Holden Comprehensive Cancer Center

Multiple Myeloma Updates from ASCO 2023

Christopher Strouse MD

August 25th, 2023

CHANGING MEDICINE.
CHANGING LIVES.®

Disclosures

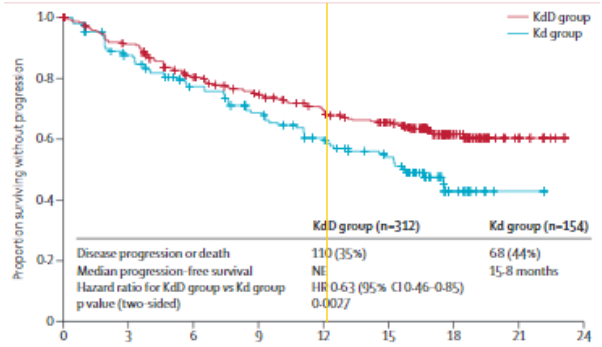
- Advisory board
  - Pfizer
- We will discuss off label / investigational uses
  - Ciltacabtagene, Idecabtagene, Talquetamab, Teclistamab

Acknowledgements

- Thank you to the abstract presenters for use of their slides:
  - Dr. Yael Cohen (Abstract # 8002)
  - Dr. Yi Lin (Abstract # 8009)
  - Dr. Binod Dhakal (Abstract # LBA4)
  - Dr. Carolina D Schinke (Abstract # 8036)
  - Dr. Ross S Firestone (Abstract # 8049)
  - Dr. Michel Delforge (Abstract # 8032)
  - Dr. Ajay Nooka (Abstract # 8008)

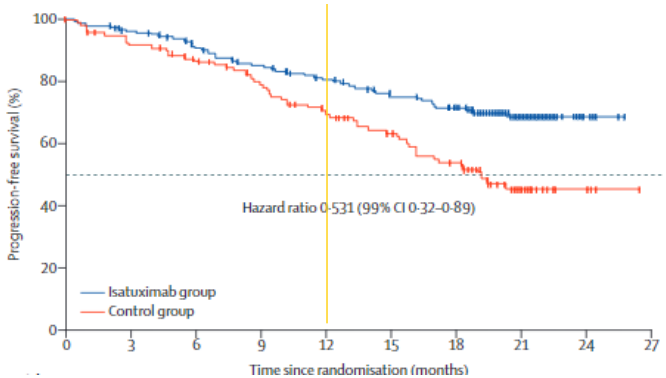
RRMM: αCD38 triplets well established

Dara-Carf-Dex vs Carf-Dex



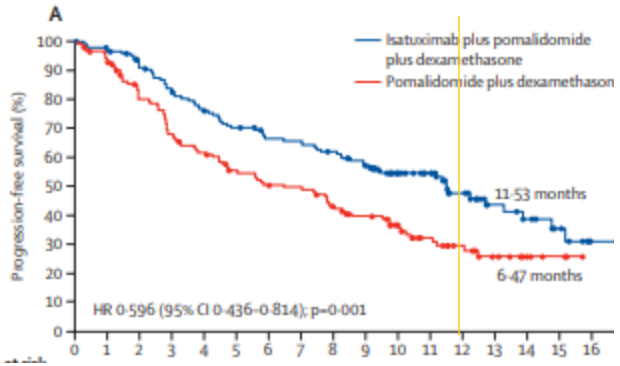
Candor
Dimopoulos et al. 2020

Isa-Carf-Dex vs Carf-Dex



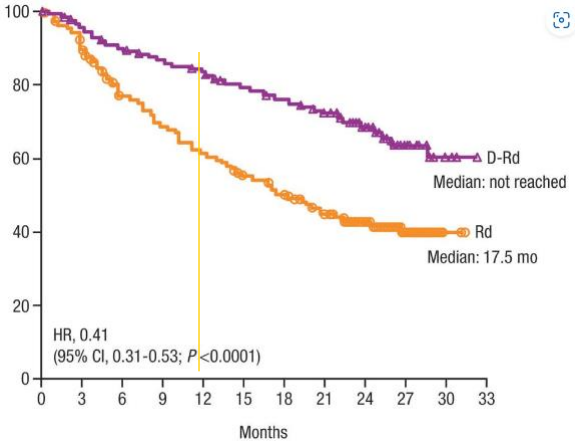
Ikema
Moreau et al. 2021

Isa-Pom-Dex vs Pom-Dex



Icaria
Attal et al. 2019

Dara-Pom-Dex vs Pom-Dex

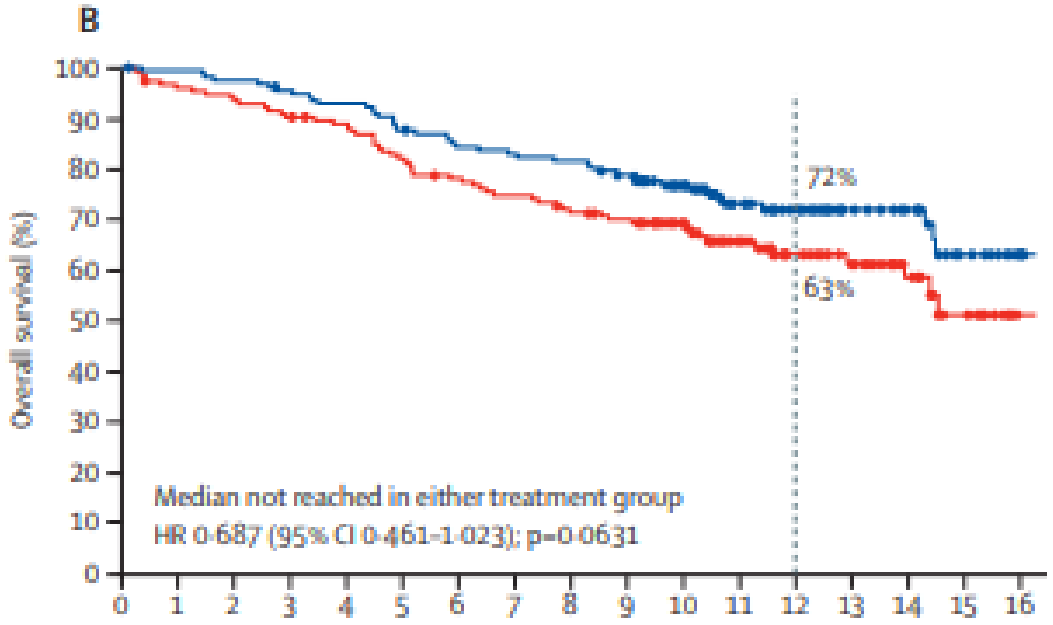


Pollux
Dimopoulos et al. 2018

Dara=Daratumumab
Carf=Carfilzomib
Pom=Pomalidomide
Dex=Dexamethasone

RRMM: αCD38 triplets with OS benefit

Isa-Pom-Dex vs Pom-Dex



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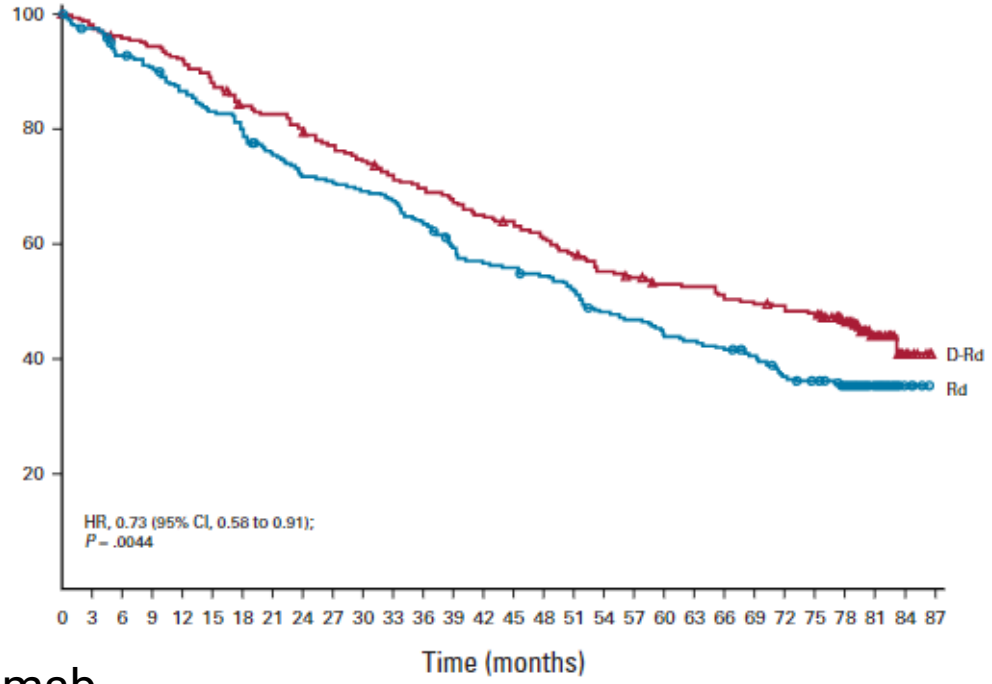
Dara-Pom-Dex vs Pom-Dex



Pollux
Dimopoulos et al. 2023

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CAR T cells in early relapse

- CARTITUDE 4
- KARMMA-3
  - Quality of life abstract from ASCO Michel Delforge 8032

CAR T in early relapse: Ide-cel in pole position

KARMMA-3

RRMM

2-4 prior lines of therapy

2:1 R

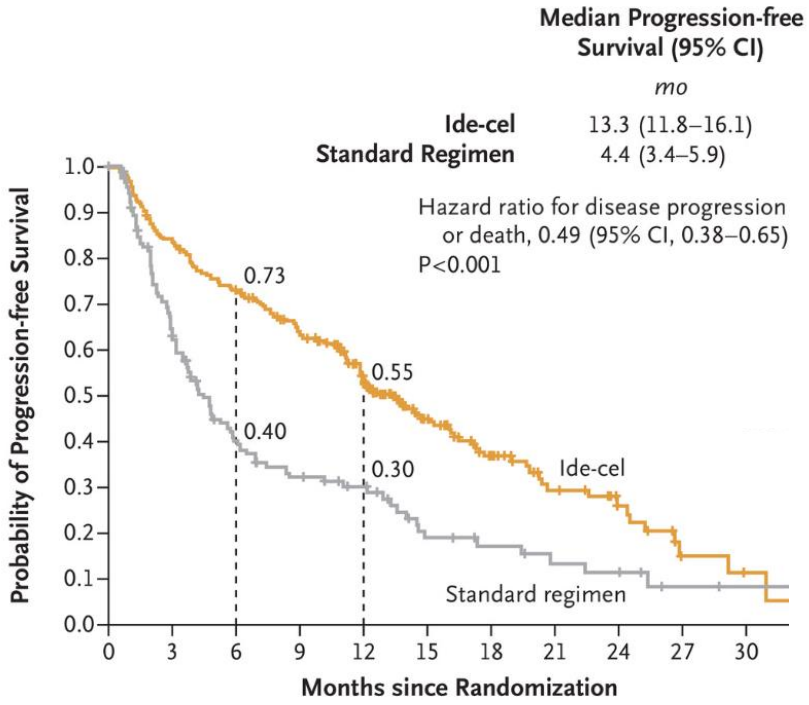
Leukapheresis

Bridging (Optional)
Same SOC options

Ide-cel Infusion

3/254 manufacturing failure (1%)
Median vein-to-vein time: 49 days (34-117)

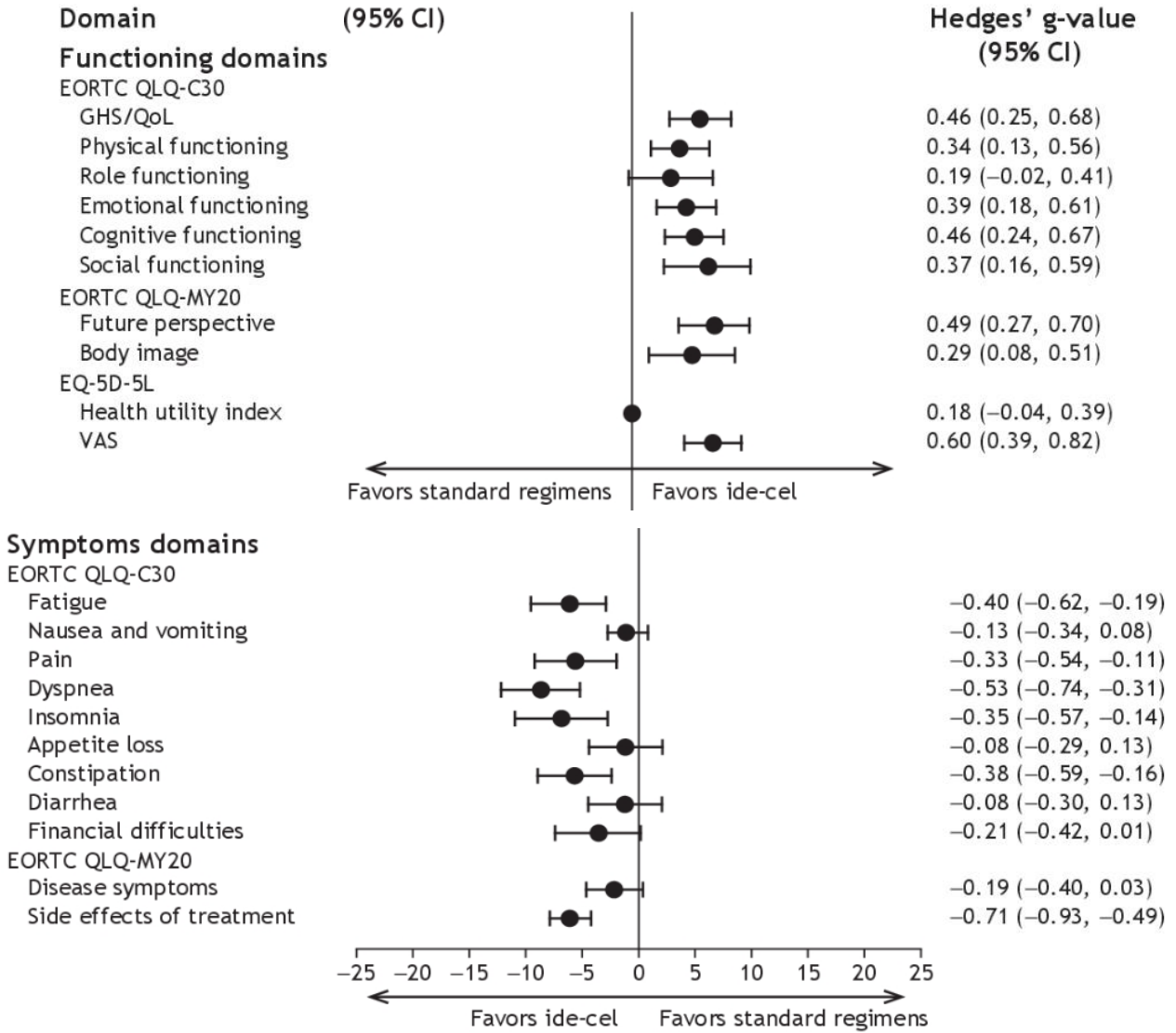
Standard of Care
DPd (33%)
Kd (23%)
EPd (23%)
Ixa-Rd (17%)
DVd (5%)



Rodriguez-Otero et al. NEJM 2023

HRQOL in KARMMA-3

- Ide-cel outperforms SOC options in most domains
- Well tolerated infusion, prolonged off-therapy duration
- Caveat: unblinded assessments



Delforge ASCO 2023 abst # 8032

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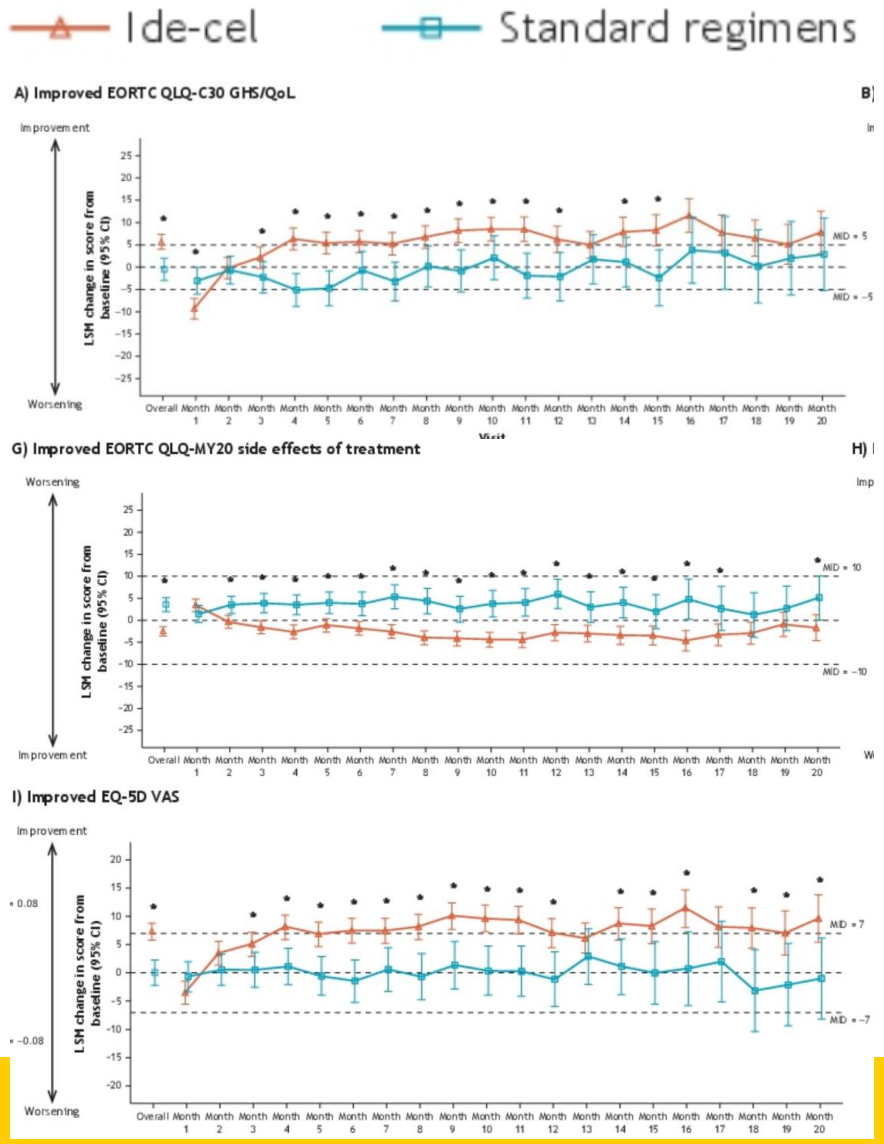


Delforge ASCO 2023 abst # 8032

Late Breaking Abstract 106: CARTITUDE 4

CARTITUDE 4

RRMM
1-3 prior lines of therapy

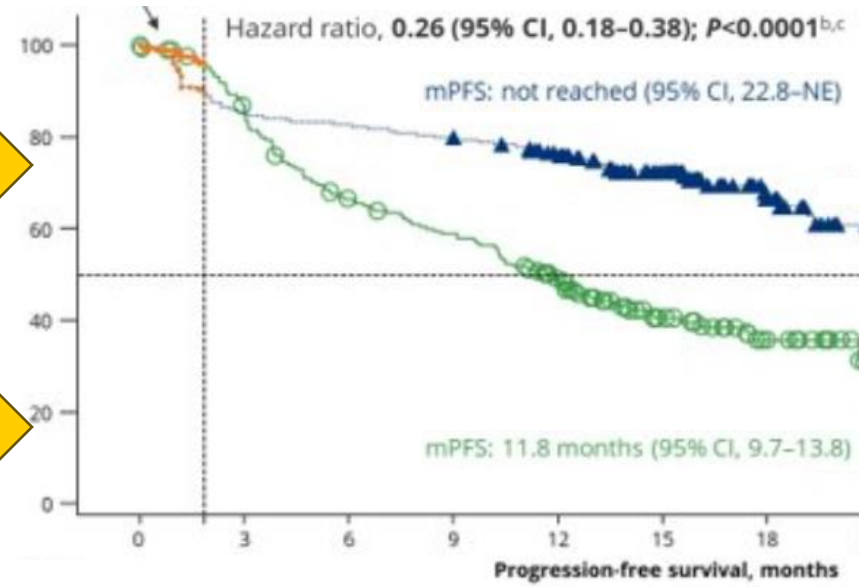
Len-refractory

1:1 R

Leukapheresis → Bridging (Optional) Same SOC options → Cilta-cel Infusion

0/208 manufacturing failure (0%)
Median vein-to-vein time: 44 days (25-127)

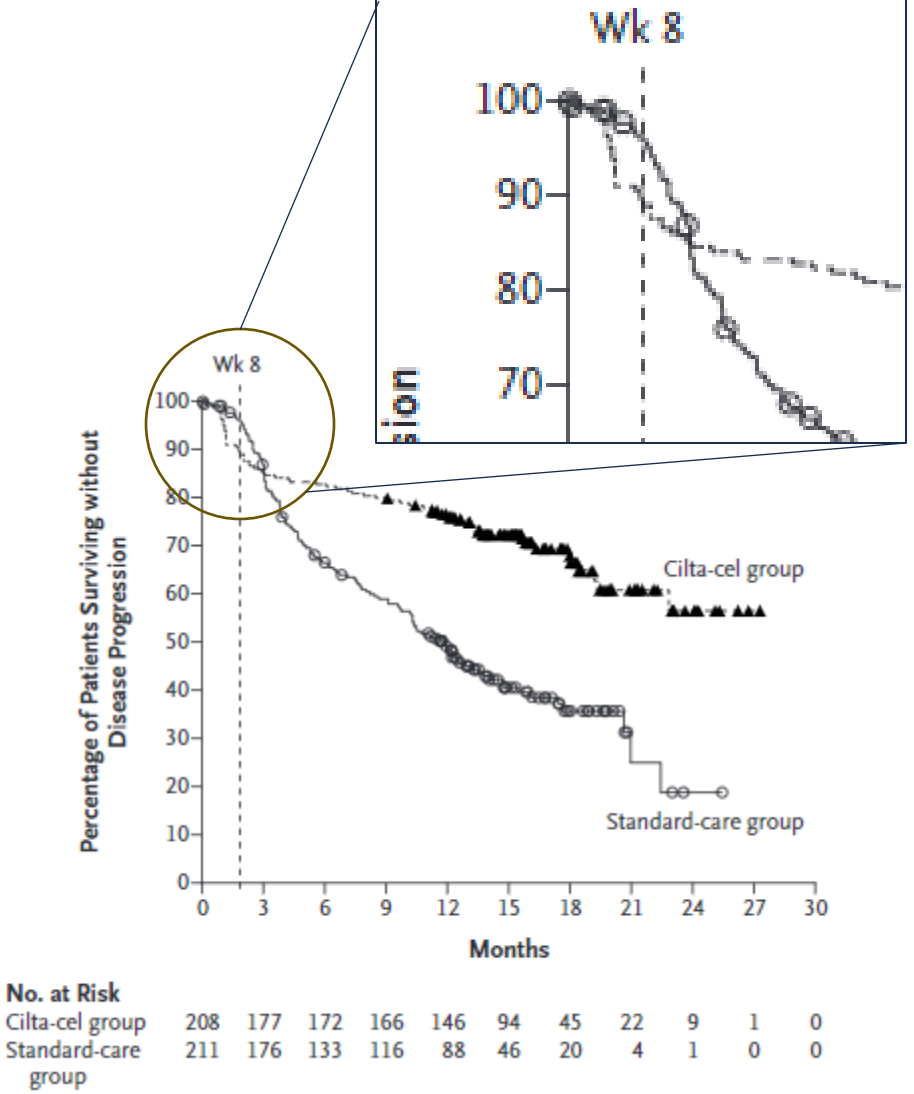
Standard of Care
DPd (88%)
PVd (12%)



Dhakal, ASCO 2023 Abst #LBA4

CARTITUDE 4

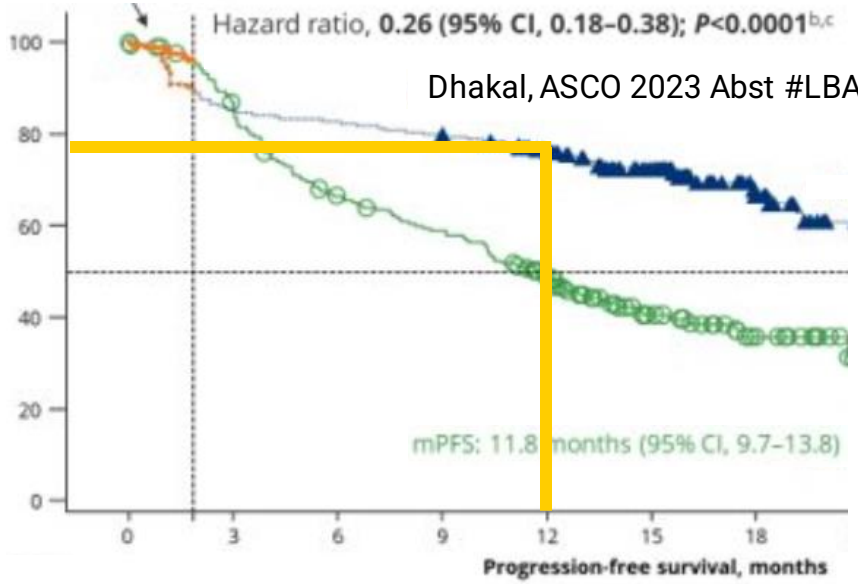
- Early progression events in Cilta-cel group
  - Coordination of leukapheresis date is challenging
  - Delayed start of bridging common
  - Logistics of CAR T continue to require work
  - Early referral likely very important
- Despite initial disadvantage, cilta-cel still demonstrated clear efficacy advantage



NEJM San-Miguel et al. 2023

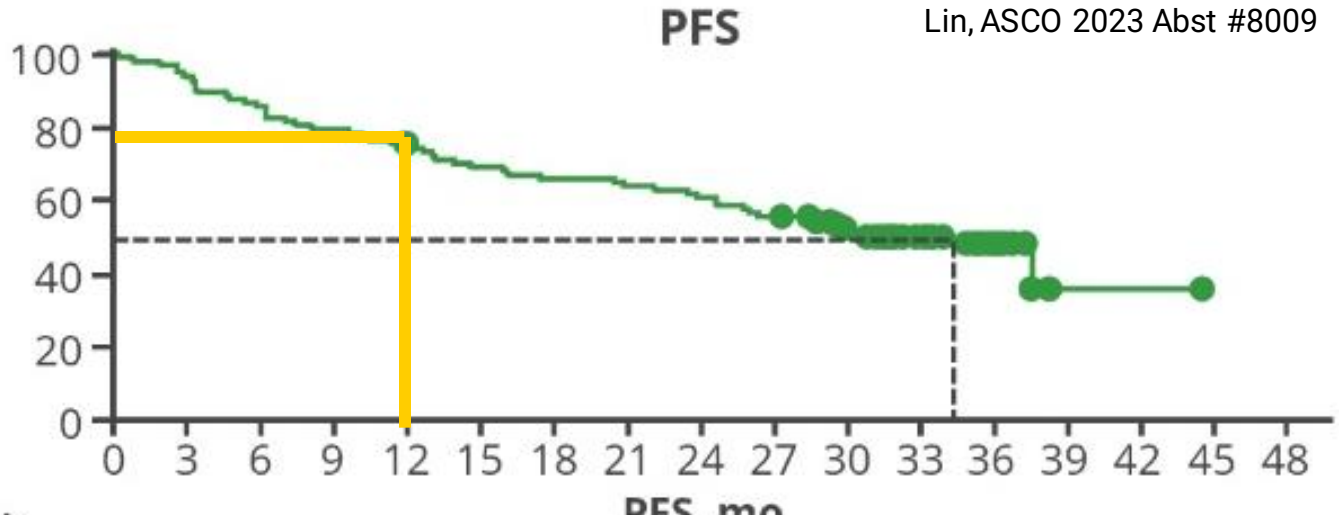
In Context: Cilta-cel vs Ide-cel

CARTITUDE 4



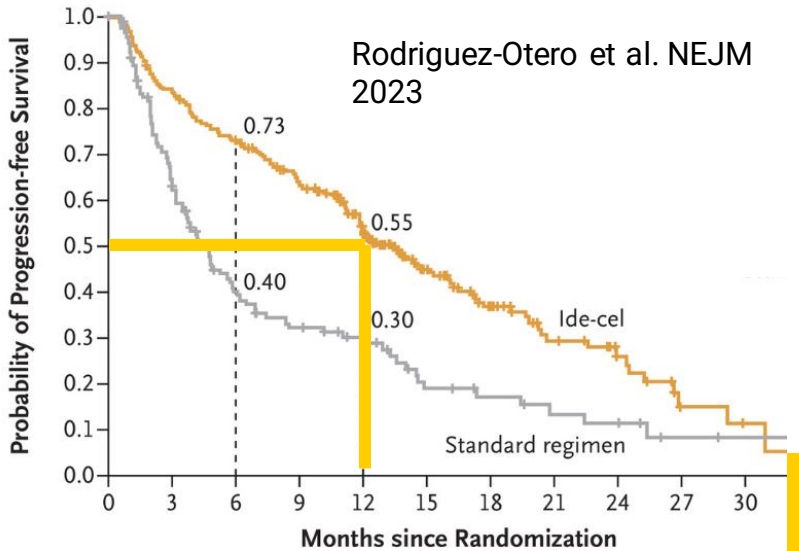
Dhakal, ASCO 2023 Abst #LBA4

CARTITUDE-1



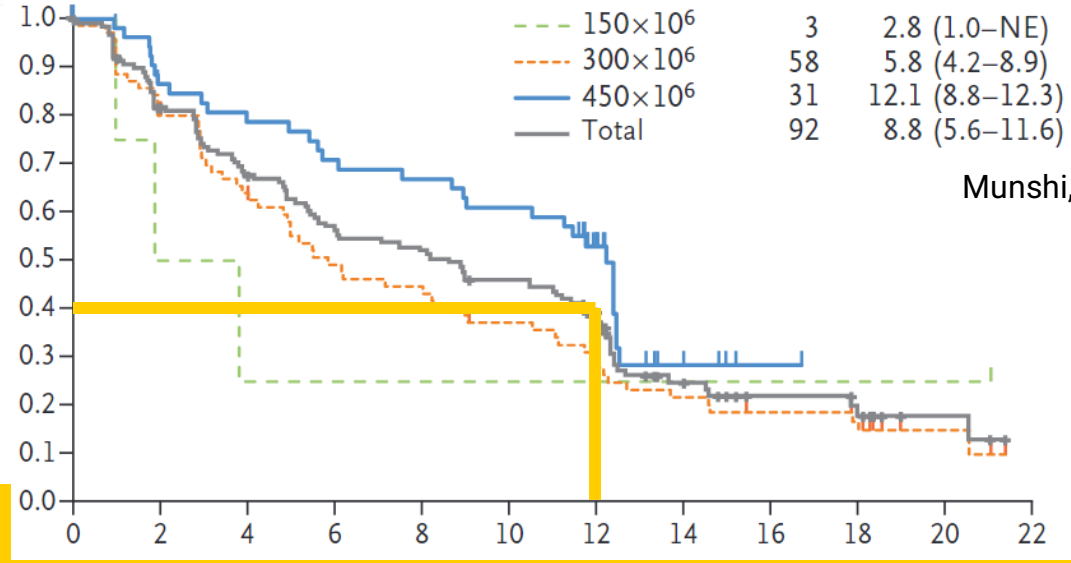
Lin, ASCO 2023 Abst #8009

KARMMA-3



Rodriguez-Otero et al. NEJM 2023

KARMMA-1



Munshi, NEJM 2021

CARTITUDE 4: Toxicities

- CARTITUDE 1: most deaths (49%) are from progressive disease (17/35)
  - Infections = 8 / 35
- CARTITUDE 4: plurality of deaths (36%) still from progressive disease (14/39)
  - Infection = 90% (9/10 of TEAEs, non-TEAEs not reported)

CARTITUDE 1	Patients (N=97)	Time of death post cilta-cel infusion, days
Total deaths during the study	35	45–980
Due to progressive disease	17	253–980
AEs unrelated to treatment	**12**	
Pneumonia	2	109; 887
AML[a]	3	418; 582; 718
Ascites[b]	1	445
MDS	1	803
Respiratory failure	3	733; 793; 829
Septic shock and/or sepsis	2	917; 945
AEs related to treatment	**6**	
Septic shock and/or sepsis	2	45; 162
CRS/HLH	1	99
Lung abscess	1	119
Respiratory failure	1	121
Neurotoxicity	1	247

CARTITUDE 4	Cilta-cel (n=208)	Standard care (n=208)
Deaths, n (%)	39 (18.8)	46 (22.1)
Progressive disease	14 (6.7)	30 (14.4)
Non–treatment-emergent adverse event[a]	15 (7.2)	11 (5.3)
Treatment-emergent adverse event	10 (4.8)[b]	5 (2.4)
COVID-19 pneumonia[b]	7 (3.4)	1 (0.5)
Neutropenic sepsis	1 (0.5)	0
Pneumonia	1 (0.5)	0
Progressive multifocal leukoencephalopathy	0	1 (0.5)
Respiratory tract infection	0	1 (0.5)
Septic shock	0	1 (0.5)
Respiratory failure	1 (0.5)[c]	0
Pulmonary embolism	0	1 (0.5)

Lin, ASCO 2023 Abst #8099

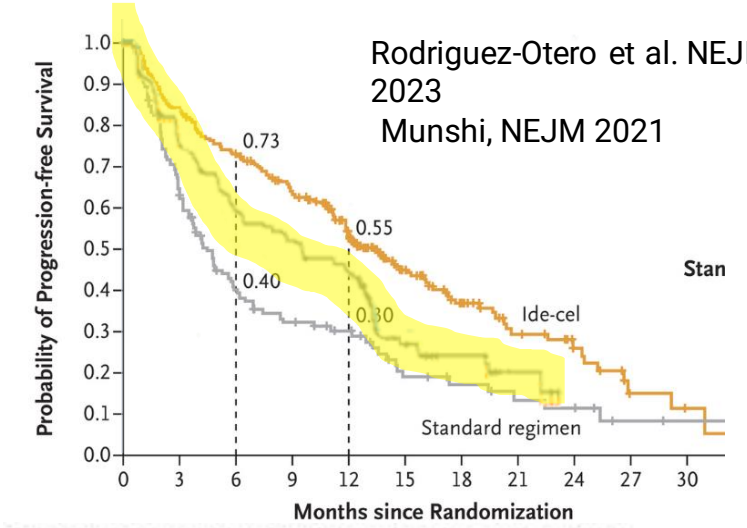
Dhakal, ASCO 2023 Abst #LBA4

CARTITUDE 4: Toxicities

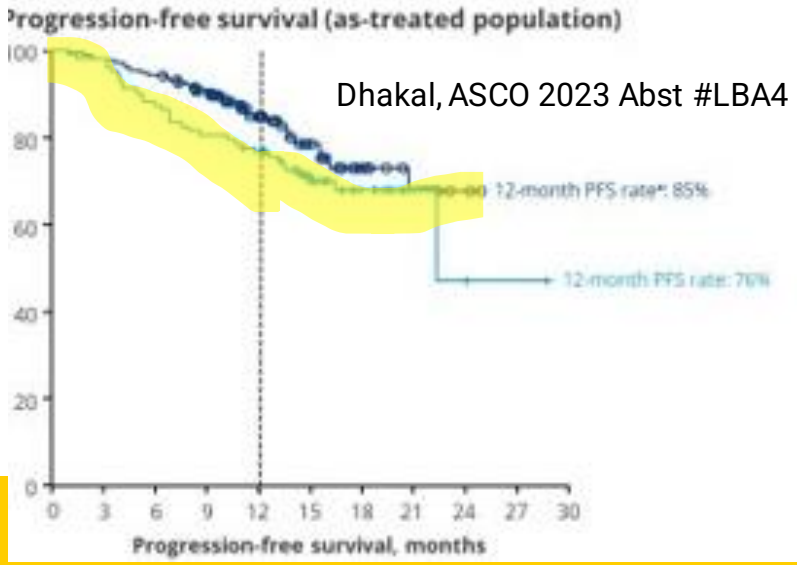
- Motor Neuron Toxicity: Parkinson-like presentation.
  - 6 / 97 (6%) patients in CARTITUDE 1 (Martin JCO 2023)
    - 3 died, 1 from parkinsonism, 2 from infections
    - 2 recovered/recovering
    - 1 stable/functioning
  - 1 / 208 (0.5%) patients in CARTITUDE 4 (Dhakal ASCO 2023, LBA4)
    - "Lower likely related to patient management strategies implemented to mitigate this risk"
    - Bridging therapy – lower tumor burden
    - Excluded patients with significant pre-existing neuropathy
    - Aggressive early management of CRS / ICANS

In Context: Do CAR T cells work better earlier?

- Better than current SOC in terms of PFS and QOL
- Likely updates to label coming
- Progression Free Survival may be a bit better in earlier lines (highlighted)
  - Difference doesn't seem dramatic



Rodriguez-Otero et al. NEJM 2023
Munshi, NEJM 2021



Dhakal, ASCO 2023 Abst #LBA4

Around the corner

- Faster manufacturing
  - GC012F BCMA/CD19 Dual Targeted FasTCAR-T (Abstract # 8005)
    - 22-36 hour manufacturing time
    - ORR = 100%, MRD- = 83%, median PFS 38 months
  - PHE833: BCMA-directed CAR T cell with “T-CHARGE” manufacturing (Abstract # 8004)
    - <2 day manufacturing time, goal vein-to-vein of 10 days
    - ORR = 98%, MRD- = 74%, PFS not reported
- Cilta-cel in NDMM
  - CARTITUDE 5: VRd -> Rd vs VRd -> Cilta-cel
  - CARTITUDE 6: Dara-VRd -> ASCT -> Dara-R vs Dara-VRd -> Cilta-cel -> Dara-R
- GPRC5D CAR T cells (Mailankody NEJM 2022)
  - Prior BCMA therapy: 70% response rate

Bispecific Antibodies: Currently Approved

	FDA Approval	Indication	ORR	DOR (mon)	CRS (GR3+)	ICANS	Step-up
Teclistamab BCMAxCD3	October 2022	>4 prior LOT	63%	18.4	72% (0.6%)	3.0% (0%)	2 doses
Talquetamab GPCR5dxCD3	August 2023	>4 prior LOT	70%	10.2	80% (0%)	9.0% (0%)	2-3 doses
Elranatamab BCMAxCD3	August 2023	>4 prior LOT	58%	NR	58% (0.5%)	3.3% (0%)	2 doses

Leshokin Nat. Med 2023

Chari NEJM 2022

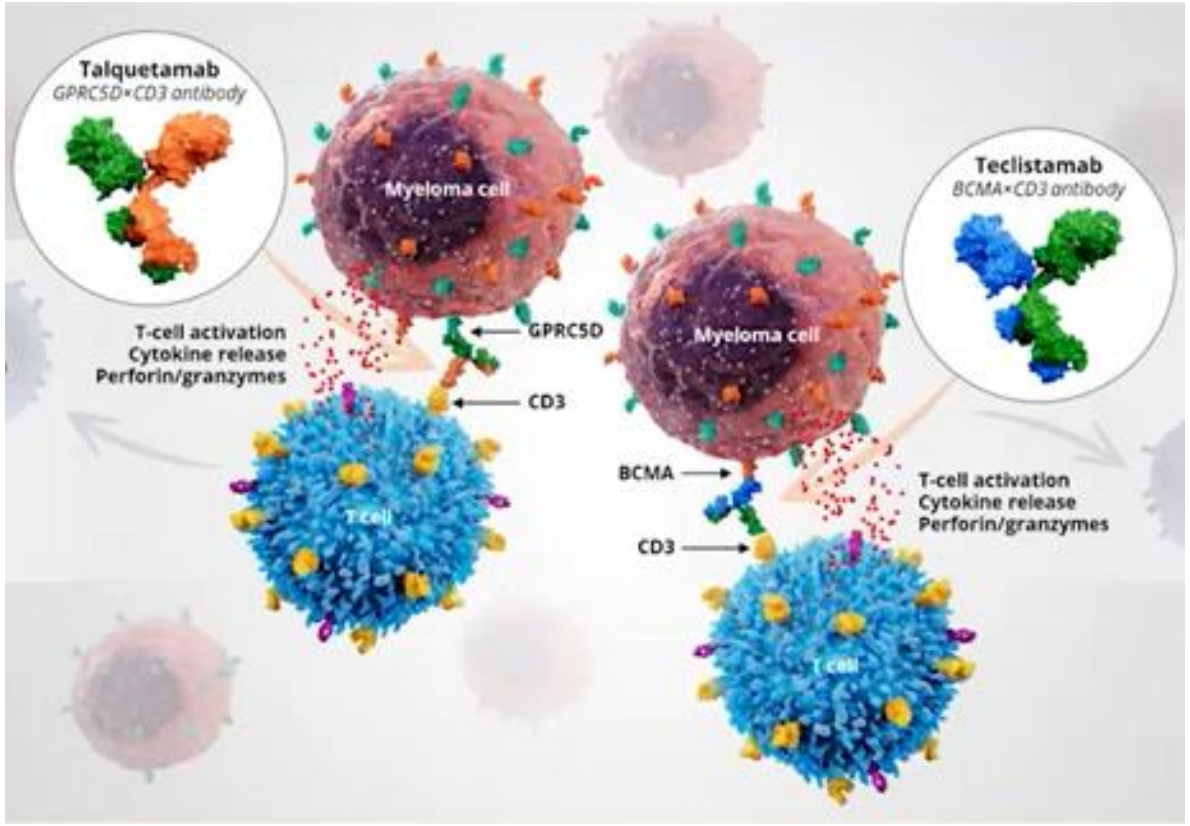
Moreau NEJM 2022

Bispecific Antibodies: New Data

- RedirecTT-1 Trial Results (Cohen ASCO 2023 Abst # 8002)
- Elranatamab in prior BCMA therapy (Nooka ASCO 2023 Abst # 8008)
- Teclistamab in prior BCMA therapy (Firestone ASCO 2023 Abst # 8049)
- Talquetamab Updated (Schinke ASCO 2023 Abst # 8036)

RedirecTT-1

- Combination Regimen:
  - teclistamab (αBCMA x αCD3)
  - telquetamab (αGPRC5d x αCD3)



Cohen ASCO 2023 Abst # 8002

RedirecTT-1

- Combination overall well tolerated
  - Standard CRS/ICANS rates
    - Not different from either agent separately
  - Infections still main side effect
  - Known Talquetamab related skin toxicity / dysgeusia /nail disorders

TEAE[a] (≥25% overall), n (%)	All dose levels (N=93)		Tec 3.0 mg/kg Q2W + tal 0.8 mg/kg Q2W (n=34)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Nonhematologic TEAEs				
CRS	71 (76.3)	3 (3.2)	25 (73.5)	0
Dysgeusia[b,c]	57 (61.3)	–	16 (47.1)	–
Pyrexia	47 (50.5)	2 (2.2)	13 (38.2)	1 (2.9)
Skin toxicity[d]	50 (53.8)	0	18 (52.9)	0
Nail disorders[e]	43 (46.2)	0	14 (41.2)	0
Diarrhea	38 (40.9)	2 (2.2)	14 (41.2)	1 (2.9)
Cough	36 (38.7)	0	8 (23.5)	0
Dry mouth	35 (37.6)	0	11 (32.4)	0
Rash[f]	32 (34.4)	1 (1.1)	10 (29.4)	1 (2.9)
COVID-19	31 (33.3)	9 (9.7)	14 (41.2)	1 (2.9)
Pneumonia	25 (26.9)	10 (10.8)	4 (11.8)	2 (5.9)
Fatigue	24 (25.8)	7 (7.5)	6 (17.6)	2 (5.9)

Cohen ASCO 2023 Abst # 8002

RedirecTT-1: Fairly well tolerated

- Standard **CRS/ICANS** rates
  - Not different from either agent separately
- **Infections** still main side effect
  - Grade 3-4 in 53%!
- Known Talquetamab related skin toxicity / dysgeusia /nail disorders

TEAE[a] (≥25% overall), n (%)	All dose levels (N=93)		Tec 3.0 mg/kg Q2W + tal 0.8 mg/kg Q2W (n=34)	
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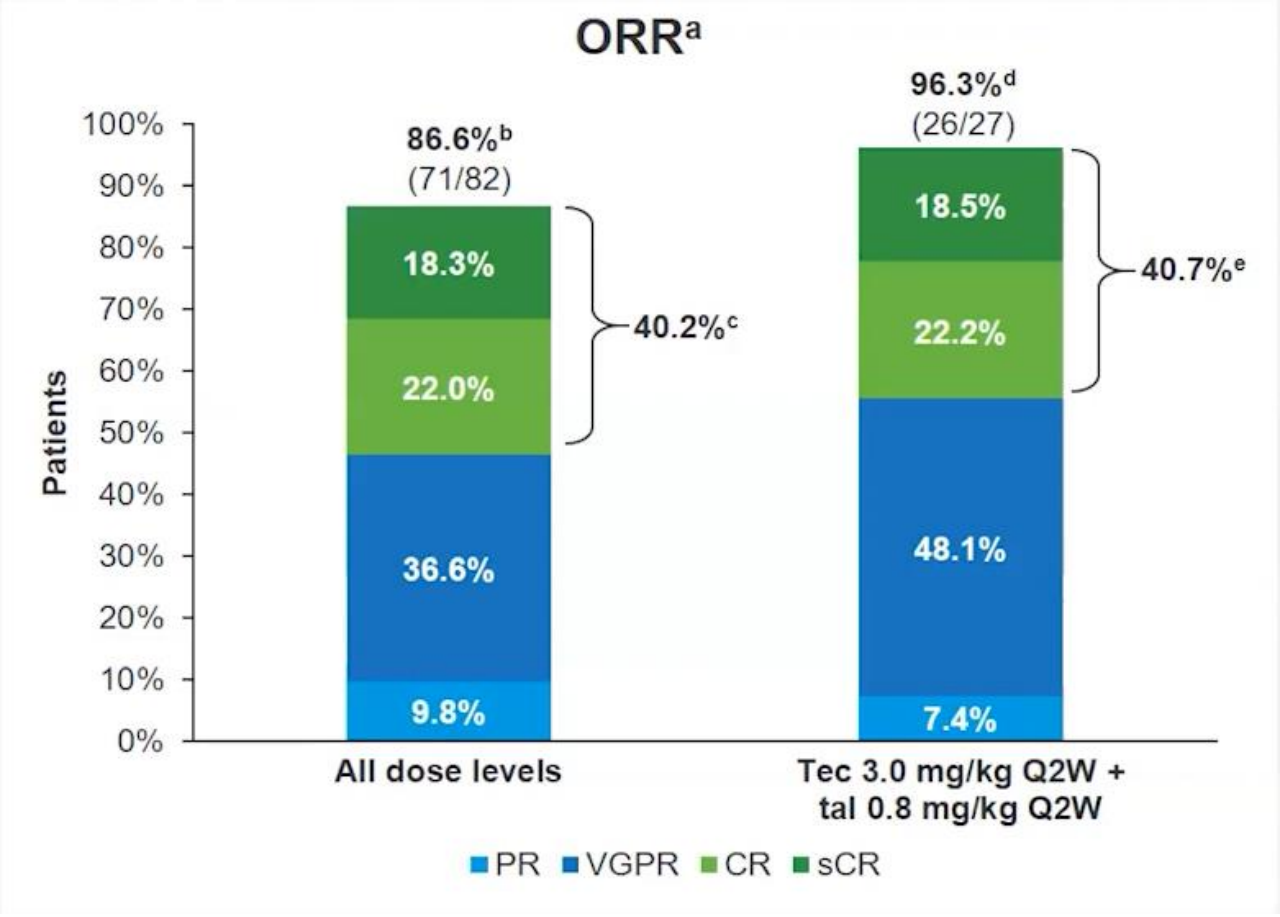
Dysgeusia[b,c]	57 (61.3)	–	16 (47.1)	–
Pyrexia	47 (50.5)	2 (2.2)	13 (38.2)	1 (2.9)
Skin toxicity[d]	50 (53.8)	0	18 (52.9)	0
Nail disorders[e]	43 (46.2)	0	14 (41.2)	0
Infections	**78 (83.9)**	**49 (52.7)**		
COVID-19	31 (33.3)	9 (9.7)		
Pneumonia	25 (26.9)	10 (10.8)		
Upper respiratory tract infection	11 (11.8)	2 (2.2)		
Nasopharyngitis	8 (8.6)	0		
Rhinovirus infection	8 (8.6)	2 (2.2)		
Oral candidiasis	7 (7.5)	1 (1.1)		
Septic shock	7 (7.5)	6 (6.5)[b]		

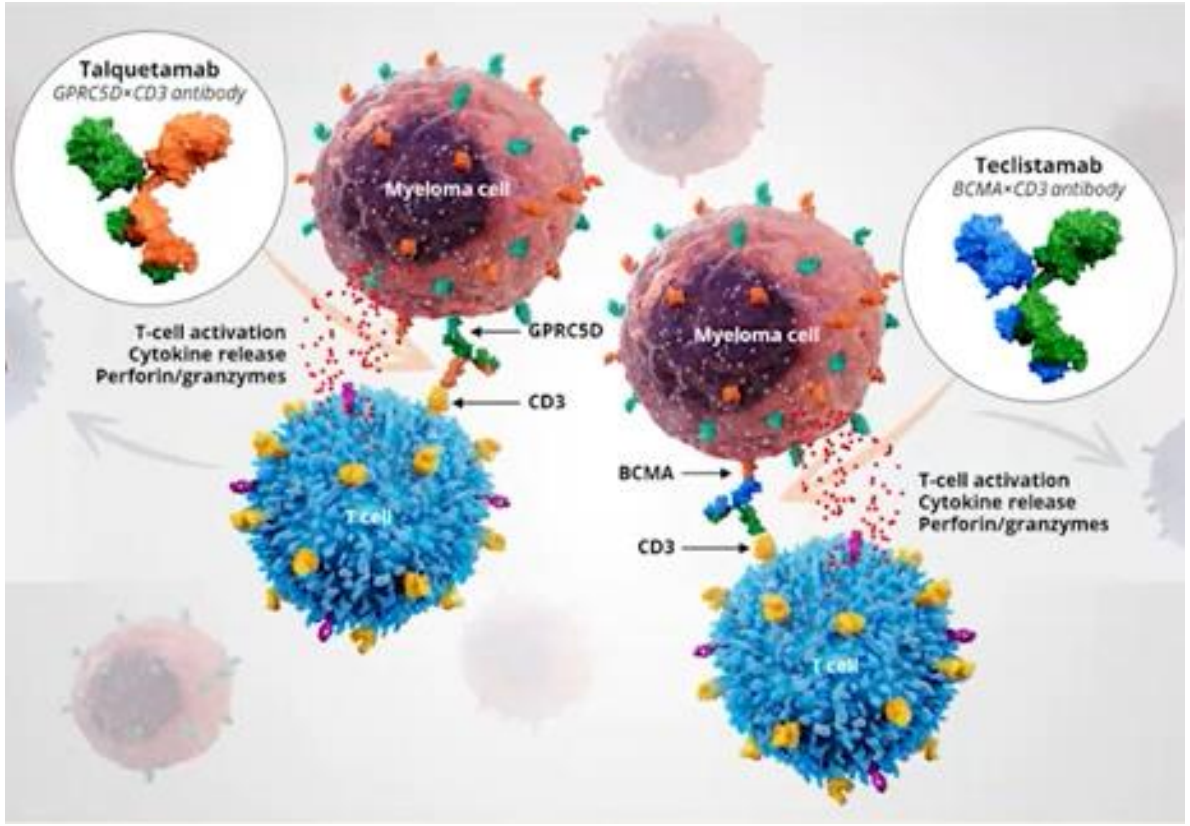
RedirecTT-1: Impressive efficacy

- Median PFS 20.9 months
- Responses in 96% of patients
  - Pts w/ soft tissue plasmacytomas: 86%



RedirecTT-1: What Next?

- Duration of treatment?
  - Is it appropriate to continuously dose?
- Combination vs Sequential?
  - Many benefit from these agents alone
- Encouraging result in extramedullary disease
  - Expansion cohort is accruing… stay tuned



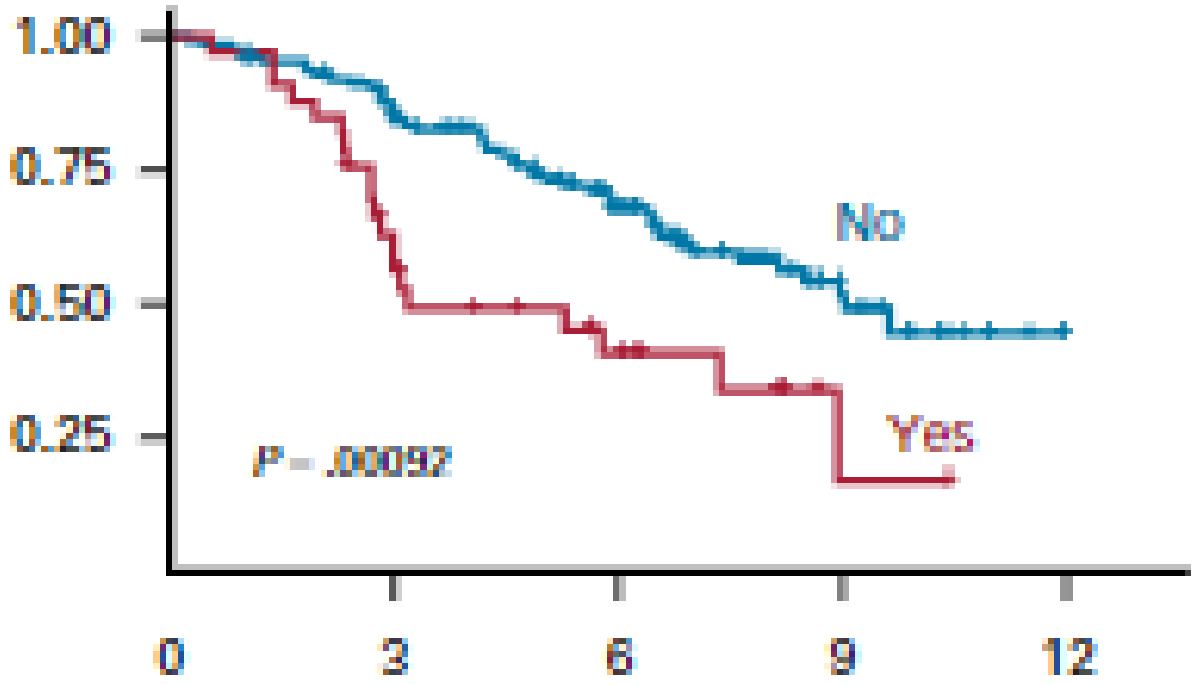
Cohen ASCO 2023 Abst # 8002

How do we strategically use these agents?

- Multiple agents targeting same antigens (BCMA, GPRC5D)
  - How many bites at the apple?
- Multiple agents reliant on immune fitness
  - Bispecific antibodies
  - CAR T cells

Order of Operations

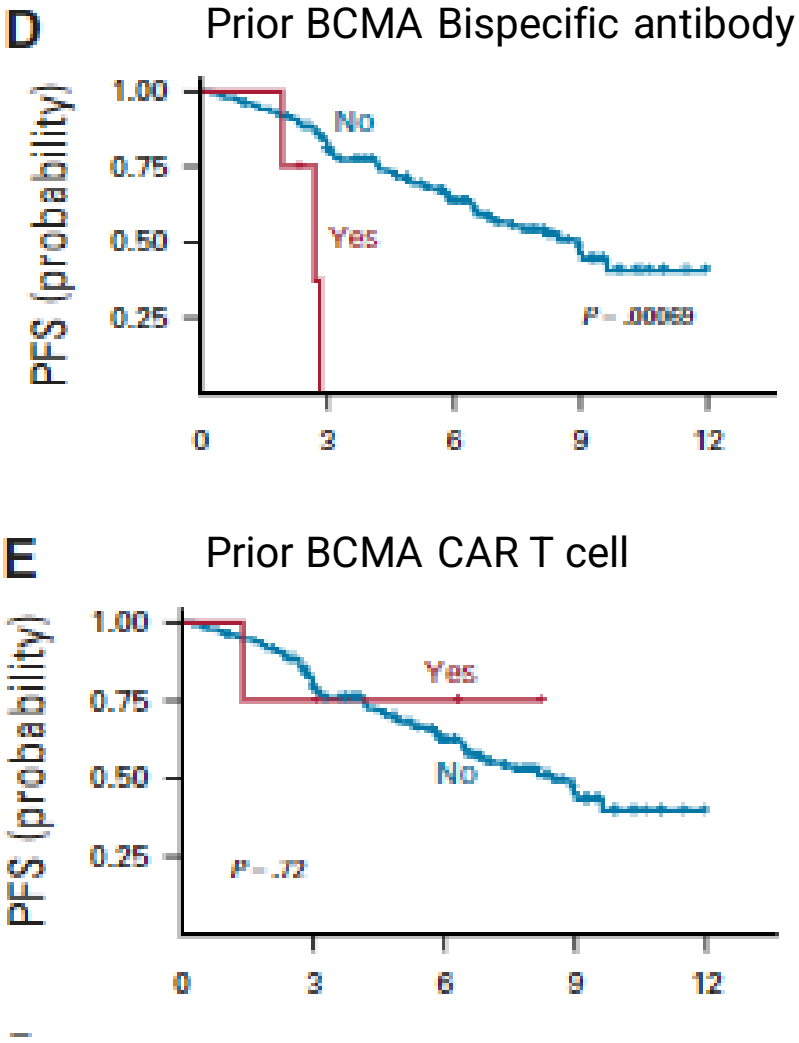
- CAR T cells affected by exposure to prior BCMA targeted agents
  - Idecabtagene “Real World” consortium data



Hansen JCO 2023

Order of Operations

- Impact differs by type of BCMA agent
  - BCMA CAR T works poorly post BCMA bispecific
  - BCMA CAR T works well post BCMA CAR T
- Likely to vary by time interval between treatments too



Hansen JCO 2023

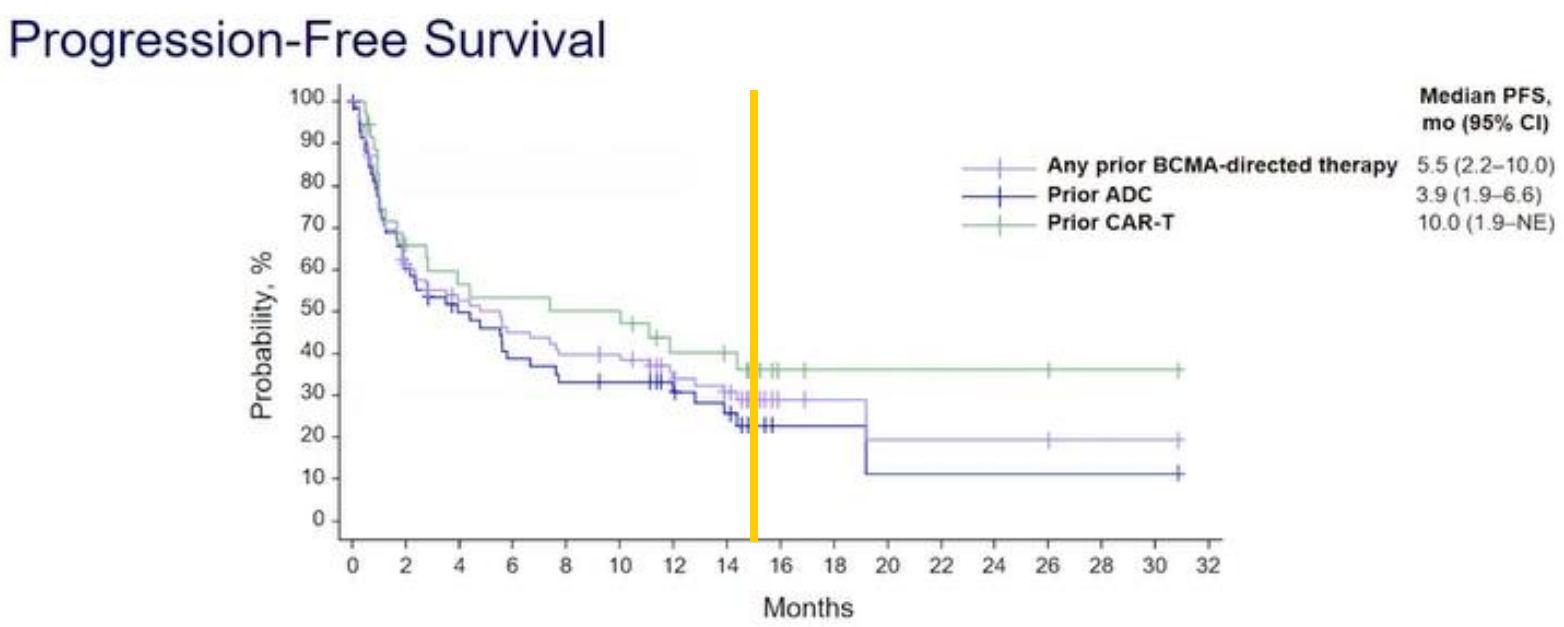
Elranatamab (BCMAxCD3) in prior BCMA therapy

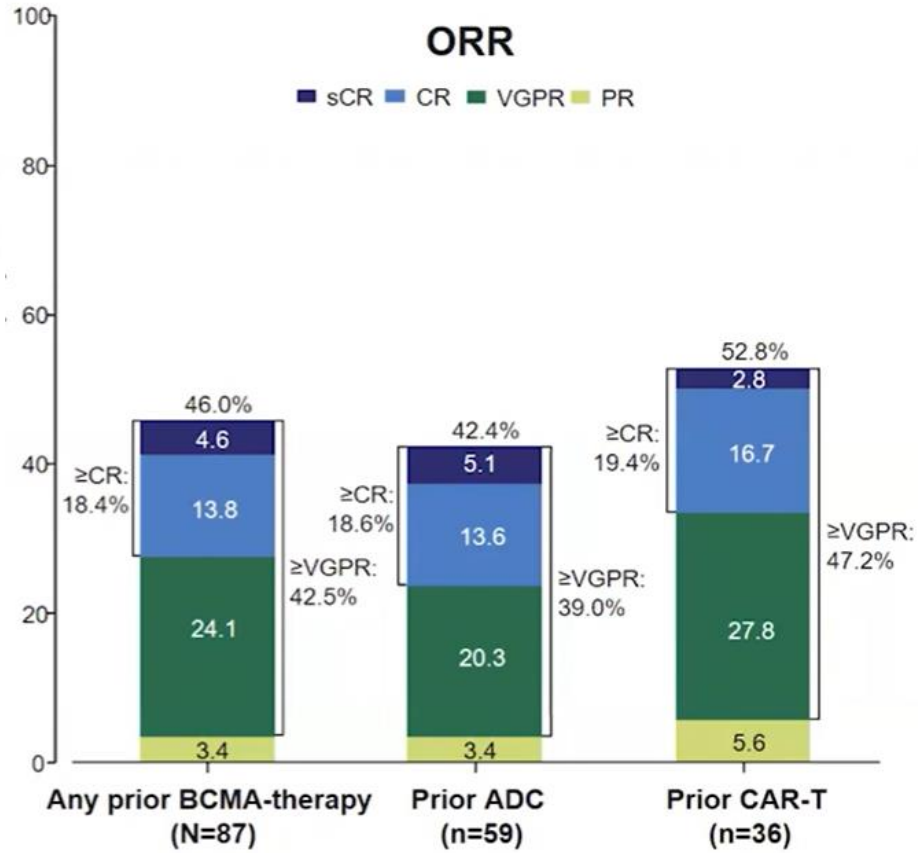
- A subset of patients permitted to have prior BCMA targeted therapy
  - MagnetisMM-1: 13
  - MagnetisMM-2: 1
  - MagnetisMM-3: 64
  - MAgnetisMM-9: 9

	Patients:
Any prior BCMA	87
Prior ADC	59
Prior CAR-T	36
Both ADC & CAR-T	8

Nooka ASCO 2023 Abst # 8008

Elranatamab (BCMAxCD3) in prior BCMA therapy



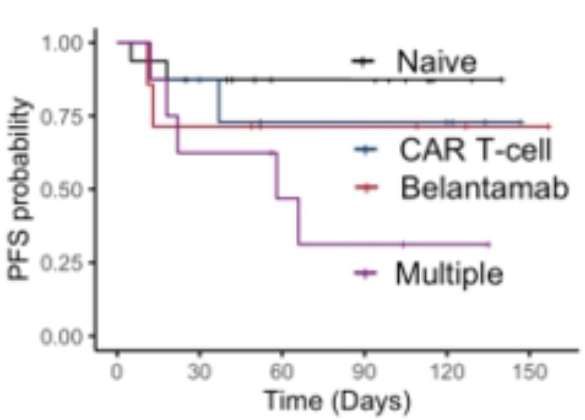


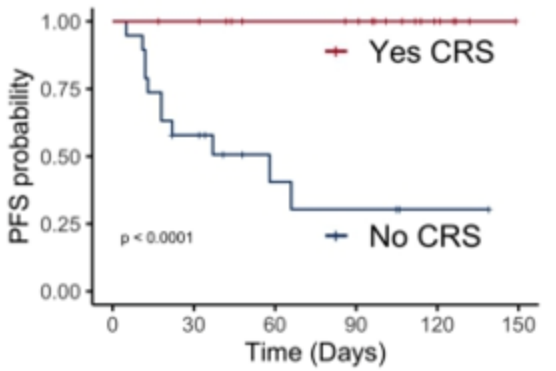
For Reference:
MagnetisMM-3 (BCMA Naïve)
ORR = 58%
PFS @ 15 months = 50.9%

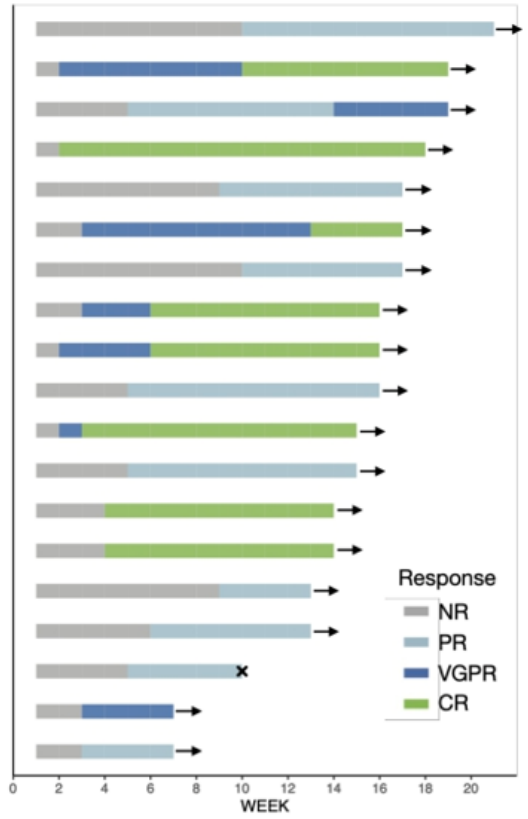
Nooka ASCO 2023 Abst # 8008

Teclistamab (BCMAxCD3) in prior BCMA therapy

- N=23 patients
  - Prior αBCMA ADC: 15
  - Prior αBCMA CAR T: 16
  - Prior αBCMA BiAb: 1
  - Multiple prior: 8
- Prior CAR-T & ADC results a bit worse than BCMA naïve
- Absence of CRS portends treatment failure







Firestone ASCO 2023 Abst # 8008

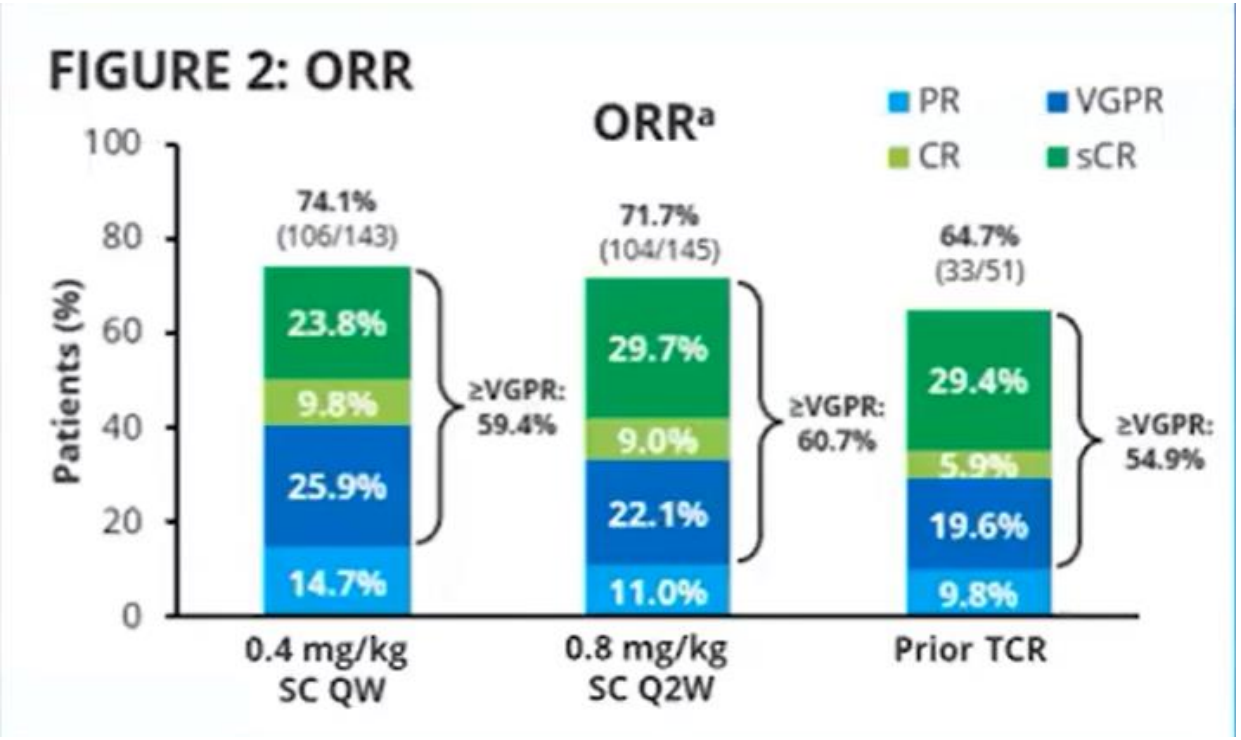
Talquetamab (GPRC5DxCD3) in prior T cell redirection therapy

- Distinct antigen target (GPRC5D)
  - May overcome antigen loss
- Still reliant on T cell redirection (TCR)
  - Prior TCR exposure allowed (n=51)

	Patients:
Any prior TCR	51
Prior Bispecific	18 (35%)
Prior CAR-T	36 (71%)
Both BsAB & CAR-T	3 (6%)

Schinke ASCO 2023 Abst # 8008

Talquetamab (GPRC5DxCD3) in prior T cell redirection therapy



Outcome	0.4 mg/kg SC QW (n=143)	Prior TCR (n=51)
mFU, mo	18.8	14.8
mDOR, mo (95% CI)	9.5 (6.7–13.3)	11.9 (4.8–NE)
12-mo DOR rate in patients with ≥CR, %	78.9	80.5
12-mo PFS rate, %	34.9	38.1
12-mo OS rate, %	76.4	62.9

Schinke ASCO 2023 Abst # 8008

Order of Operations

- BCMA antigen generally not lost @ relapse
- Exposure to antigen x CD3 bispecific antibodies vs CAR T cell have distinct immunologic consequences
  - Immune fitness may be better preserved by CAR T cell therapy
  - CAR T therapy before Bispecific therapy may be preferred
- More data needed!

Summary ASCO 2023

- CAR T cell therapy will be given in earlier lines
  - Better efficacy than current SOC
  - QOL may be better than current SOC too
- Many options for bispecific antibodies on market
  - Great efficacy of currently available options
  - Optimal duration of therapy to be determined
  - Optimal combinations to be determined
  - Likely to move in earlier lines in the future
- Sequencing will be increasingly important
  - CAR T before Bispecific for optimal outcomes?

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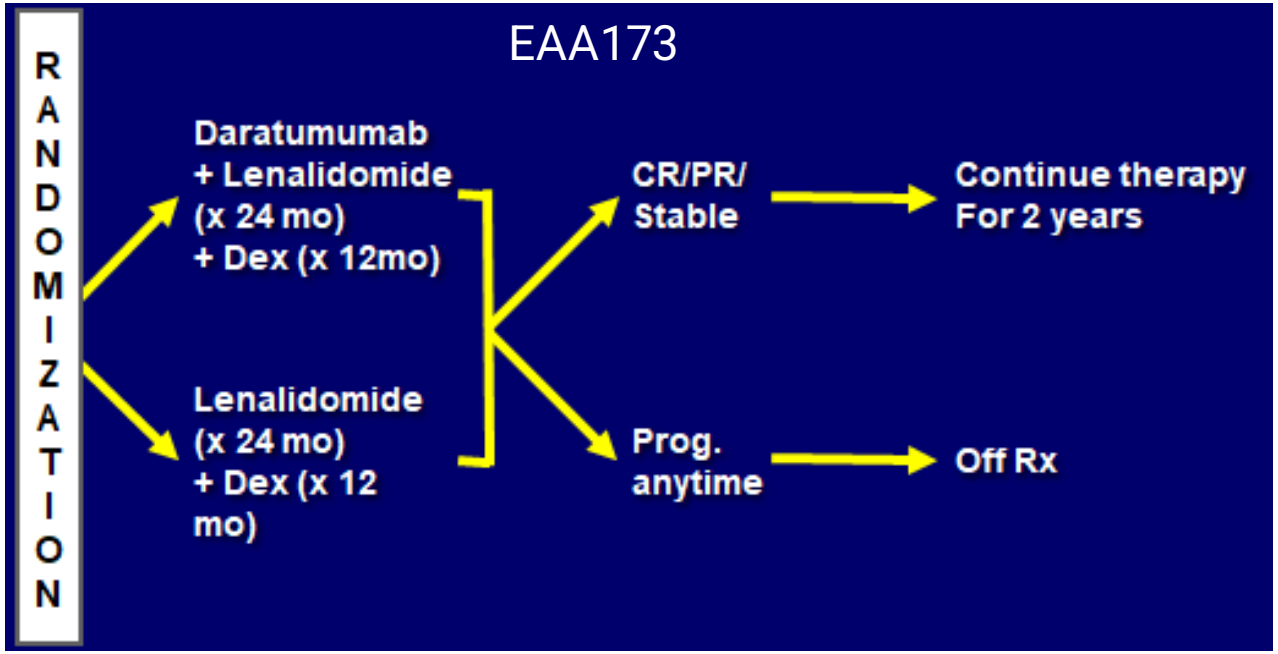
Myeloma Clinical Trials @ Iowa

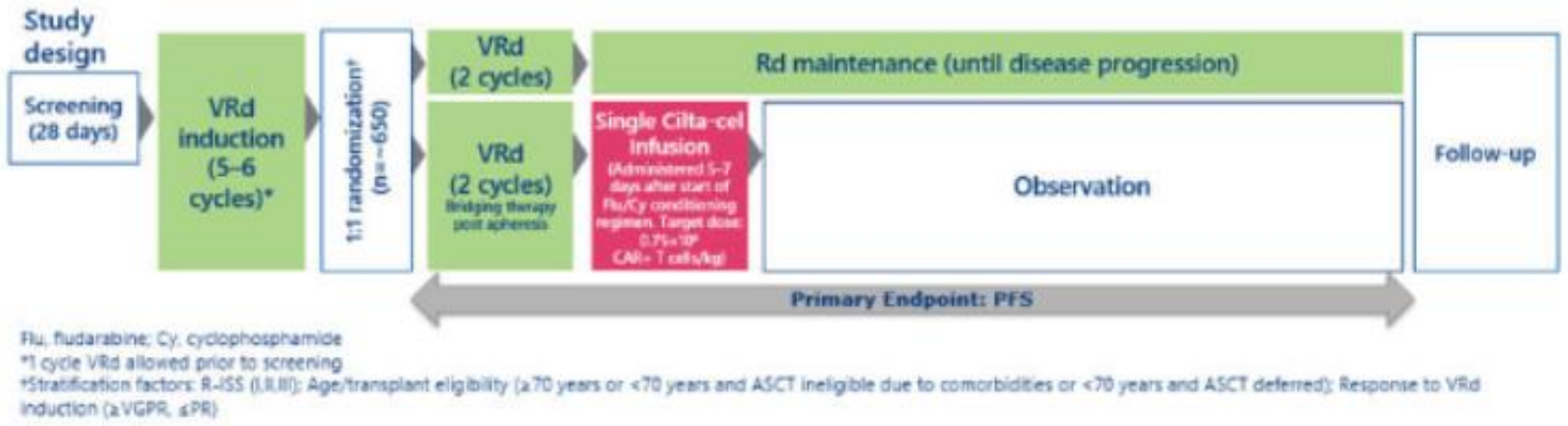
- High risk smoldering myeloma
  - High risk cytogenetics
  - Marrow plasma cells >20%
  - Light chain ratio > 20:1
  - M protein > 2.0 g/dl



Myeloma Clinical Trials @ Iowa

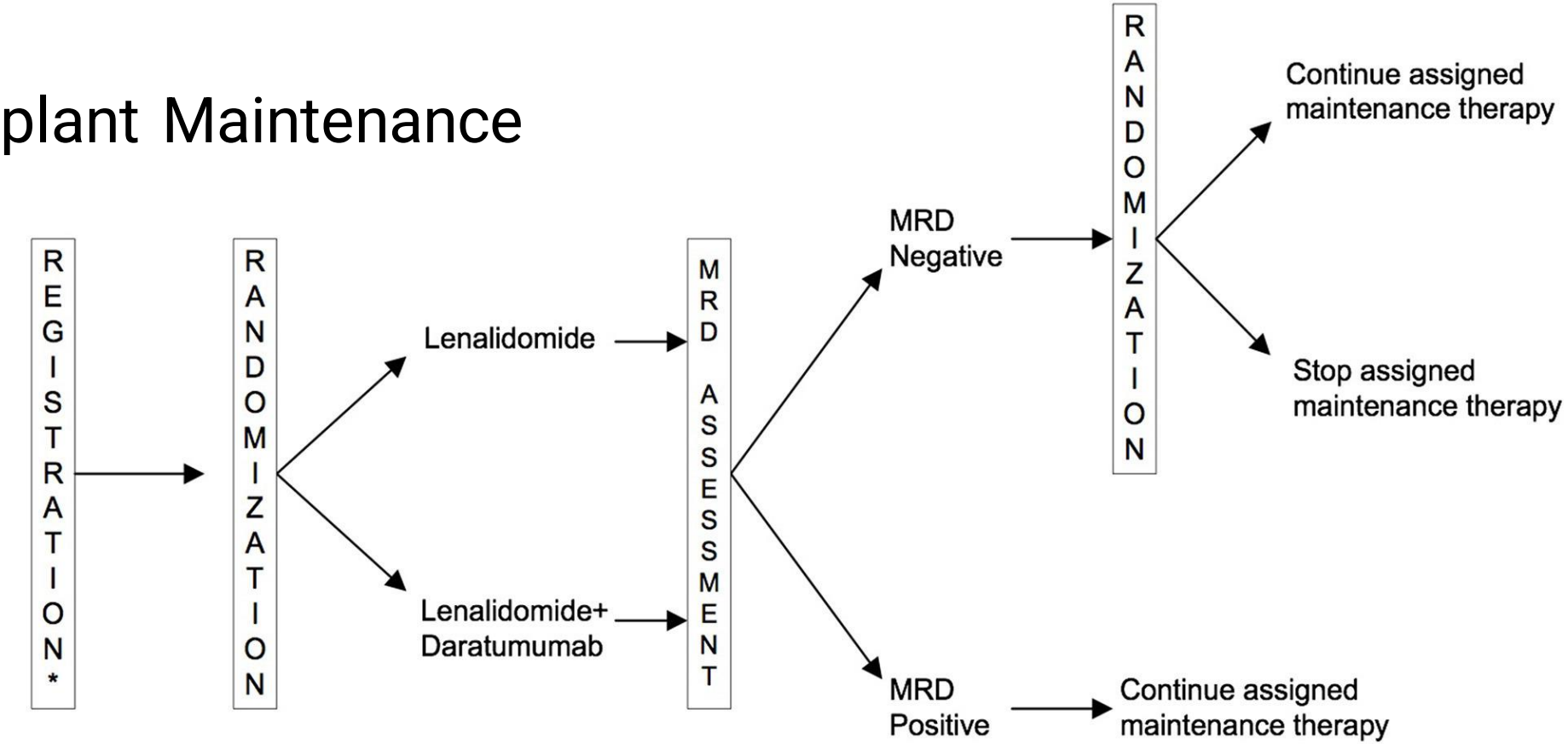
- Newly Diagnosed Myeloma
  - CARTITUDE 5
  - CARTITUDE 6
    - Likely 2024

Figure: CARTITUDE-5 study design



Myeloma Clinical Trials @ Iowa

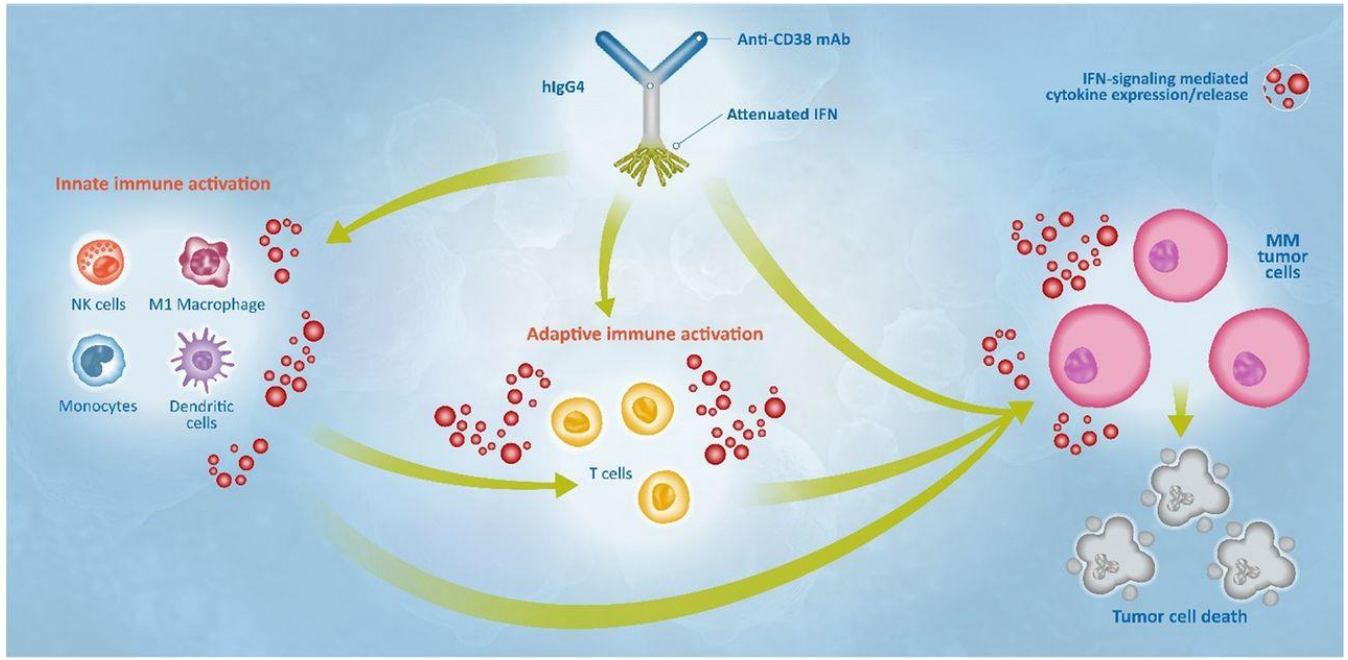
- Post-transplant Maintenance
  - S1803



*Patients may register any time following induction therapy.

Myeloma Clinical Trials @ Iowa

- Relapsed/Refractory
  - Modakafusp alfa
    - CD38-INFa conjugate
    - R/R myeloma, 1-3+ prior lines
  - MagnitisMM 20 (Elranatamab)
    - Elranatamab + Carfilzomib
    - Elranatamab + aCD-47
    - R/R myeloma, 1-3 prior lines
  - Melphalan + High Dose Ascorbic Acid
    - Triple exposed RRMM



Clinical Trials Coming Soon

- Relapsed/Refractory
  - P-BCMA-CAR-T
    - Allogeneic CAR-T cell product
    - Prior BCMA exposure allowed
  - GC012F
    - BCMA/CD19 dual targeted FasTCAR-T
- Newly Diagnosed, Non-transplant
  - S2209:
    - Dara-Rd -> R maintenance
    - Dara-Rd -> Dara-R maintenance
    - VRd -> R maintenance