia	33 (26.8)	31 (25.2)
Nonhematologic		
Cytokine 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

[a]Preferred terms included in hematologic treatment-emergent adverse events are provided in Supplementary Table 2. [b]Includes preferred terms in COVID-19 (narrow) standardized MedDRA queries. [c]25/36 (69.4%) patients developed COVID-19 or COVID-19 pneumonia and 10/36 (30.6%) only had a positive SARS-CoV-2 test without developing the disease. MedDRA, Medical Dictionary for Regulatory Activities.

Nature Medicine volume 29, pages2259–2267 (2023)

Talquetamab - MonumenTAL-1- GPRC5D

- phase 1/2 study
- Phase I published NEJM December 2022
- Primary endpoints - frequency and type of DLTs, AE's, and laboratory abnormalities
- secondary end points: response, pharmacokinetics, pharmacodynamics, and immunogenicity, MRD
- Phase I portion examined weekly vs biweekly subcutaneous and intravenous schedules
- **Ultimately settled on recommened phase 2 and subsequent FDA approved doses of either 0.4 mg/kg weekly or 0.8 mg/kg biweekly**



N Engl J Med 2022; 387:2232-2244

HEMATOLOGIC MALIGNANCIES—PLASMA CELL DYSCRASIA

8036 **Poster Session**

Pivotal phase 2 MonumenTAL-1 results of talquetamab (tal), a GPRC5DxCD3 bispecific antibody (BsAb), for relapsed/refractory multiple myeloma (RRMM).

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Background: Tal is a first-in-class BsAb targeting the novel antigen G protein–coupled receptor family C group 5 member D. In MonumenTAL-1 (NCT03399799/NCT04634552), tal showed promising efficacy and clinically manageable safety in patients (pts) with RRMM. We report pivotal phase 2 results in pts with and without prior T-cell redirection therapy. **Methods:** Eligible pts were intolerant to or progressed on established therapies (phase 1) or had ≥3 prior lines of therapy (LOT), including ≥1 proteasome inhibitor, ≥1 immunomodulatory drug, and ≥1 anti-CD38 antibody (phase 2). Pts received RP2Ds of SC tal 0.4 mg/kg QW or 0.8 mg/kg Q2W with step-up doses. CRS and ICANS were graded by ASTCT criteria; all other AEs were graded by CTCAE v4.03. Response was assessed by IMWG criteria. Data cut-off was Sep 12, 2022 for efficacy and Oct 19, 2022 for safety. Data will be updated for the meeting. **Results:** From the pivotal cohorts, 288 pts received tal 0.4 mg/kg QW (n = 143) or 0.8 mg/kg Q2W (n = 145), and 51 pts with prior T-cell redirection therapy received either dose. In the QW, Q2W, and prior T-cell redirection cohorts, respectively, median prior LOT was 5–6; 74%, 69%, and 84% were triple-class refractory and 29%, 23%, and 41% were penta-drug refractory; 15%, 11%, and 12% received prior belantamab. In the prior T-cell redirection cohort, 71% received CAR-T therapy, 35% received a BsAb, and 6% received both. In the pivotal cohorts, ORR was 74% (QW, 14.9 mo median follow-up [mF/U]) and 73% (Q2W, 8.6 mo mF/U), with very good partial response or better (≥VGPR) in 59% (QW) and 57% (Q2W). ORR was consistent across subgroups, including baseline ISS stage III disease, cytogenetic risk, number of prior LOT, and belantamab exposure. In pts with baseline plasmacytomas, ORR was 49% in both pivotal cohorts. In the prior T-cell redirection cohort, ORR was 63% (53% ≥VGPR) at 11.8 mo mF/U. Median PFS was 7.5, 11.9 (61% censored), and 5.1 mo in the QW, Q2W, and prior T-cell redirection cohorts, respectively. Common AEs included CRS (79%, 75%, 77%), skin-related AEs (56%, 71%, 69%), nail-related AEs (54%, 53%, 61%), and dysgeusia (50%, 48%, 61%); most were grade 1/2 and clinically manageable. ICANS occurred in 11%, 11%, and 3% of pts. Infections occurred in 58%, 65%, and 71% (grade 3/4: 22%, 16%, 26%) of pts, with low rates of opportunistic infections. AEs resulted in dose reductions in 15%, 8%, and 10% of pts and discontinuation in 5%, 8%, and 6%. There were no tal-related deaths. Responders to tal had higher T cell counts and lower frequencies of exhausted T cells and CD38+ Tregs vs non-responders. **Conclusions:** Pivotal phase 2 tal data showed > 70% ORR in heavily pretreated pts with RRMM. High response rates were also seen in pts with prior T-cell redirection therapy. The safety profile was clinically manageable with low rates of high-grade infections and tal discontinuations. Clinical trial information: NCT03399799, NCT04634552. Research Sponsor: Janssen Research & Development, LLC.

ASCO 2023 update:

- phase 2 results in pts with and without prior T-cell redirection therapy following up on december 2022 NEJM phase I data
- updated Pivotal phase 2 tal data showed persistent > 70% ORR in heavily pretreated pts with RRMM
- High response rates were also seen in pts with prior T-cell redirection therapy
- Median PFS -7.5, 11.9, and 5.1 mo in the QW, Q2W, and prior T-cell redirection cohorts
- Updated data led to aug 2023 FDA approval

Abstract 8026. ASCO 2023 Annual Meeting.

Talquetamab – MonumenTAL-1 – AE's

Table 2. Adverse Events.*

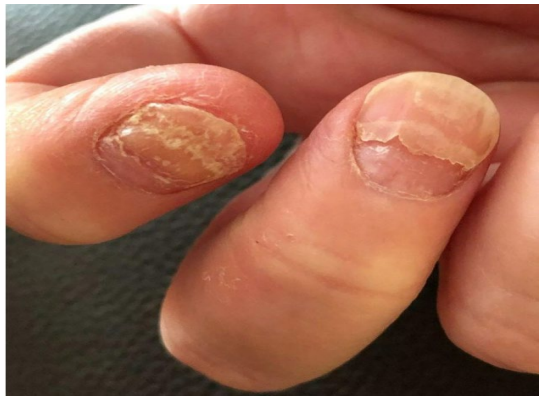
Event	Subcutaneous Talquetamab, 405 μg Weekly (N=30)		Subcutaneous Talquetamab, 800 μg Every 2 Wk (N=44)		Intravenous Talquetamab, All Doses (N=102)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)					
Any adverse event	30 (100)	26 (87)	44 (100)	38 (86)	102 (100)	92 (90)
Hematologic event						
Anemia	18 (60)	9 (30)	19 (43)	10 (23)	59 (58)	34 (33)
Neutropenia	20 (67)	18 (60)	16 (36)	14 (32)	48 (47)	27 (26)
Lymphopenia	12 (40)	12 (40)	17 (39)	17 (39)	53 (52)	48 (47)
Thrombocytopenia	11 (37)	7 (23)	10 (23)	5 (11)	36 (35)	13 (13)
Leukopenia	12 (40)	9 (30)	8 (18)	6 (14)	38 (37)	16 (16)
Nonhematologic event						
Cytokine release syndrome	23 (77)	1 (3)	35 (80)	0	50 (49)	5 (5)
Skin-related event†	20 (67)	0	31 (70)	1 (2)	24 (24)	0
Dysgeusia	19 (63)	NA	25 (57)	NA	38 (37)	NA
Fatigue	10 (33)	1 (3)	12 (27)	0	37 (36)	1 (1)
Nail-related event‡	17 (57)	0	12 (27)	1 (2)	20 (20)	0
Pyrexia	10 (33)	0	8 (18)	0	32 (31)	0
Headache	6 (20)	0	11 (25)	0	35 (34)	2 (2)
Rash-related event§	14 (47)	0	13 (30)	7 (16)	15 (15)	1 (1)
Diarrhea	9 (30)	0	7 (16)	0	29 (28)	4 (4)
Cough	6 (20)	0	5 (11)	0	36 (35)	0
Dry mouth	9 (30)	0	25 (57)	0	7 (7)	0
Nausea	9 (30)	0	7 (16)	0	23 (23)	0
Arthralgia	7 (23)	0	4 (9)	0	33 (32)	3 (3)
Decreased weight	9 (30)	0	14 (32)	1 (2)	12 (12)	0
Increased alanine aminotransferase	6 (20)	1 (3)	13 (30)	3 (7)	13 (13)	2 (2)
Increased aspartate aminotransferase	3 (10)	0	15 (34)	3 (7)	14 (14)	2 (2)
Back pain	3 (10)	0	9 (20)	0	22 (22)	1 (1)
Hypophosphatemia	8 (27)	5 (17)	8 (18)	3 (7)	19 (19)	14 (14)
Dysphagia	11 (37)	0	12 (27)	0	5 (5)	0
Decreased appetite	6 (20)	1 (3)	9 (20)	0	15 (15)	1 (1)
Constipation	2 (7)	0	6 (14)	0	18 (18)	2 (2)
Increased γ-glutamyltransferase	6 (20)	1 (3)	10 (23)	3 (7)	14 (14)	3 (3)

* Listed are adverse events of any grade that were reported in at least 15% of the patients. NA denotes not available.
† Skin-related adverse events included asteatotic eczema, dry skin, eczema, pruritus, exfoliation, fissures, hyperpigmentation, lesions, skin toxic effects, and ulcers.
‡ Nail-related adverse events included nail-bed disorder, discoloration, disorders, dystrophy, hypertrophy, ridging, onycholysis, and onychomadesis.
§ Rash-related adverse events included contact dermatitis, dermatitis, erythematous rash, generalized exfoliative dermatitis, maculopapular rash, and rash.

N Engl J Med 2022; 387:2232-2244

Talquetamab – Majestic -1 : Unique AE's

- GPRC5D is restricted to plasma cells and hard keratinized tissues resulting AE's in skin and nails



- Consider dermatology consultations and emollients
- For dysgeusia consider GI, nutrition consultations, good oral care, and saliva substitutes particularly if causing weight loss or compromising QOL
- Best preventative and therapeutic approaches to dermatologic and oral AEs have yet to be identified

Adverse Events

Event	Talquetamab 405 μg Weekly (N=30)		Talquetamab 800 μg Every 2 Wk (N=44)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Any adverse event	30 (100)	26 (87)	44 (100)	38 (86)
Cytokine release syndrome	23 (77)	1 (3)	35 (80)	0
Skin-related event*	20 (67)	0	31 (70)	1 (2)
Dysgeusia	19 (63)	NA	25 (57)	NA

* Skin-related adverse events included asteatotic eczema, dry skin, eczema, pruritus, exfoliation, fissures, hyperpigmentation, lesions, skin toxic effects, and ulcers. NA denotes not available.

N Engl J Med 2022; 387:2232-2244

Cevostamab – CAMMA1 Trial –FcRH5

- 160 pts; phase 1; RRMM for “which no established therapy is available or appropriate”; median lines of prior therapy
- q 21 day cycle/IV infusion with step dosing Cevostamab
- Cevostamab is continued for a total of 17 cycles, unless progressive disease or unacceptable toxicity occurs –time limited therapy

	Talquetamab	Cevostamab
Target	GPRC5D	FcRH5
Schedule	Weekly and every 2 wk SC	Every 3 wk IV
Patients	55	161
Median prior lines	5–6	6
Prior BCMA-targeted therapy	22%	34%
Triple-class refractory and penta-refractory	76% and 21%	85% and 68%
CRS, all (grade 3/4)	75% (2%)	81% (1%)
ICANS, all (grade 3/4)	NA	14% (0.6%)
ORR	69% (higher-dose cohort)	57% (higher-dose cohort)
CR at higher doses	16%	8%
Other notable adverse events	Skin, nail, taste changes	—

Blood (2021) 138 (Supplement 1): 15; ASCO Post, September 2022.

Cevostamab – AE's

N (%) of pts	Any AE (N=160)	Any Gr 3–4 AE (N=160)
Any AE*	159 (99.4)	94 (58.8)
Cytokine release syndrome	128 (80.0)	2 (1.3)[‡]
Infections (SOC)	68 (42.5)	30 (18.8)
Neurological/Psychiatric (SOC)	65 (40.6)	6 (3.8)[‡]
Anemia	51 (31.9)	35 (21.9)[‡]
Diarrhea	42 (26.3)	1 (0.6)[‡]
Cough	37 (23.1)	0
Nausea	35 (21.9)	0
Neutropenia	29 (18.1)	26 (16.3)
Infusion-related reaction	28 (17.5)	0
Fatigue	26 (16.3)	3 (1.9)[‡]
Aspartate aminotransferase increased	25 (15.6)	10 (6.3)
Hypomagnesaemia	25 (15.6)	1 (0.6)[‡]
Pyrexia	25 (15.6)	0
Neutrophil count decreased	24 (15.0)	22 (13.8)
Alanine aminotransferase increased	24 (15.0)	11 (6.9)[‡]
Any serious AE	89 (55.6)	
Any TR serious AE[†]	40 (25.0)	
Any Gr 5 (fatal) AE	24 (15.0)[§]	
Any TR Gr 5 (fatal) AE[†]	1 (0.6)[¶]	
Any AE leading to withdrawal of cevostamab	16 (10.0)	
Any TR AE leading to withdrawal of cevostamab[†]	7 (4.4)	

*Listed preferred terms are those with ≥15% incidence; [†]AE considered related to cevostamab by the investigator; [‡]Gr 3 only; [§]acute kidney injury, n=1; hemophagocytic lymphohistiocytosis, n=1; malignant neoplasm progression, n=17; plasma cell myeloma, n=1; progressive disease, n=1; respiratory failure, n=3; [¶]hemophagocytic lymphohistiocytosis, n=1

AE, adverse event; SOC, System Organ Class; TR, treatment-related

Cross Trial Data- BiTEs

Name	Target	Antibody construct	Triple-class refractory (median LoT)	Trial phase	Schedule	Preliminary response/ activity	Safety	Current status (ClinicalTrials .gov)
Elranatamab[41]	BCMA-CD3	Humanized IgG2a Fc	91% (median 6 LoT; 22% prior anti-BCMA)	Phase 1	Weekly or every 2 wk Sc	ORR=64% for doses ≥215 µg/kg	67% CRS (gr 1–2)	MagnetisMM-1 Recruiting NCT03269136
Teclistamab[40]	BCMA-CD3	Humanized IgG4 Fc	77.8% (median 5 LoT; prior anti-BCMA not permit-ted)	Phase 1/2	Weekly Sc	ORR=63%	72.1% CRS (gr 3, 0.6%; no gr 4) 14.5% neurotoxicity (1 gr 4 event) 44.8% ≥ gr 3 infection	MajestTEC-1 Recruiting NCT03145181
Talquetamab[46]	GPRC5D-CD3	Humanized IgG4 Fc	Weekly: 77% (median 6 LoT; 30% prior anti-BCMA) Biweekly: 65% (median 5 LoT; 17% prior anti-BCMA)	Phase 1/2	Weekly or biweekly Sc	Weekly: ORR=70% Biweekly: ORR=71%	Weekly: 73% CRS (1 gr 3) Biweekly: 78% CRS (gr 1–2)	MonumenTal-1 Recruiting NCT03399799
Cevostamab[45]	FcRH5-CD3	Humanized IgG1 Fc	85% (median 6 LoT; 33.5% prior anti-BCMA)	Phase 1	Q21d IV	ORR=54.5% at 160-mg-dose level	80.7% CRS (1.3% ≥ gr 3) 18.8% ≥ gr 3 infection 14.3% neurotoxicity (0.3% ≥ gr 3)	Recruiting NCT03275103

Hematology Am Soc Hematol Educ Program (2022) 2022 (1): 163–172

The Step-Up Dosing Inpatient Burden and Subsequent outpatient dosing questions

- Bed utilization by a patient with often no acute issues/only G1 CRS
- Hospitals lose cost of step up doses due to lack of inpatient reimbursement
- Patients have to be in a hospital for approximately 1 full week for 3 doses of subcutaneous treatment – QOL issue

P940 AN OUTPATIENT MODEL FOR TECLISTAMAB STEP-UP DOSING ADMINISTRATION – INITIAL EXPERIENCES AT FOX CHASE CANCER CENTER BMT PROGRAM.

Topic: 14. Myeloma and other monoclonal gammopathies - Clinical

Asya Nina Varshavsky-Yanovsky*[1], Michael Styler[1], Rashmi Khanal[1], Peter Abdelmessieh[1], Henry Fung[1]

[1]*Bone Marrow Transplant And Cellular Therapies, Fox Chase Cancer Center, Philadelphia, United States*

- Teclistamab step-up doses were administered on days 1, 3 and 8
- patients were required to stay within 1 hour from cancer center with caregiver during the step-up observation period (day 1-10)
- Both the patient and caregiver received education on CRS & ICANS
- Safety monitoring protocol included daily evaluation in the outpatient clinic as well as home monitoring of vital signs and scheduled 8pm physician phone call on days 1-5 and 8-10, within 48h observation window after 3 step-up doses.
- CBC, CMP, CRP and ferritin were monitored at each visit
- Patients were observed for 6 hours in the clinic after each step-up dose administration
- Patients with symptoms of CRS or ICANS of any grade were admitted to the inpatient unit for observation and management.
- 5/9 patients never required admission

Abstract P940. European Hematology Association 2023 Annual Congress.

8033 Poster Session

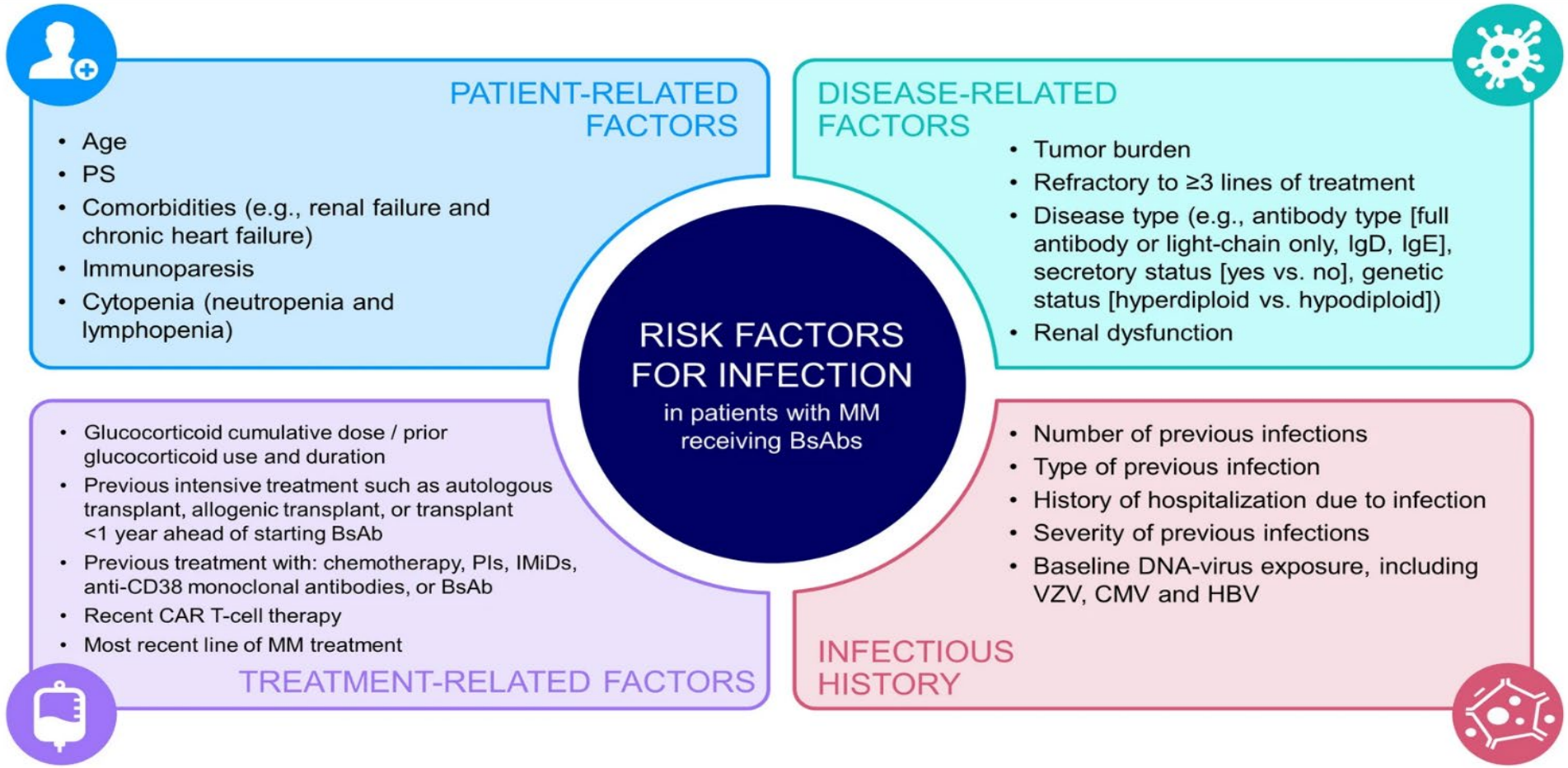
Evaluation of prophylactic tocilizumab (toci) for the reduction of cytokine release syndrome (CRS) to inform the management of patients (pts) treated with teclistamab in MajesTEC-1.

Niels W.C.J. van de Donk, Alfred L. Garfall, Lotfi Benboubker, Katarina Uttervall, Kaz Groen, Laura Rosiñol, Caroline Hodin, Tara Stephenson, Danielle Trancucci, Alfredo Perales-Puchalt, Rachel Kobos, Arnob Banerjee, Maria-Victoria Mateos; Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, Netherlands; Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; Hopital Bretonneau, Centre Hospitalier Régional Universitaire, Tours, France; Karolinska University Hospital, Stockholm, Sweden; Amsterdam UMC, Amsterdam, Netherlands; Hospital Clínic de Barcelona, IDIBAPS, Barcelona, Spain; Janssen Research & Development BE, Antwerp, Belgium; Janssen Research & Development, Spring House, PA; Janssen Research & Development, Raritan, NJ; Janssen Research & Development, Springhouse, PA; University Hospital of Salamanca, Salamanca, Spain

- 14 pts
- Toci (single 8 mg/kg IV dose) was given ≤4 hours before the first teclistamab step-up dose
- CRS occurred in 4 pts (29%; no gr ≥3 CRS); *remember 72% CRS rate in MajesTEC-1 trial*
- no new safety signals and no evidence of impact on response to teclistamab
- Potential to reduce need for admissions
- *Toci expensive but Single dose of Toci costs less than cost inpt stay/ramp up doses*
- *Need larger studies – similar studies currently being done at multiple centers*

Abstract 8033. ASCO 2023 Annual Meeting.

BiTEs- Infection Risk



BsAb bispecific antibody, CAR-T chimeric antigen receptor T-cell, CMV cytomegalovirus, HBV hepatitis B virus, IMiD immunomodulatory drug, MM multiple

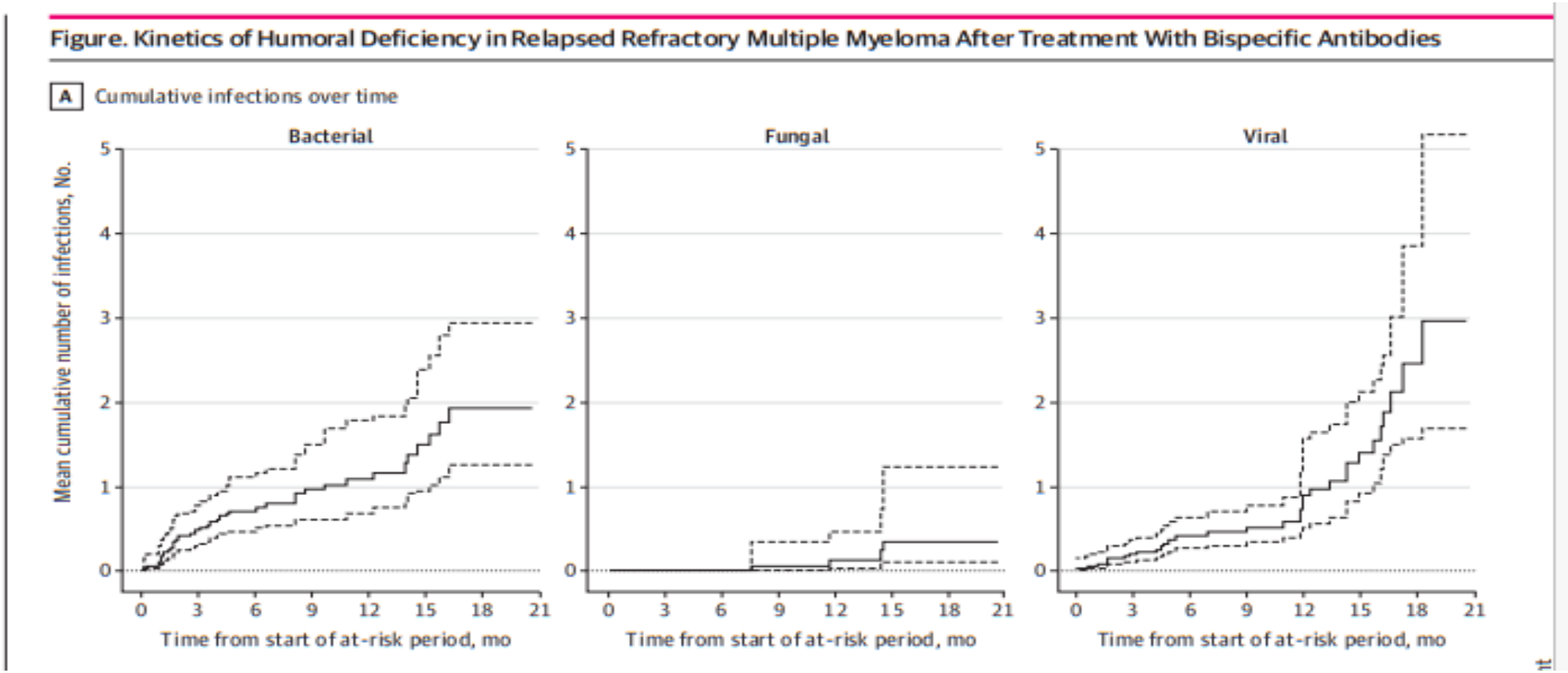
Blood Cancer Journal volume 13, Article number: 116 (2023)

BiTEs: Infection Risk

Table 3. Literature summary of infection data from BsAb clinical trials in MM patients.

Drug	Target	Study	Phase	Safety cohort *N*	No. of patients receiving RP2D *n*	Duration of treatment (range)	Infection AEs *n* (%)	Treatment-related infection AEs *n* (%)	Serious infection TEAEs *n* (%)	Infection AEs leading to discontinuation *n* (%)	Infection AEs resulting in death *n* (%)
Teclistamab		MajesTEC-1 [24]	I/II	165[a]	165	8.5 months (0.2–24.4)	Any grade: (76.4)	Any grade: –	–	2 (1.21)[b,†]	16 (8.48%)[c]
							Grade 3/4: (44.8)	Grade 3/4: –			Considered related: 4 (2.4)
	BCMA x CD3	MajesTEC-2 [40] (+daratumumab +lenalidomide)	Ib	32[e]	19	–	Any grade: 29 (90.6)	–	–	2 (6.3)[f]	2 (6.3)[g]
							Grade 3/4: 12 (37.5)				
Elranatamab	BCMA x CD3	MagnetisMM-1 [46–48]	I	55[h]	–	–	–	–	–	–	1
							Grade 3/4: 15 (27.3)				
		MagnetisMM-3 [32]	II	123[i]	123	5.6 months (0.03–19.8)	Any grade: (66.7)	–	–	8 (6.5)	2 (1.6)
							Grade 3/4: [illegible]				
Talquetamab	GPRC5D x CD3	MonumenTAL-1 [9, 33, 37, 115]	I/II	0.4 mg/kg QW: 143[u]	288	–	Any grade: 46.7%[v]	–	–	–	–
							Grade 3/4: 6.7%[v]				
				0.8 mg/kg Q2W: 145[u]			Any grade: 38.6%[v]	–		–	–
							Grade 3/4: 9.1%[v]				

BiTEs Infection Risk – 88 patients – 4 deaths (5%)



- cumulative risk with duration of therapy
  - 3 months- 41%
  - 9 months- 64%
  - 15 months-70%.

- Type of infection
  - Bacterial – 54%
  - Viral – 41%
  - Fungal- 5%

JAMA Network Open. October 28, 2022.

BiTE Infection Risk - Mitigation Measures

- No RCT exists– expert panel opinion only
- Vaccinations
- Heighted surveillance/monitoring
- Prophylactic Anti-infectives
- IVIG replacement

Vaccines and heighted surveillance/monitoring

- All age appropriate vaccines, including influenza, covid, new RSV vaccine should be up to date
- Low index of suspicion to test/screen for viral OI (hep, parvo, Adeno, cmv, ebv, etc) if clinical syndrome but routine asymptomatic screening not recommended
- Low threshold to consult ID

Prophylactic Anti-infectives with BiTE therapy

- Bacterial:
  - not recommended unless…
  - prolonged neutropenia high risk of infections and patients with a history of recurrent bacterial infections
  - If using anti-bacterial prophylaxis-levofloxacin
- Fungal
  - Not recommended unless prior history of fungal infections
- PJP
  - recommended for all patients (Bactrim, dapsone, or atovaquone); 3-5% PJP incidence in respective BiTE trials
- Viral
  - recommended for all patients (Acyclovir or Valacyclovir)

Blood Cancer Journal volume 13, Article number: 116 (2023)

• IVIG replacement

- >70% hypoIgG incidence in FDA approved BiTE trials
- Patients whose IgG levels <400 mg/dl
- Patients who have experienced ≥2 severe recurrent infections by encapsulated bacteria, regardless of IgG level
- Patients with a life-threatening infection
- Patients with documented bacterial infection with no or insufficient response to antibiotic therapy

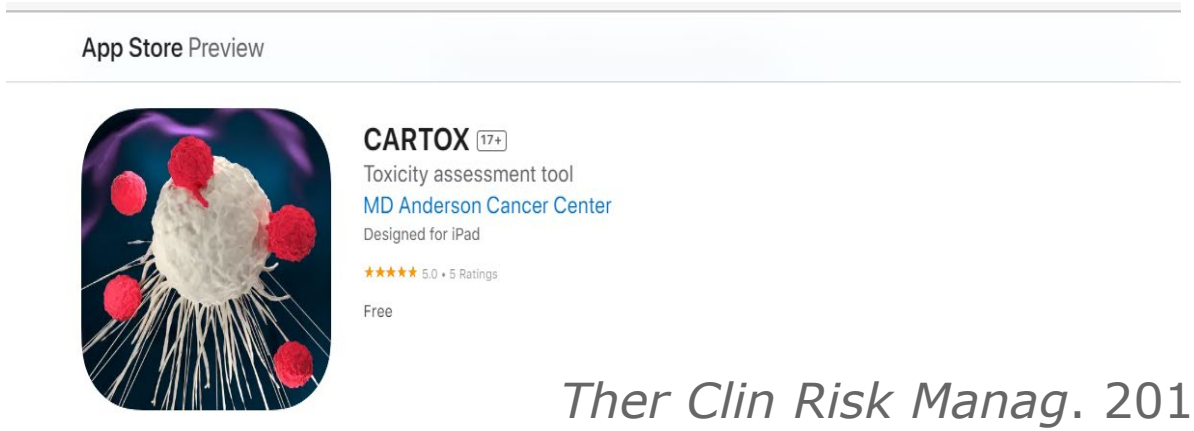
Blood Cancer Journal volume 13, Article number: 116 (2023)

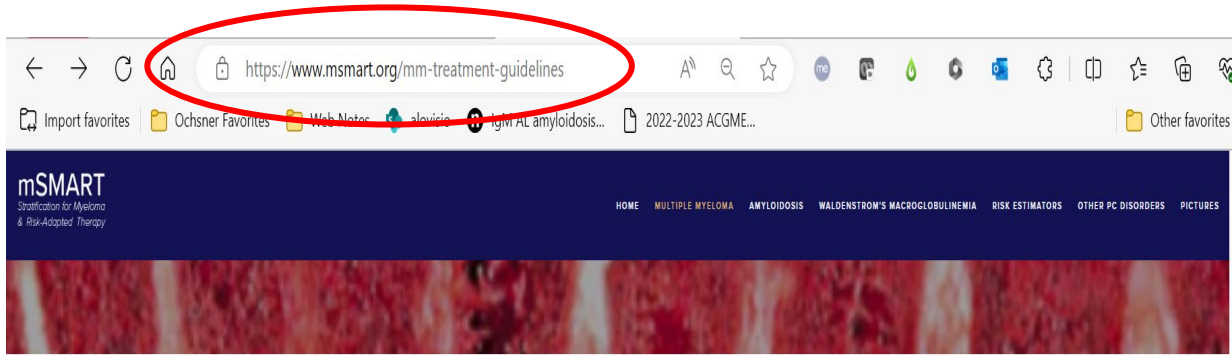
IVIG replacement

- Monthly IVIG treatment for the duration of immunoparesis, and in the absence of life-threatening infectious manifestations, until Ig levels are ≥400 mg/dl
- Ig levels should be monitored monthly during Ig treatment serum
- Levels alone are not adequate to inform on an individual's capacity to mount an antibody response
- Monitor the frequency of infections
- Maintain BsAb dosing during Ig treatment

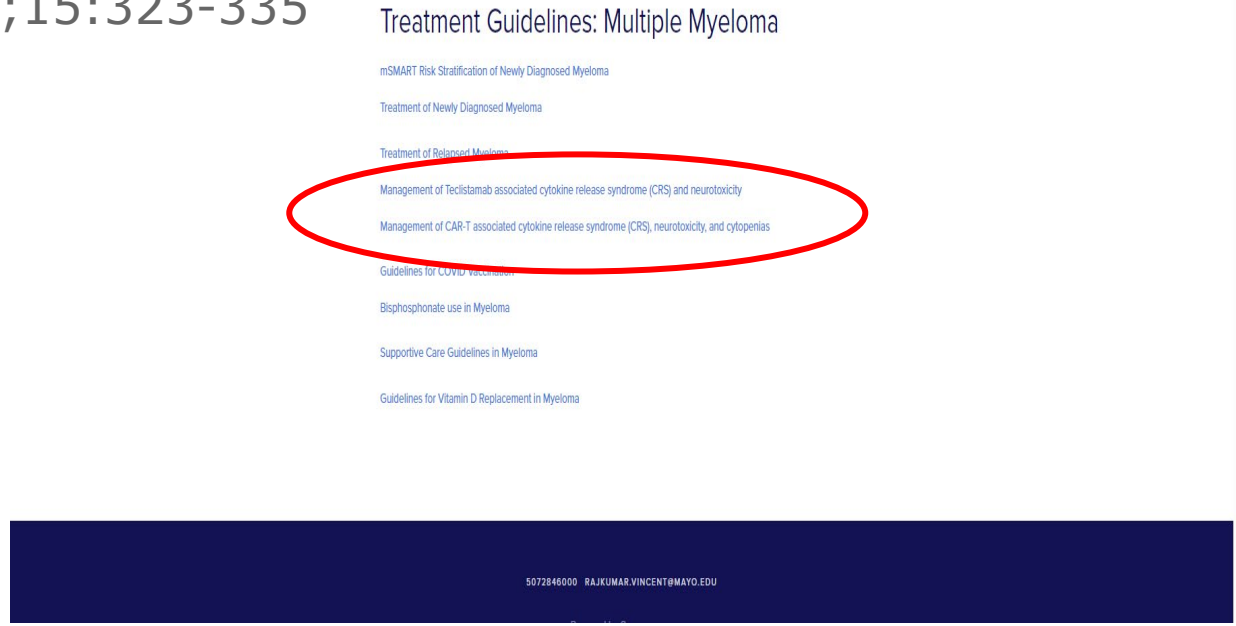
Blood Cancer Journal volume 13, Article number: 116 (2023)

Management of BiTE Toxicities –CRS/ICANS





Ther Clin Risk Manag. 2019;15:323-335



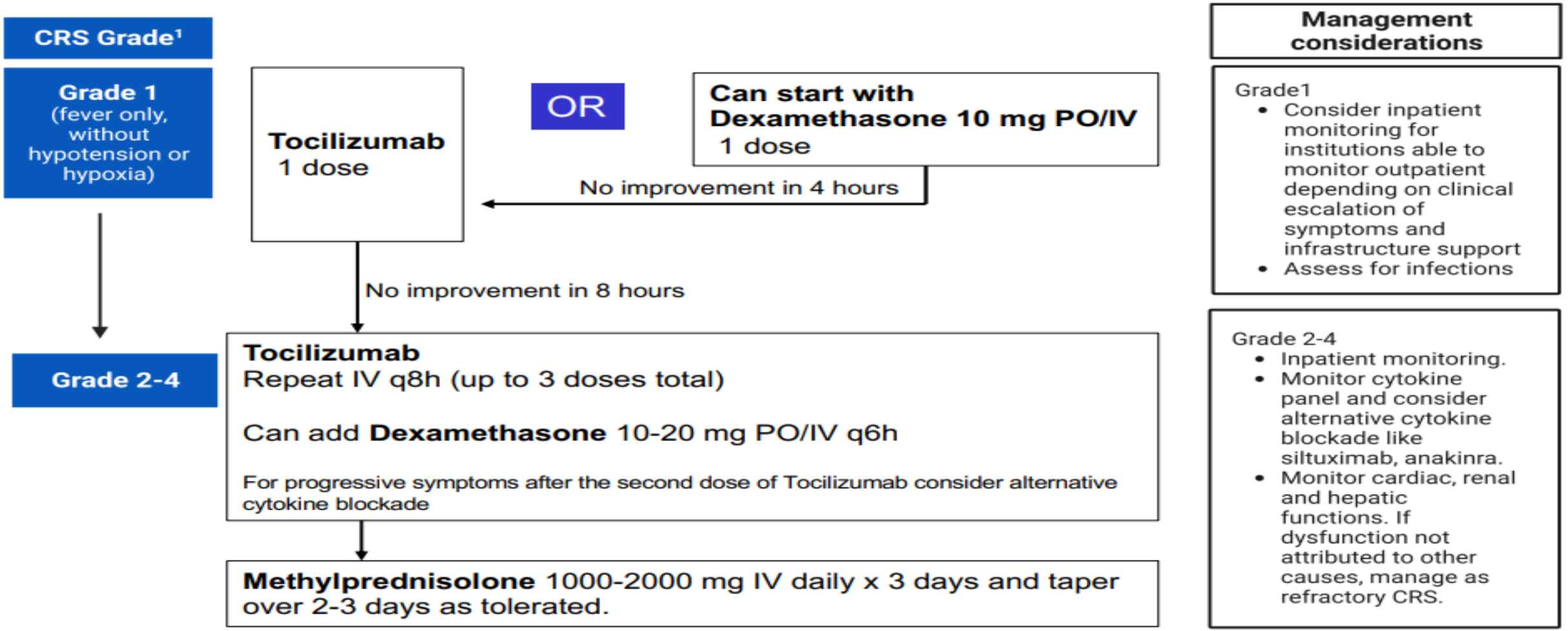
Management of BiTE Toxicities - CRS

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Symptoms are not life-threatening and require symptomatic treatment only (fever, nausea, fatigue, headache, myalgias, malaise)	Symptoms require and respond to moderate intervention: 1. Oxygen requirement <40% FiO_2 OR 2. Hypotension responsive to IV fluids or low dose of one vasopressor OR 3. Grade 2 organ toxicity	Symptoms require and respond to aggressive intervention: 1. Oxygen requirement ≥40% FiO_2 OR 2. Hypotension requiring high dose or multiple vasopressors OR 3. Grade 3 organ toxicity or grade 4 transaminitis	Life-threatening symptoms: 1. Requirement for ventilator support OR 2. Grade 4 organ toxicity (excluding transaminitis)	Death

Ther Clin Risk Manag. 2019;15:323-335

MAYO CLINIC

Management of Teclistamab associated CRS



v1 //last reviewed Jan 2023.

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Options for Management of Teclistamab associated CRS

Additional medications have been used to manage CAR-T and T cell engagers associated severe CRS, HLH/MAS. Use may be off label usage and not covered by insurance

Medication	Starting Dose	Comment(s)
Anakinra	100 mg subQ BID	• IV doses can be given if concerns for subQ absorption. • Dose up to 48 mg/kg/day and 3500 mg/day IV for 3 days have been tolerated in infection and COVID-19. • Max dose: 100 mg bolus, 2mg/kg/hr IV.
Siltuximab	11mg/kg IV over 1-hour x 1	• If cytokine blockade in IL-6 strongly consider.
Basiliximab	20 mg IV x1	• If cytokine blockade in IL-2 strongly consider • Assess response after 6 to 8 hours; for robust responses additional doses can be given 4 days after the first.
Etoposide	150 mg/m^2 IV twice a week	• Not exceeding a cumulative dose of 2 grams.
Ruxolitinib	5mg po BID with a max of 20 mg po BID	
Etanercept	25 mg subQ 2 times a week	
Cyclosporine	trough of 200 to 250	
Emapalumab	1 mg/kg IV 2 times a week	• Non-formulary treatment and may increase administration time. • If cytokine blockade in IFN-γ strongly consider. • Max Dose: 10 mg/kg IV 2 times a week.

v1 //last reviewed Jan 2023.

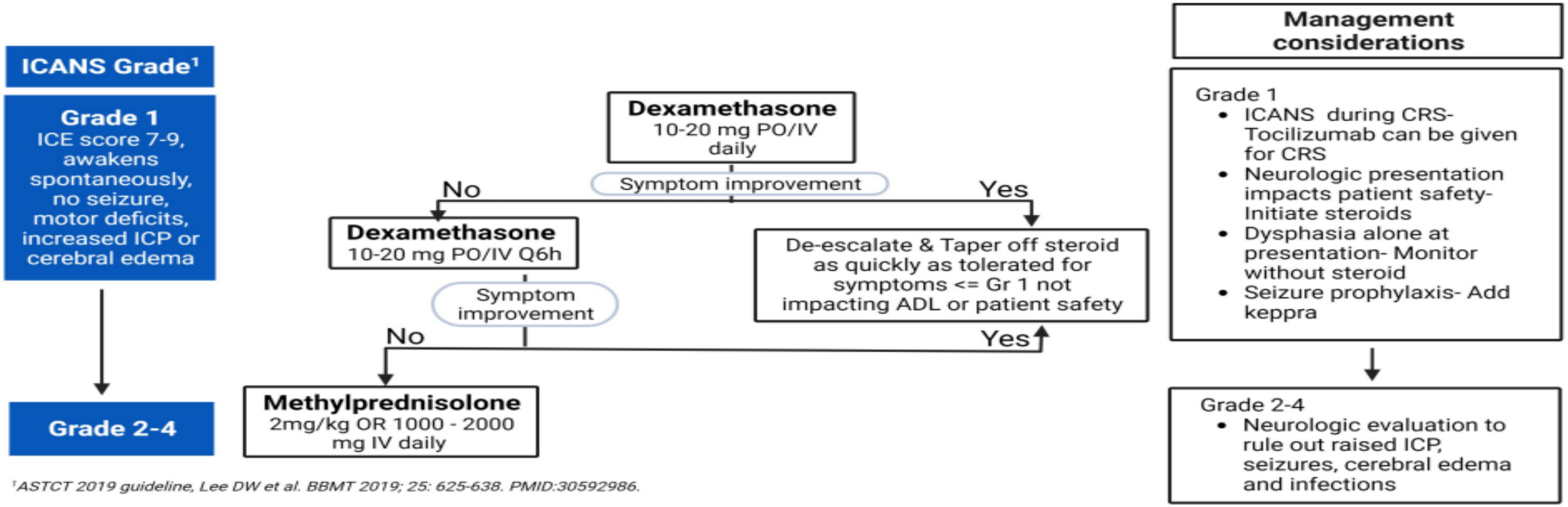
Management of BiTE Toxicities - ICANS

ICANS Grading				
ICANS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score*	7 -9	3 – 6	0 – 2	0
Level of Consciousness	Awakens spontaneously	Awakens to voice	Awakens to tactile stimuli	Unarousable or difficult to arouse; stupor or coma
Seizure	--	--	< 5 minutes	≥ 5 minutes
Motor findings	--	--	--	Hemiparesis or paraparesis
Elevated ICP / Cerebral edema	--	--	Focal edema seen on imaging	Diffuse edema on imaging; posturing; Cushing's triad

https://www.acep.org/

MAYO CLINIC

Management of Teclistamab associated ICANS



[1]*ASTCT 2019 guideline, Lee DW et al. BBMT 2019; 25: 625-638. PMID:30592986.*

v1 //last reviewed Jan 2023.

Conclusions and Future horizons

- Outcomes for triple class and penta refractory MM have significantly improved with BiTEs and CART with 2-3x improvement from historical PFS/OFS
- No Randomized data exists to confirm one BiTE is more efficacious or safer than the other
  - Cross trial comparison suggests fairly similar response rates/DOR/PFS between BiTEs - need longer follow up
  - Potentially Less infection risk with talquetamab vs elra or tec
- Optimal Treatment Schedule for BiTEs still in question despite trials:
  - Do we really need weekly dosing?
  - Should we be treat until optimal response then stop and retreat at progression?
- Will BiTEs eventually move entirely to outpatient setting?

Conclusions and future directions

- No randomized data on sequencing of various BiTES and CARTs
- CART cost /coverage/processing time will remain an issues for majority of patients for at least next 1-3 years making off the shelf BiTEs potentially more attractive option
- These new classes of medications have unique risks including infections, CRS, ICANS, for which we are still learning that optimal management
- What is optimal way to mitigate infection risk with BiTE's?
  - no randomized data just expert opinion at this point
  - Vaccines, heightened surveillance, IVIG replacement, prophlaxis?

- Multiple Ongoing trials to see if these agents moved into earlier lines where more competent immune systems/T-cells can result in improved outcomes/less AE's – early line CART approval likely coming in 2024
- Multiple Ongoing trials combining BiTEs with different MOAs and with other novel agents

Thank You ! Questions?

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