



Triple Exposed Patients with RRMM: Is there a Golden. Moment for CART

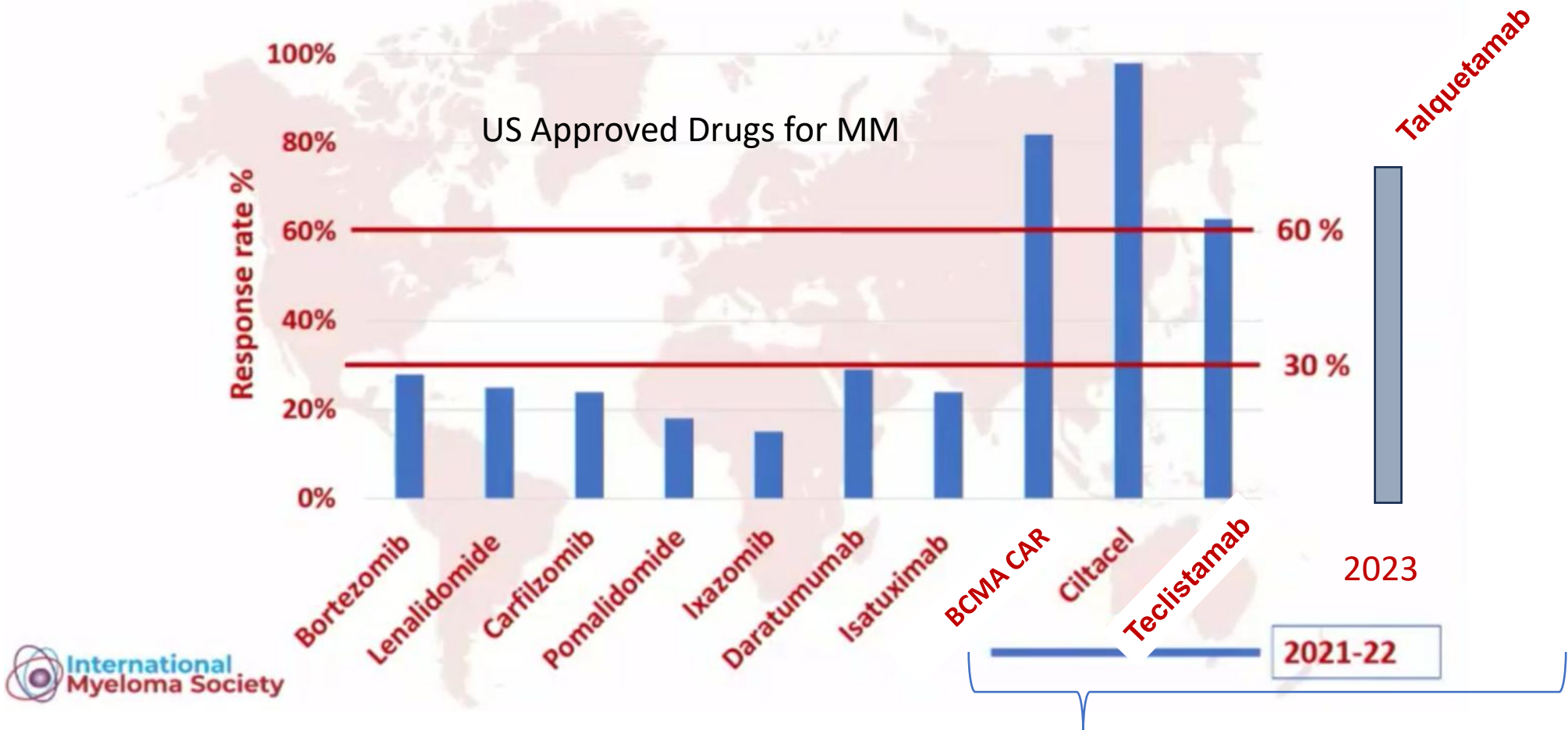


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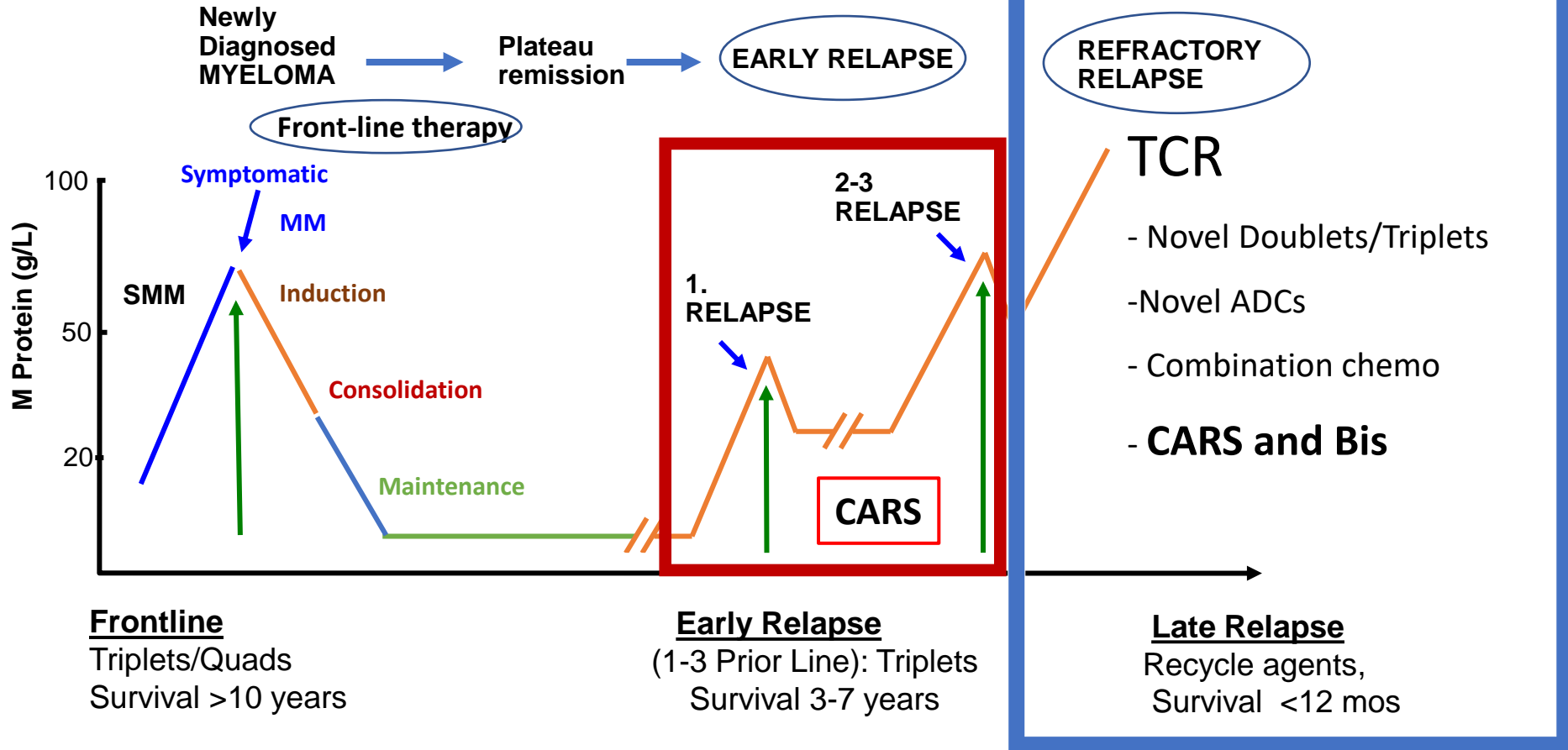
Amazing Success in Immunotherapy for MM

Single Agent Response Rate – Changing Landscape



Immunotherapy era, but which treatment, for which patient and at what time?

Immunotherapy in MM



Treatment Attrition in Multiple Myeloma

- Real-world assessment of lines of therapy and outcomes based on 3 US insurance claims databases

Line of Therapy	Sample Size, N	Attrition (%)	Deaths (%)	No subsequent Treatment in Follow-Up (%)	Subsequent Treatment (%)
Non-Transplant Patients					
1	22,062	--	12.9%	44.0%	43.1%
2	9505	56.9%	12.2%	33.3%	54.5%
Transplant Patients					
1	2763	--	1.3%	19.6%	79.0%
2	2184	21.0%	2.7%	28.1%	69.2%

Put your best players on the field!!!

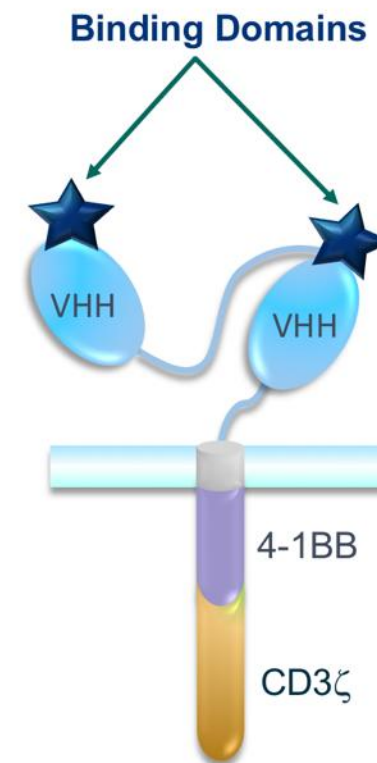
Durable remissions with BCMA specific chimeric antigen receptor (CAR)-modified T cells in patients with refractory/relapsed multiple myeloma

Wanhong Zhao (alternative presenter)

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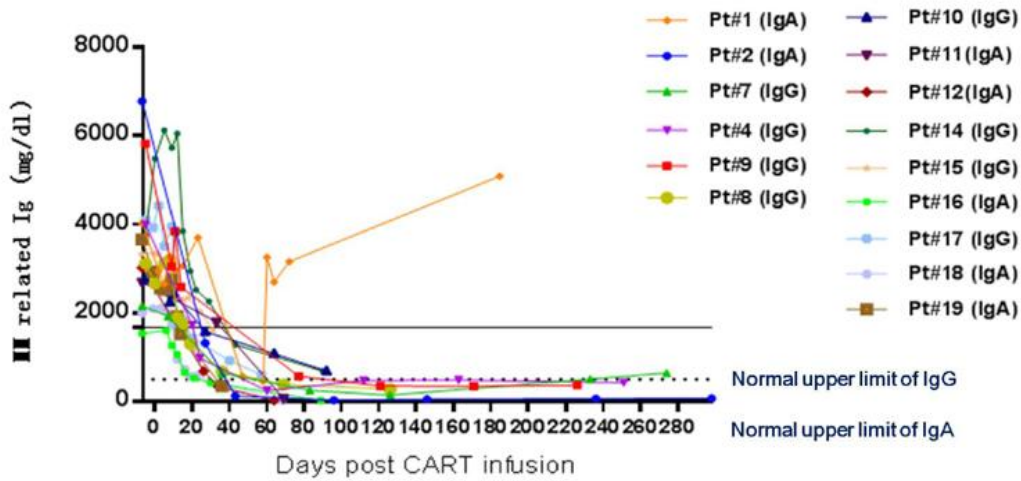


LCAR-B38M



UCSF => First experience with LCAR-B38M

ASCO 2017: Cellular Therapies: LCAR-B38M-CART



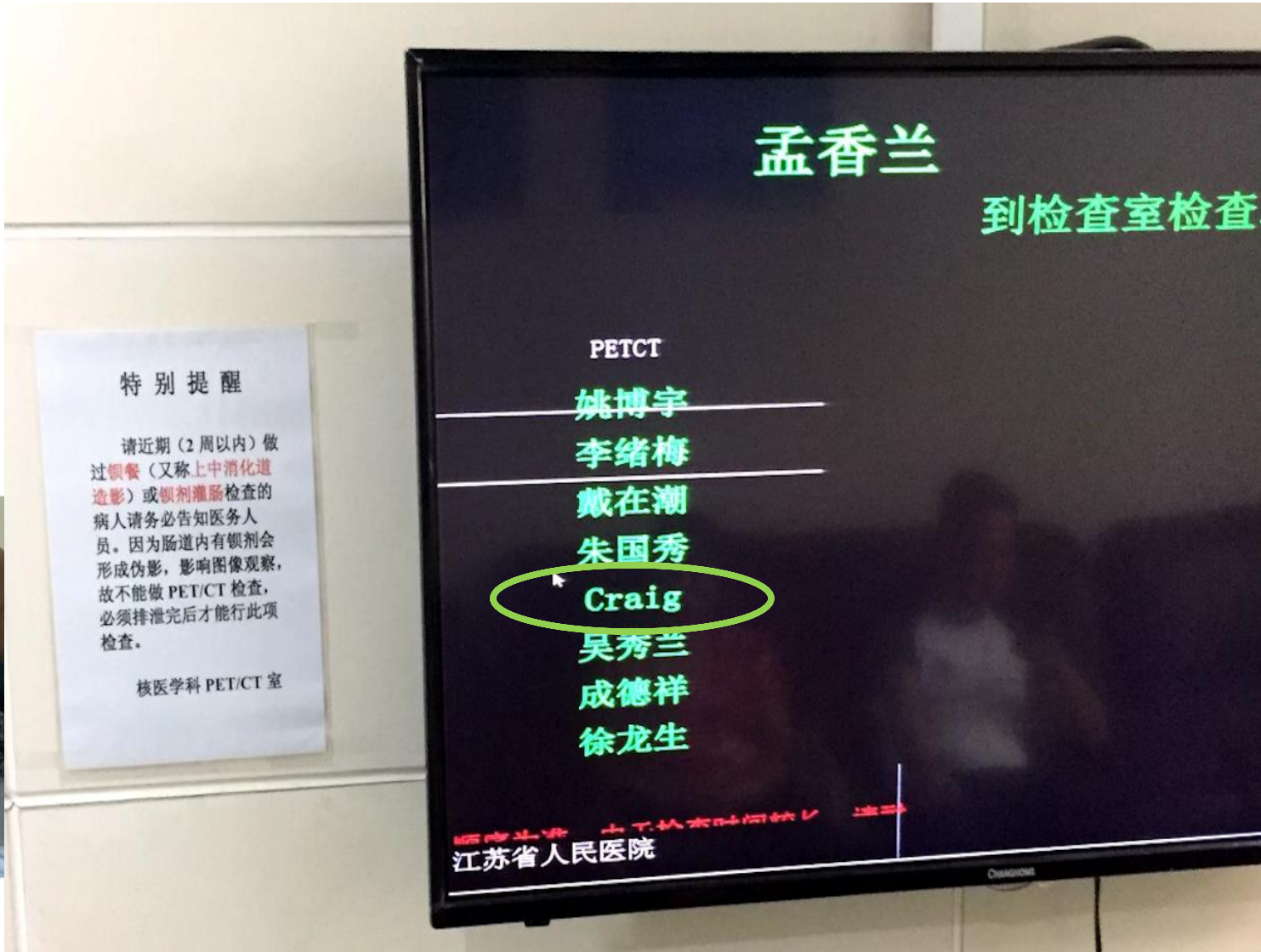
Before treatment



Day 18 after CAR-T



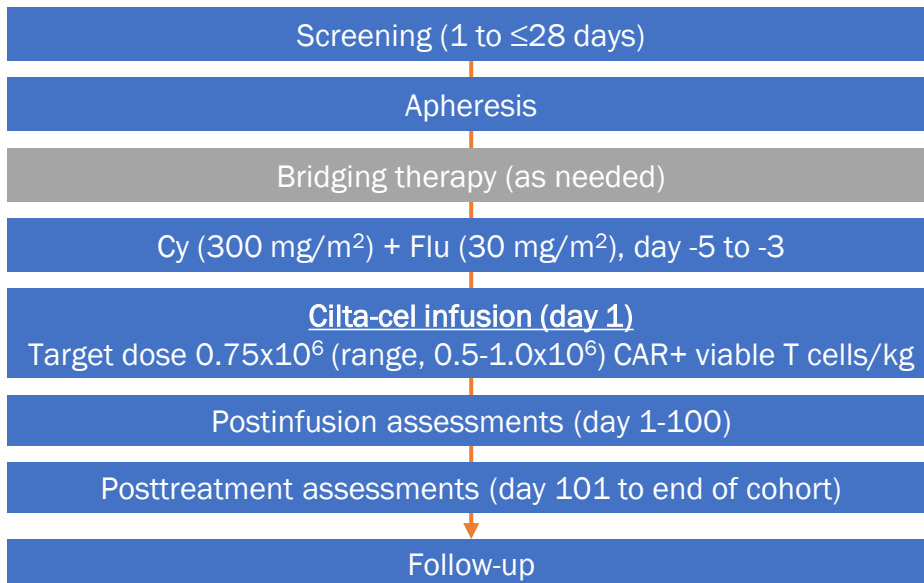
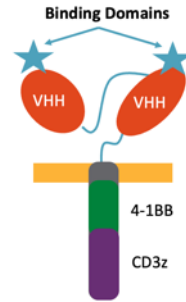
Day 83 after CAR-T



CARTITUDE-1 Phase 1/2: Landmark 2 Years Post-Last Patient-in Results of Cilta-Cel in Patients With RRMM: Study Design and Patients¹⁻³

Key Eligibility Criteria

- Progressive MM per IMWG criteria
- ECOG PS ≤1
- 3 or more prior lines or double refractory
- Prior PI, IMiD, and anti-CD38 mAb



Primary Endpoints

Safety and confirm RP2D (phase 1b); efficacy (phase 2)

Patient Characteristics	Phase 1b (n=29)	Phase 2 (n=68)	Total (N=97)
Median age, years (range)	60 (57-67)	62 (55-70)	61 (56-68)
Extramedullary plasmacytomas, n (%)	4 (14)	9 (13)	13 (13)
BM plasma cells ≥60%, n (%)	7 (24)	14 (21)	21 (22)
High-risk cytogenetics, n (%)	7 (24)	16 (24)	23 (24)
del(17p)	4 (14)	15 (22)	19 (20)
t(14;16)	2 (7)	0	2 (2)
t(4;14)	1 (3)	2 (3)	3 (3)
Tumor BCMA expression ≥50%, n/N (%)	18/20 (90)	39/42 (93)	57/62 (92)
Median prior lines of therapy, n (range)	5 (4-8)	6 (4-8)	6 (4-8)
Prior ASCT, n (%)	26 (90)	61 (90)	87 (90)
Triple-class refractory, n (%)	25 (86)	60 (88)	85 (88)
Penta-refractory, n (%)	9 (31)	32 (47)	41 (42)
Refractory to last line of therapy, n (%)	28 (97)	68 (100)	96 (99)
Median years since diagnosis (range)	5.1 (3.5-7.8)	6.7 (4.6-8.5)	5.9 (4.4-8.4)

- Median administered dose: 0.71x10⁶ (range, 0.51-0.95x10⁶)/kg CAR+ viable T cells/kg

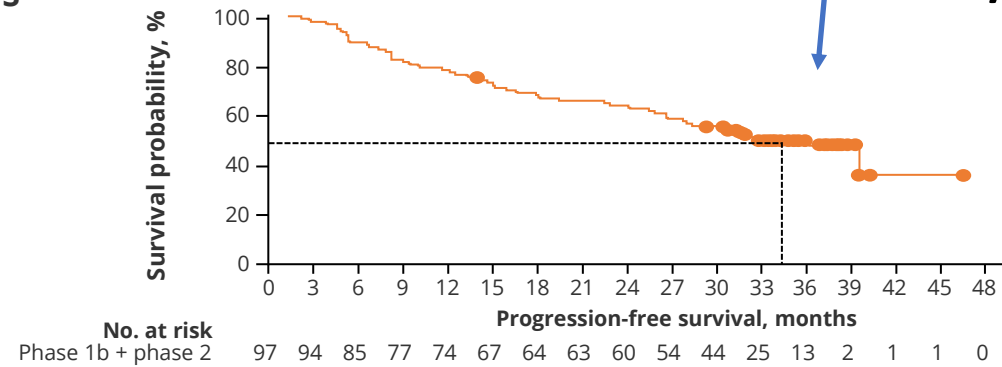
1. Martin T, et al. *J Clin Oncol*. 2022;JCO2200842. doi:10.1200/jco.22.00842. 2. Usmani SZ, et al. ASCO 2022. Abstract 8028.
3. Lin Y, et al. EHA 2022. Abstract P961.

CARTITUDE-1 Results ASCO 2023 – 3 yr f/u

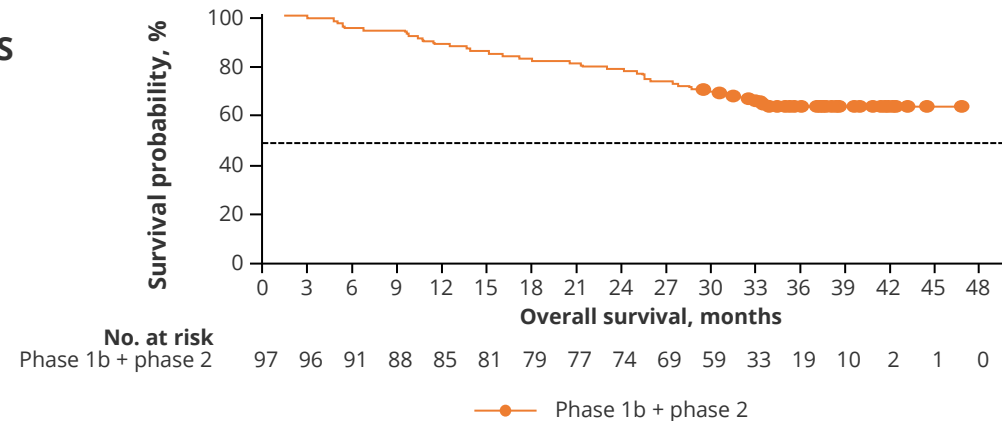
- ORR 98%, sCR 83%
- At study closeout:
 - Median DOR was **33.9 m** (95% CI, 25.5–NE)
 - Median PFS was **34.9 m** (95% CI, 25.2–NE)
 - Median OS was not reached
 - An estimated 62.9% of patients were alive at ~3-year follow-up

Time-to-event outcomes

A) PFS



B) OS



ASCO 2025 (5yr)

?

60

?

60

CARTITUDE-1 Subgroup Analysis: Efficacy Outcomes in Subgroups of Patients Defined by Baseline Characteristics

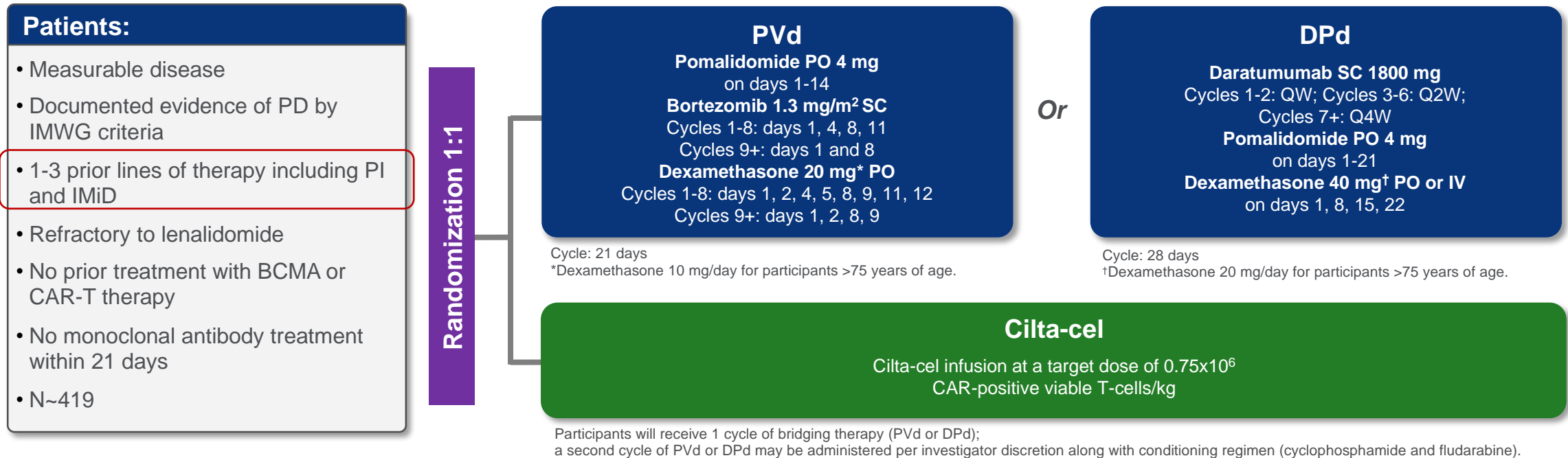
		Patients, n (%)	ORR, % (95% CI)	Median DOR, Months (95% CI)	MRD 10 ⁻⁵ negativity, ^b % (95% CI)	2-year PFS, % (95% CI)	2-year OS, % (95% CI)
Overall		97 (100)	97.9 (92.7–99.7)	NE (21.8–NE)	91.8 (81.9–97.3)	60.5 (48.5–70.4)	74.0 (61.9–82.7)
≥65 years ^a		35 (36)	97.1 (85.1–99.9)	NE (24.3–NE)	91.3 (72.0–98.9)	74.0 (55.9–85.5)	70.9 (45.4–86.1)
Black/African American		17 (18)	100.0 (80.5–100)	NE (6.8–NE)	83.3 (51.6–97.9)	58.2 (31.7–77.5)	57.0 (18.0–83.2)
3 prior LOT		17 (18)	100.0 (80.5–100)	NE (12.9–NE)	80.0 (44.4–97.5)	66.2 (35.5–84.8)	81.4 (52.6–93.6)
≥4 prior LOT		80 (82)	97.5 (91.3–99.7)	NE (20.2–NE)	94.1 (83.8–98.8)	60.2 (47.7–70.7)	71.9 (57.7–82.1)
Triple-class refractory		85 (88)	97.6 (91.8–99.7)	NE (24.3–NE)	92.6 (82.1–97.9)	63.5 (51.8–73.1)	72.7 (59.4–82.2)
Penta-drug refractory		41 (42)	95.1 (83.5–99.4)	NE (NE–NE)	85.0 (62.1–96.8)	68.3 (51.7–80.2)	68.0 (45.9–82.6)
Cytogenetic risk	Standard risk	68 (70)	97.1 (89.8–99.6)	NE (21.8–NE)	95.2 (83.8–99.4)	64.1 (49.5–75.5)	73.6 (58.2–84.0)
	High risk	23 (24)	100.0 (85.2–100)	20.2 (9.4–NE)	82.4 (56.6–96.2)	48.4 (25.1–68.4)	73.7 (50.5–87.2)
ISS Stage III at baseline		14 (14)	100.0 (76.8–100)	13.8 (5.1–NE)	100.0 (54.1–100)	NE (NE–NE)	NE (NE–NE)
Baseline bone marrow plasma cells	≤30%	58 (60)	98.3 (90.8–100)	NE (21.8–NE)	96.6 (82.2–99.9)	66.5 (51.1–78.1)	75.9 (59.1–86.5)
	>30 to <60%	17 (18)	100.0 (80.5–100)	NE (15.9–NE)	87.5 (61.7–98.4)	54.6 (23.0–78.0)	94.1 (65.0–99.1)
	≥60%	21 (22)	95.2 (76.2–99.9)	NE (5.5–NE)	87.5 (61.7–98.4)	51.6 (28.7–70.4)	52.4 (22.4–75.6)
Baseline tumor BCMA expression	≥median (80%)	31 (32)	96.8 (83.3–99.9)	NE (21.8–NE)	94.1 (71.3–99.9)	67.3 (44.8–82.3)	80.9 (58.2–92.0)
	<median (80%)	31 (32)	100.0 (88.8–100)	NE (20.5–NE)	95.7 (78.1–99.9)	63.9 (41.2–79.7)	67.6 (40.8–84.3)
Presence of baseline plasmacytomas ^c		19 (20)	100.0 (82.4–100)	12.9 (4.0–NE)	90.9 (58.7–99.8)	47.4 (24.4–67.3)	46.4 (15.8–72.6)

^aThere were 8 patients aged ≥75 years. No difference was observed in ORR between these patients and other age subgroup; ^bIn MRD-evaluable patients; MRD was assessed in evaluable samples at 10⁻⁵ threshold by next-generation sequencing (clonoSEQ, Adaptive Biotechnologies) in all treated patients at day 28, and at 6, 12, 18, and 24 months regardless of the status of disease measured in blood or urine. Only MRD assessments (10⁻⁵ testing threshold) within 3 months of achieving CR/sCR until death/progression/subsequent therapy (exclusive) are considered; ^cIncludes bone-based and extramedullary plasmacytomas.

BCMA, B-cell maturation antigen; CR, complete response; DOR, duration of response; ISS, International Staging System; LOT, lines of therapy; MRD, minimal residual disease; NE, not estimable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; sCR, stringent complete response



CARTITUDE-4 (Phase 3) Study Design: 1-3 PLT



Primary Outcome:	Secondary Outcomes:
<ul style="list-style-type: none"> • Progression-free survival 	<ul style="list-style-type: none"> • CR or sCR • MRD negativity status • Sustained MRD negative rate • HRQoL • OS, ORR, PFS2 • Safety

Primary endpoint of PFS was met and study now reported

CARTITUDE 4: Randomization and Results

- Results

- FIGURE 1: Primary Endpoint PFS:

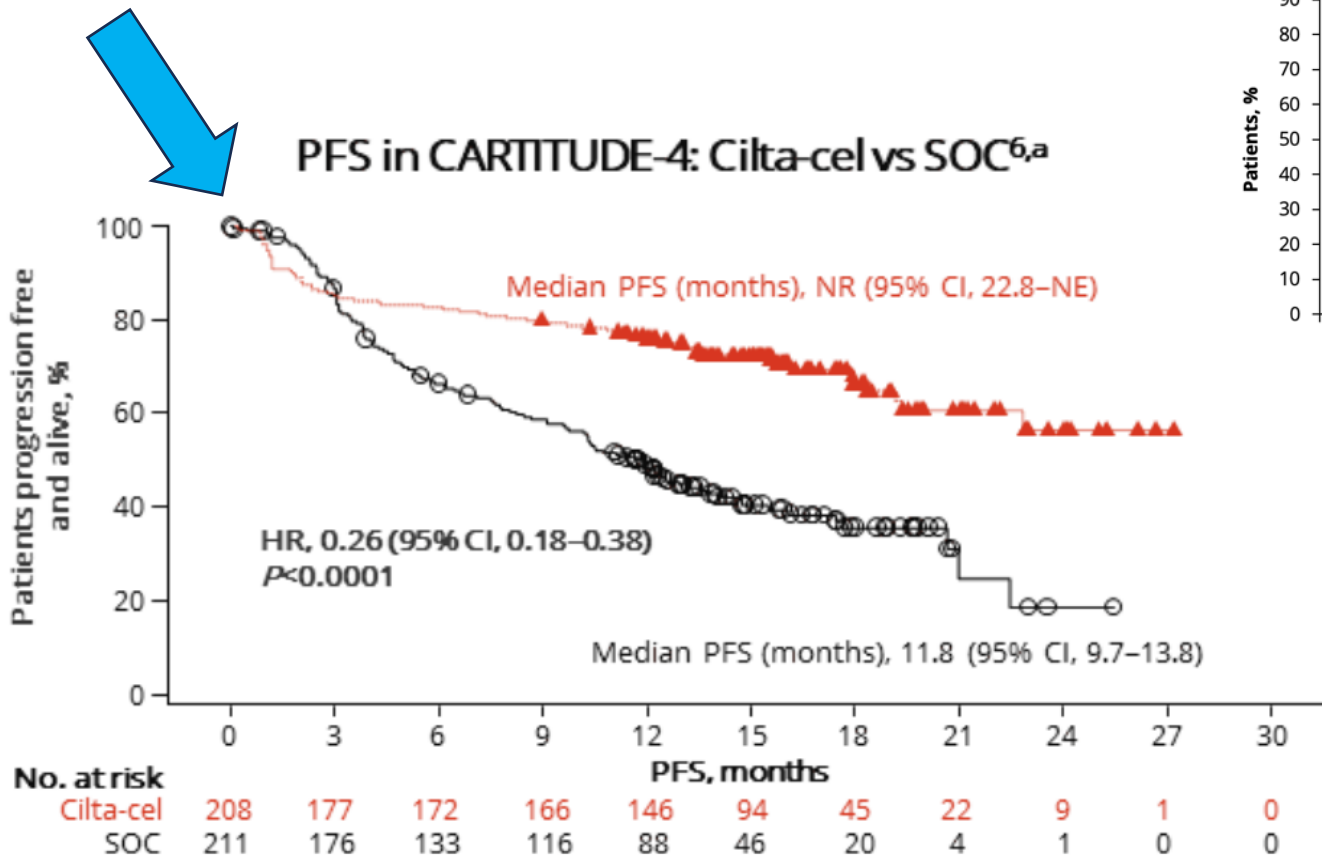
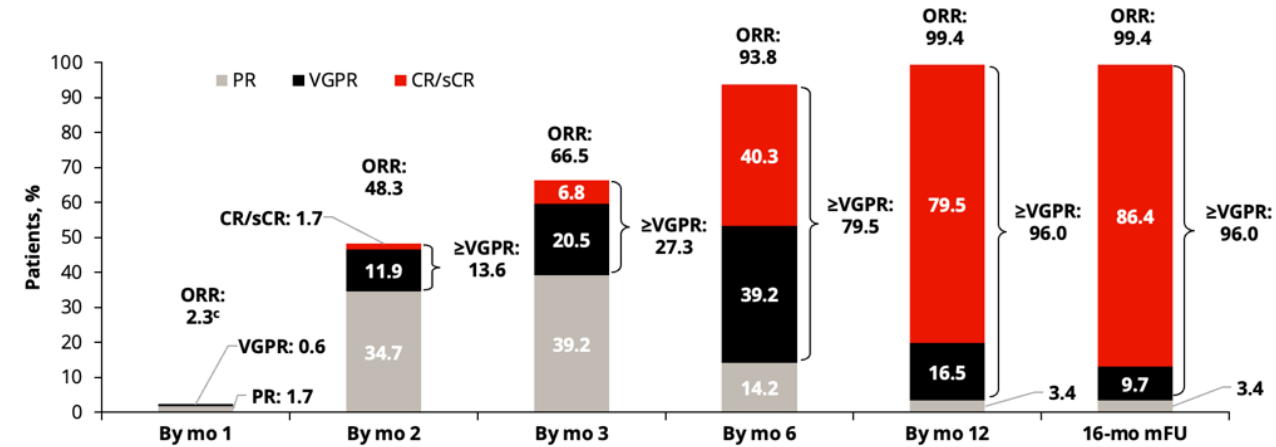
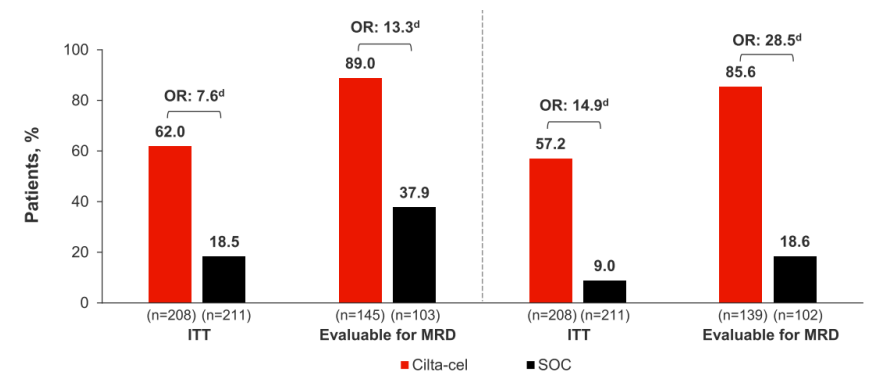


FIGURE 2: Responses deepened over time^{a,b}

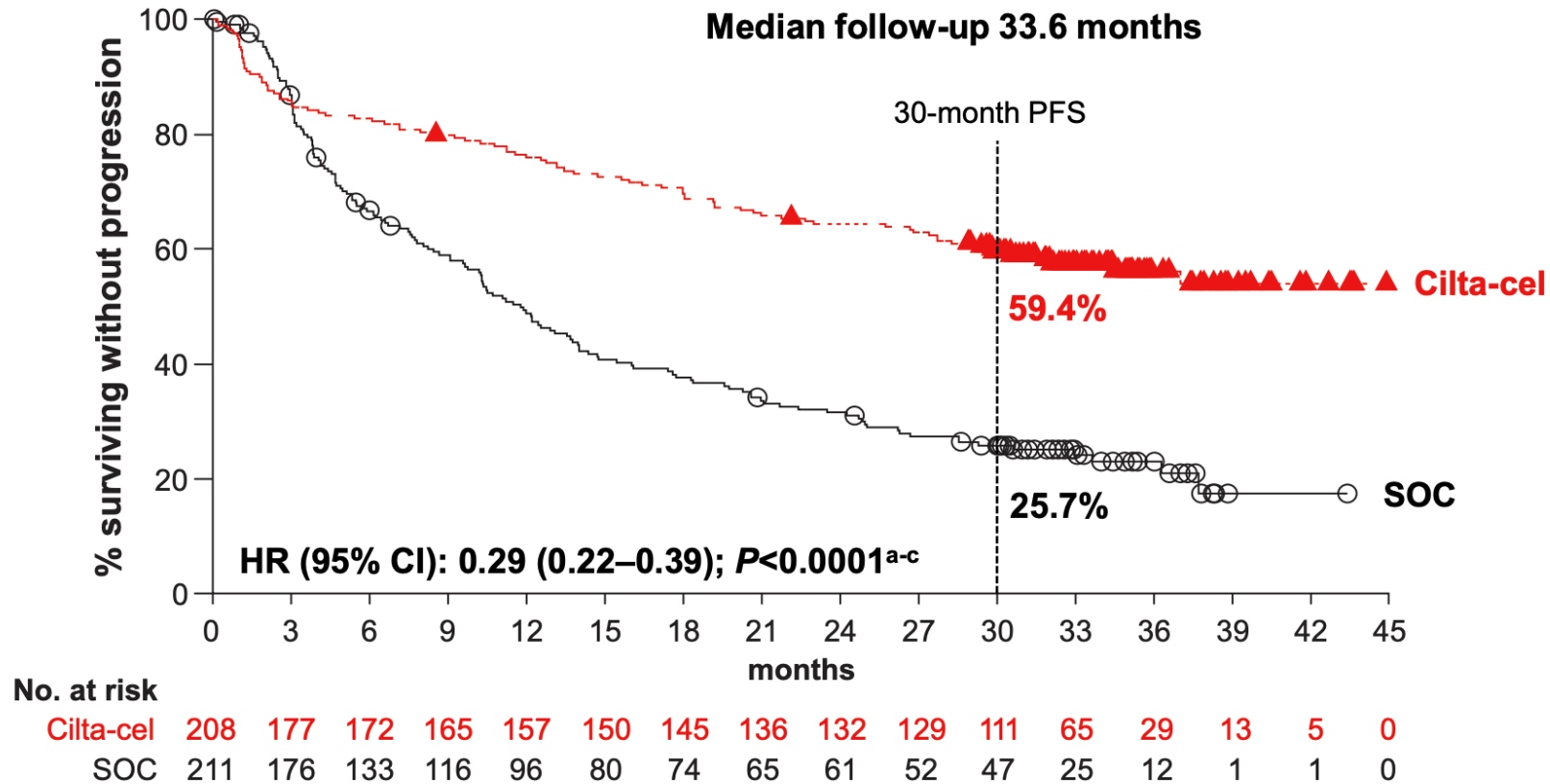


MRD(-)



^aStart of study treatment. ^bPhysicians' choice. ^cCyclophosphamide 300 mg/m² plus fludarabine 30 mg/m² daily for 3 days. DPd, daratumumab, pomalidomide, and dexamethasone; PD, pharmacodynamics; PK, pharmacokinetics; PVd, pomalidomide, bortezomib, and dexamethasone.

Long-Term CARTITUDE-4 Update (34 Months): Cilta-cel Maintained Significant Improvement in Progression-Free Survival



~70% reduction in the risk of progression or death in patients who received cilta-cel and mPFS has not been reached

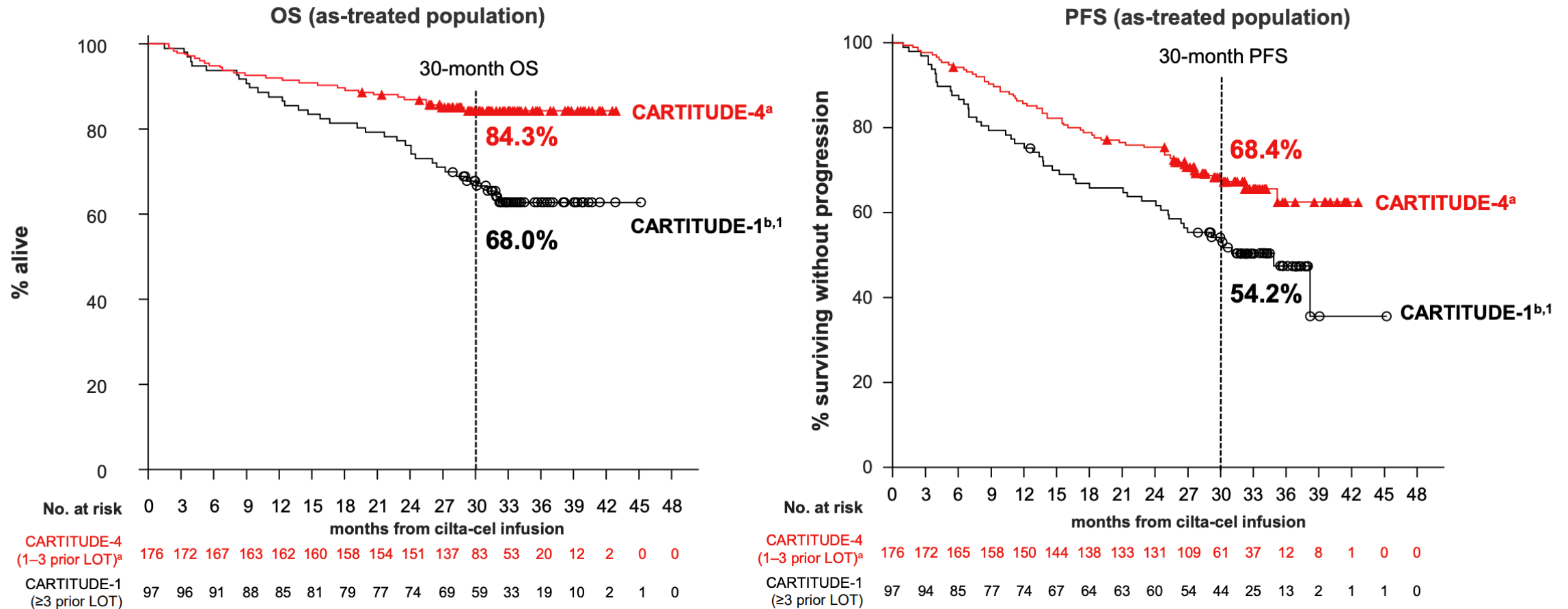
^aConstant piecewise weighted log-rank test. ^bHR and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable, including only PFS events that occurred >8 weeks post randomization.

^cNominal P value.

Cilta-cel, ciltacabtagene autoleucel; HR, hazard ratio; mPFS, median progression-free survival; PFS, progression-free survival; SOC, standard of care.



Long-Term CARTITUDE-4 Update (34 Months): Numerically Higher Overall and Progression-Free Survival Rates Versus CARTITUDE-1



Cilta-cel use in earlier lines demonstrated numerically higher rates of overall and progression-free survival

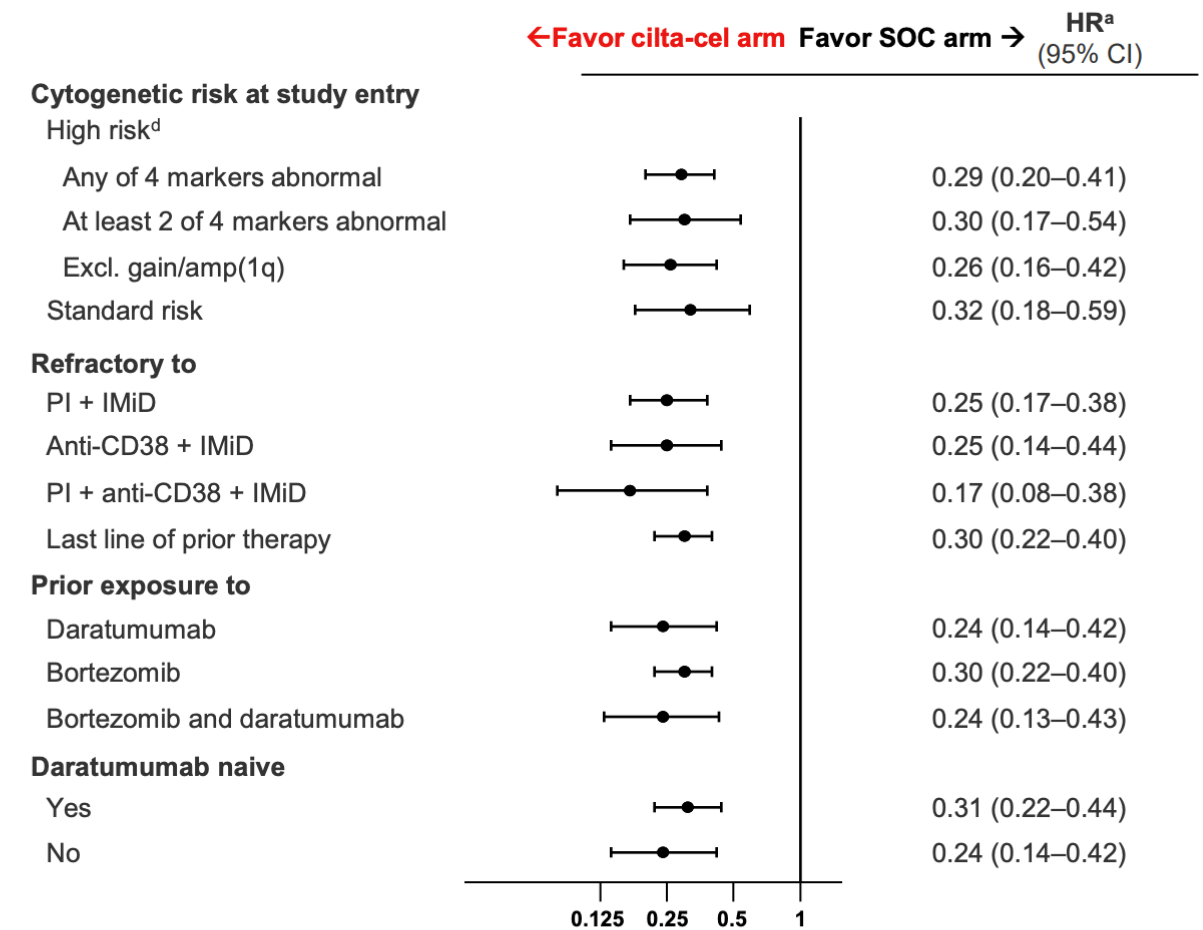
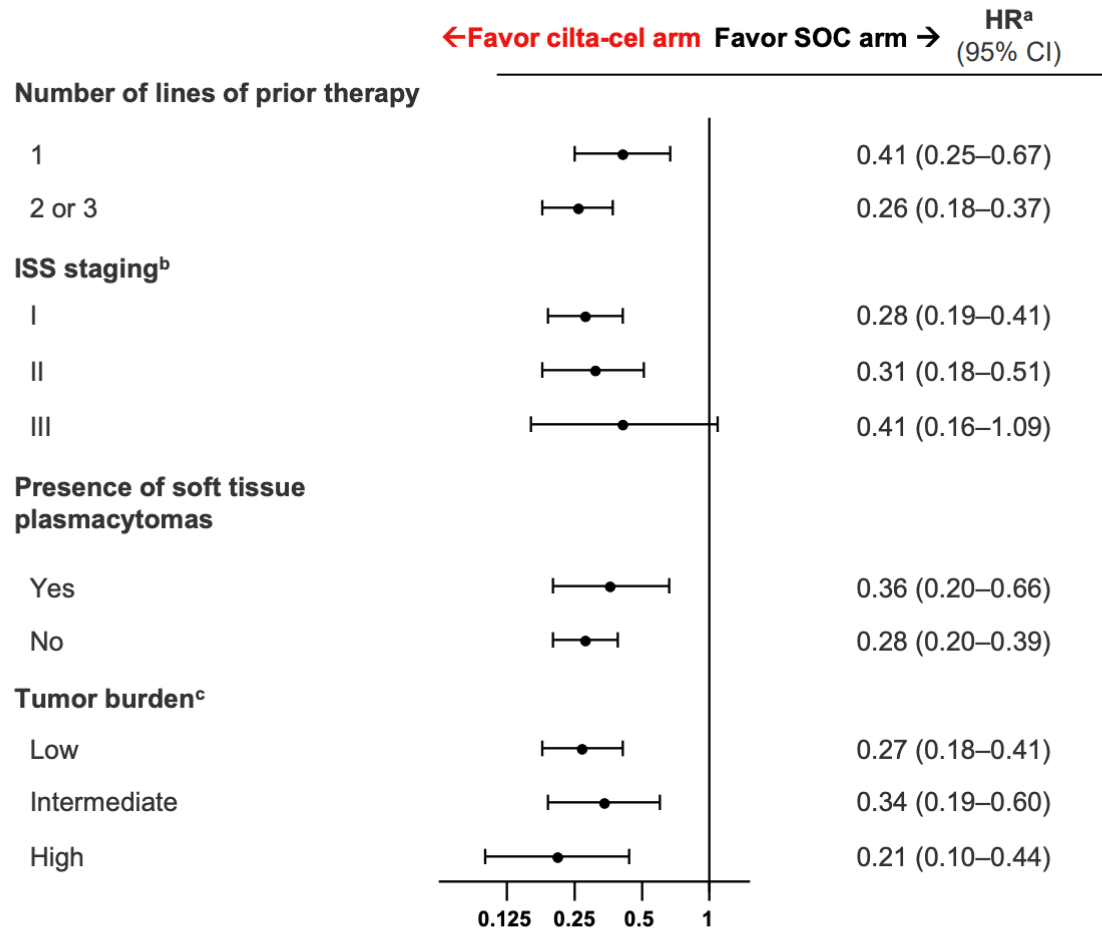
^aRe-baselined to begin at time of cilta-cel infusion for patients who received cilta-cel as study treatment, with median follow-up of 30.5 months. ^b33.4-month median follow-up.

Cilta-cel, ciltacabtagene autoleucel; LOT, line of therapy; OS, overall survival; PFS, progression-free survival; SOC, standard of care.

1. Lin et al. Abstract 8009, presented at ASCO; June 2-6, 2023; Chicago, IL, USA & Virtual.



Long-Term CARTITUDE-4 Update (34 Months): Consistent Progression-Free Survival Benefit for Cilta-cel Across All Prespecified Subgroups



Consistent reduction in the risk of progression or death across all prespecified subgroups

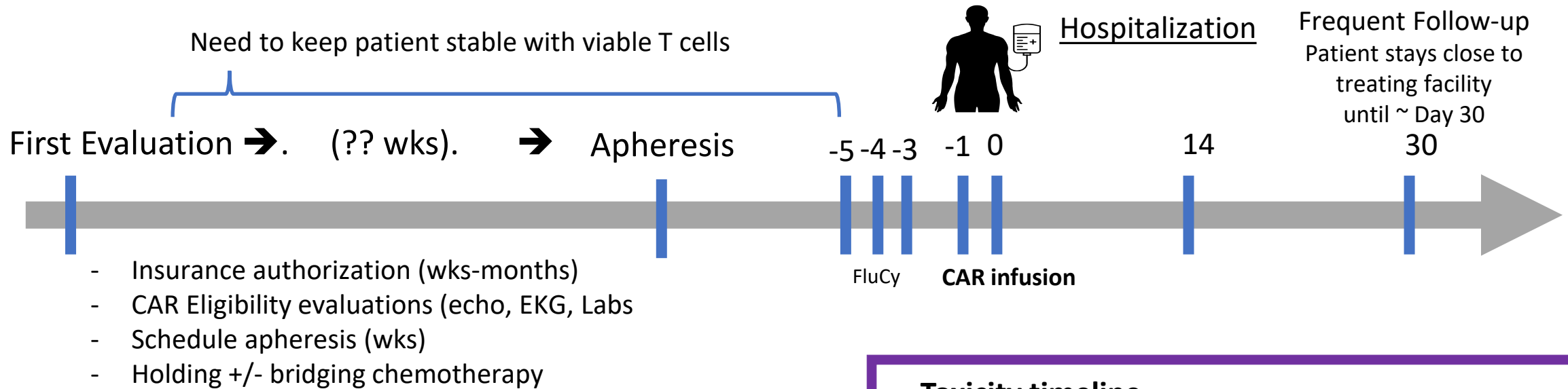
^aHR and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable, including only PFS events that occurred >8 weeks post randomization. ^bBased on serum β_2 -microglobulin and albumin. ^cLow tumor burden defined as meeting all following parameters (as applicable): bone marrow % plasma cell <50%, serum M-protein <3 g/dL, serum free light chain <3000 mg/L; high tumor burden defined as meeting any of the following parameters: bone marrow % plasma cell \geq 80%, serum M-protein \geq 5 g/dL, serum free light chain \geq 5000 mg/L; intermediate tumor burden did not fit either criteria of high or low tumor burden. ^dPositive for del(17p), t(14;16), t(4;14), and/or gain/amp(1q) by fluorescence in situ hybridization testing. Protocol-defined high-risk cytogenetics refers to "Any of 4 markers abnormal." Cilta-cel, ciltacabtagene autoleucel; HR, hazard ratio; IMiD, immunomodulatory drug; ISS, International Staging System; PFS, progression-free survival; PI, proteasome inhibitor; SOC, standard of care;



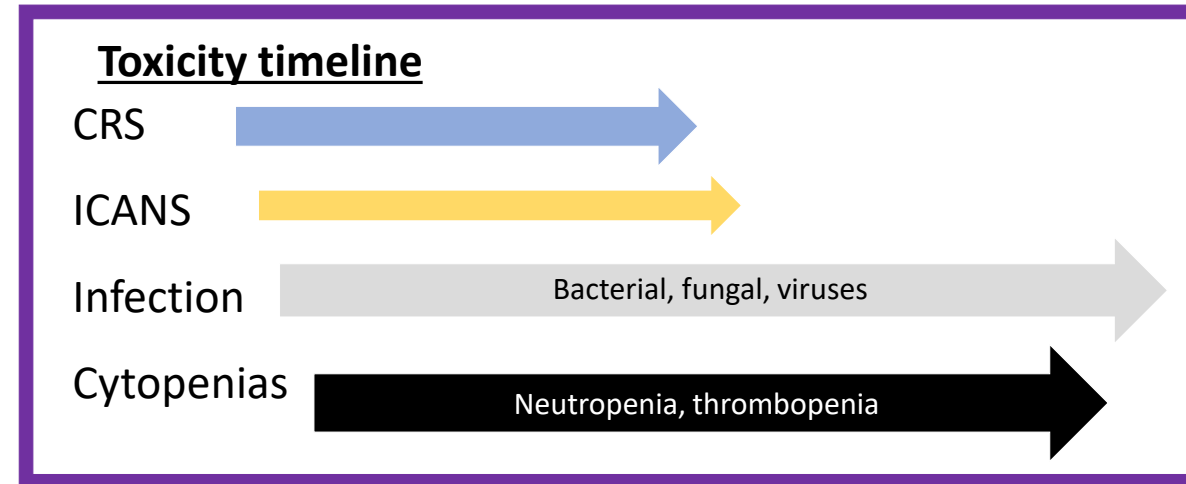
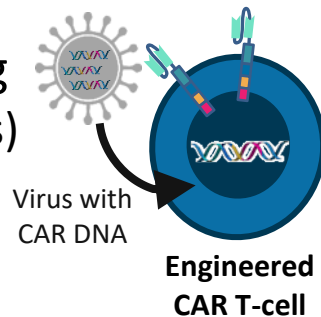
Toxicity With CAR T-Cell Therapy in MM

CAR T-Cell Associated Adverse Events	Management of Adverse Events
Cytokine-release syndrome (70-90%)	Day 1-21 → tocilizumab, steroids, anti-inflammatories
Neurotoxicity. (10-28%) aka, immune effector cell–associated neurotoxicity syndrome	Day 1-28 and <u>late effects</u> → seizure prophylaxis, steroids, cyclophosphamide, hyperventilation
Cytopenias (90%) – Late cytopenias (20-30%)	Cytopenias → growth factors (after CRS)
Immunosuppression: (>50%) “B-cell aplasia”/hypogammaglobulinemia	Hypogammaglobulinemia → prophylactic IVIG
Infection (30-60%)	Infection → HSV, VZV, encapsulated bacteria; acyclovir, sulfamethoxazole/trimethoprim, other
IEC-HS (MAS-like syndrome (<5%))	IEC-HS → IL-1 targeted therapy, steroids

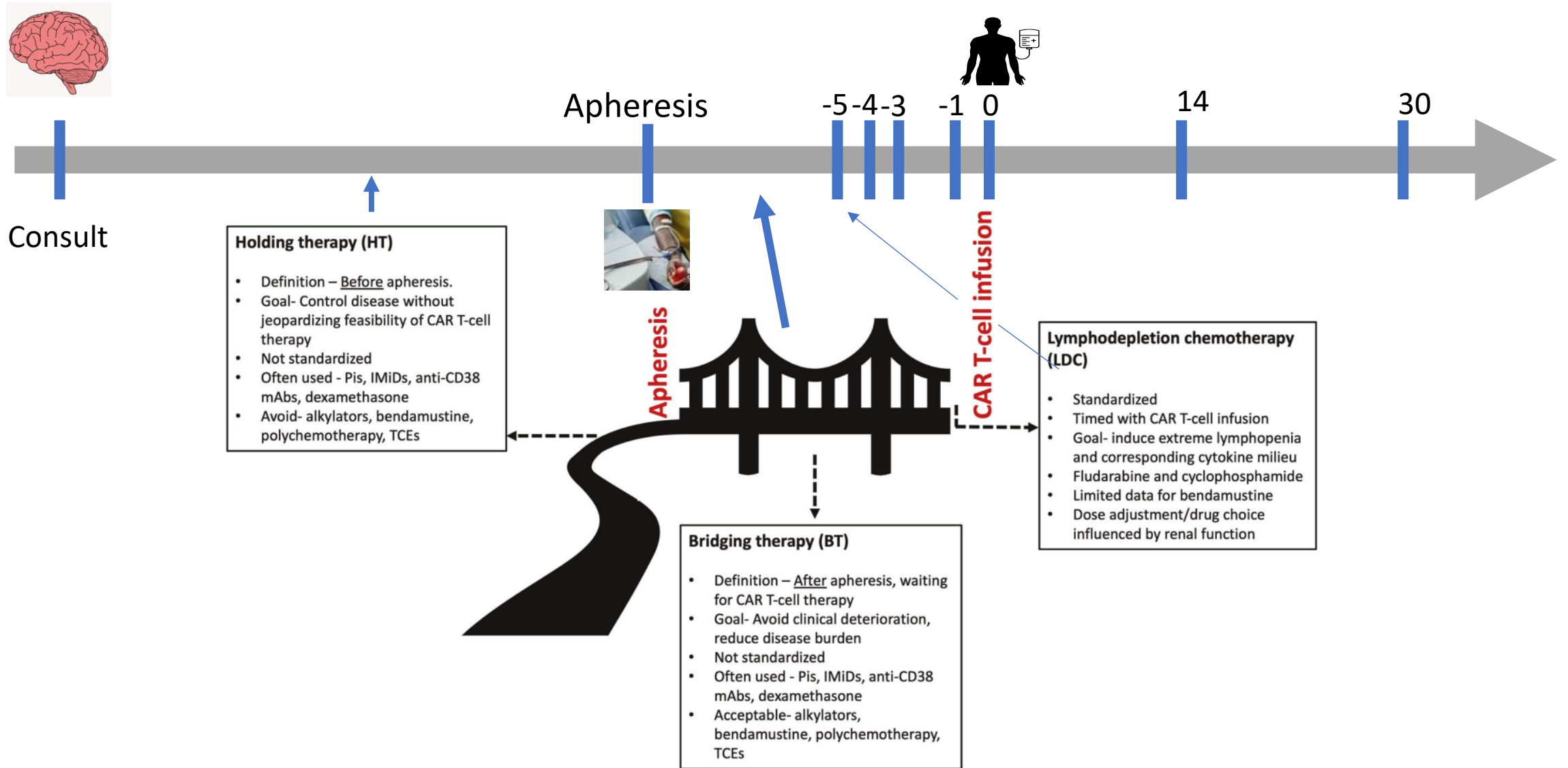
CAR T-Cell Journey: Need to optimize to succeed



T-cell manufacturing
And release (6-9 weeks)

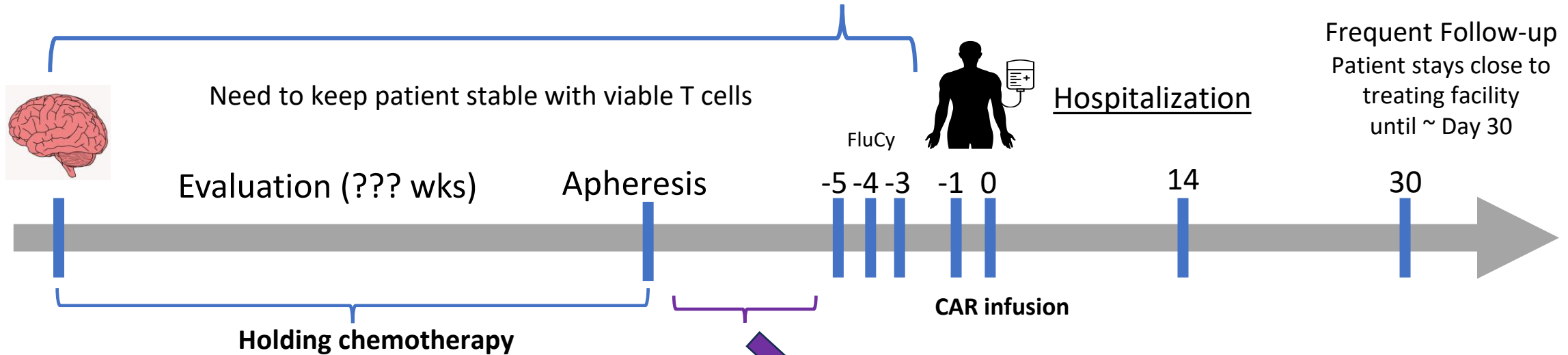


CAR T-Cell Journey: Brain to Vein to Vein



CAR T-Cell Journey

Brain to Vein time



Goals (pre-apheresis)

- Preserve T cell Fitness
 - **Avoid** lymph-toxic Rx
 - High-dose **Alkylators**
 - **Bispecific Antibodies**
 - If not (need >6-8 week treatment-free interval, ANC >0.3)
- Maintain disease control
 - Don't wait – start treatment urgently
 - Use new agents or “sensitive” agents

Bridging therapy

- Can use bispecifics
- Can use high-dose alkylators
 - May have higher risk for Cytopenias
 - ? Risk for secondary malignancies

Practice Considerations/Implementation

Choosing the right patient

- IMWG CAR Guidelines – Lancet Oncology 5/2024
- Prepare patient for CAR @ Line “minus one”
 - Example – 3rd line (if not len-refractory)
 - W/u in 3rd line – all ready
 - When 4th line starts => can get insurance auth....
 - Ideal is to proceed in response/before relapse
 - Goal is to collect T-cells in response
- Apheresis is ideal when
 - ALC > 0.5
 - Limited steroids/alkylator therapy (> 8 wks)
 - No bispecific antibody therapy for >8 wks

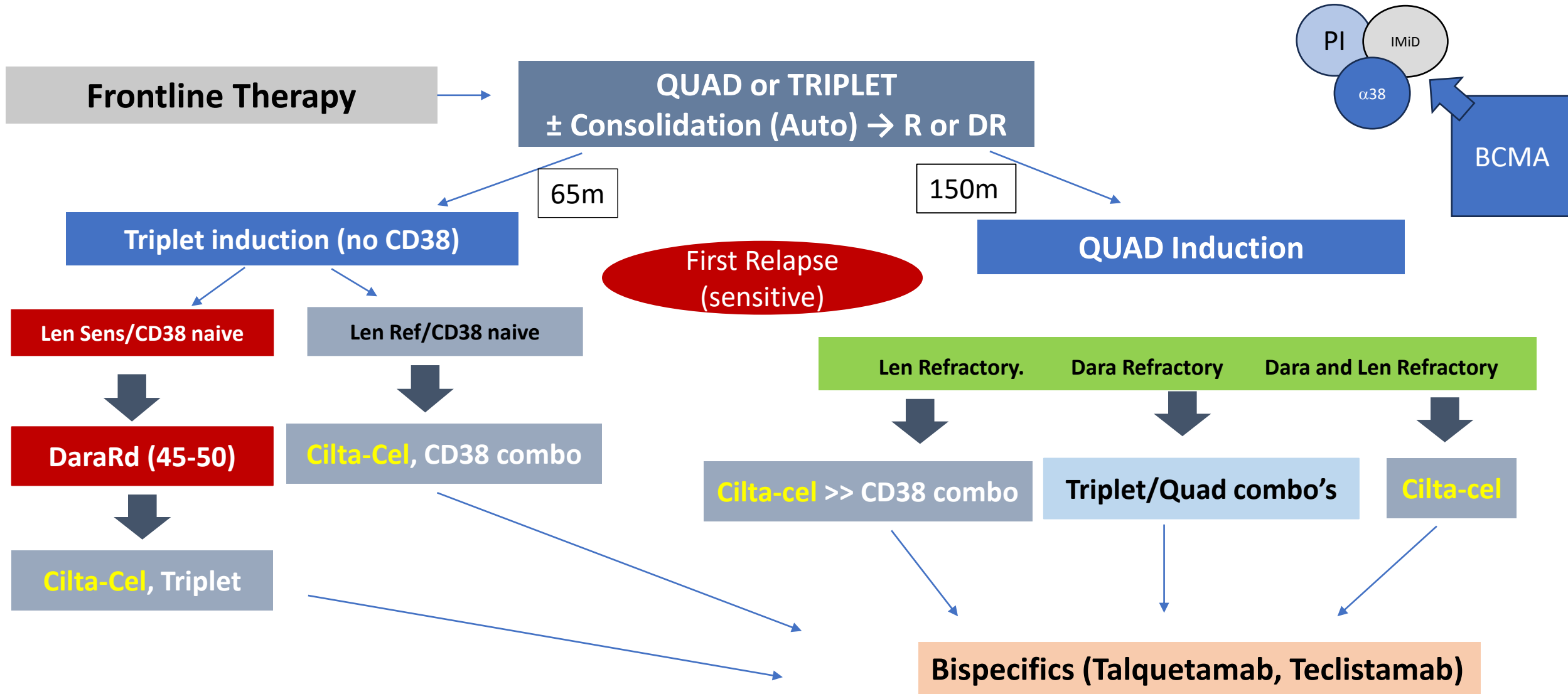
Building the right TEAM

- **Education**
 - Heme/BMT/CT, ICU, ER, Neurology
 - MDs, Nurses pharmacists
 - Patient wears “CART” wrist brace
 - Patient and caregiver
- **Good Communication amongst the team**
 - 24 hour call line for patients and caregivers
 - Close collaboration with Community MDs!!
- **Good Social Support**
 - Housing and Financial support
 - Patient Navigator
- **Quality Management**
- **Know your Center’s Data**

Case(s) #1: Presentation

- MV is a 44 y/o male with RRMM – s/p 4 lines of therapy
- Baseline:
 - DX: 2021 IgA Lambda MM
 - BMBx (2/16/21): 80% PCs; del 13q/-13
 - Hypercalcemia, IgA 5086 mg/dL, LLC 1521, FLCr 492.29
 - B2M-4.2, Alb 3.4, LDH 191
 - DS stage 3, ISS-2, R-ISS-2
- Treatment:
 - LINE1: **Dara-VRd=> Mel 200 (7/10/21) => Dara-Rev maint Resp; VGPR=> PFS 18M**
 - **FUNCTIONAL HIGH-RISK! And REFRACTORY to DARA-LEN**
 - LINE2: ? What are the choices ?

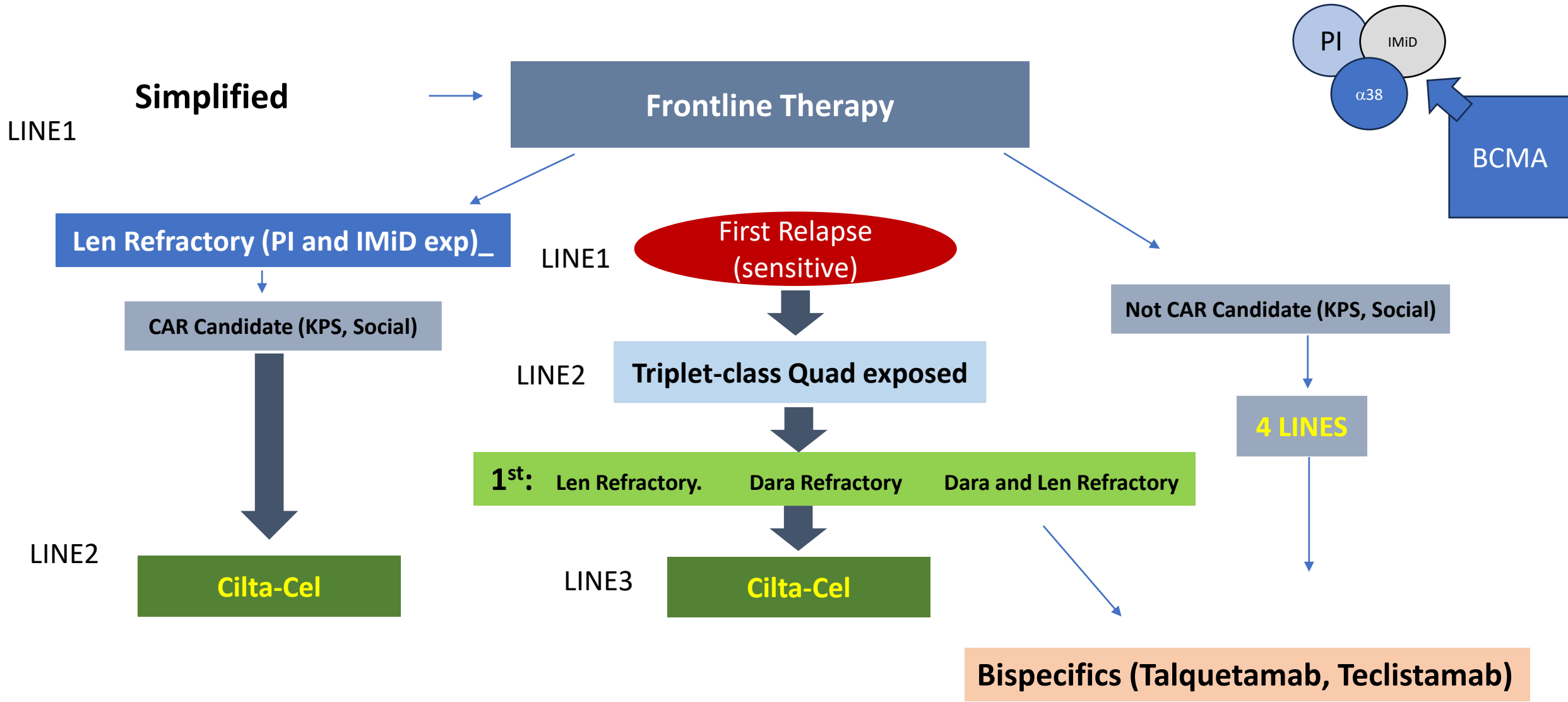
Sequencing Therapy for Patients With R/R MM



Clinical trial should be considered for all eligible patients

*UCSF : Protocol

Sequencing Therapy for Patients With R/R MM



Golden Moment for CART is Line 2 or 3 For RRMM patients

*UCSF : Protocol

Case(s) #1: Presentation

- MV is a 44 y/o male with RRMM – s/p 4 lines of therapy
- Baseline:
 - DX: 2021 IgA Kappa MM, DS stage 3
 - BMBX (12/16/21): 80% PCs; del 13q/-13
 - Hypercalcemia, IgA 5086 mg/dL, LLC 1521, FLCr 492.29, B2M-ND
- Treatment:
 - LINE1: **Dara-VRd**=>6-cycles – VGPR
 - **Mel 200** (7/10/22) => **Dara-Rev maint** Resp; **VGPR=> PFS 18M**
 - **[FUNCTIONAL HIGH-RISK!] – m-prot 3.2 g/dL →. START Thinking CAR**
 - LINE2: KPd. Started at relapse (2/2024) → **VGPR after 3 cycles**
 - Insurance approval sought for CAR T and pre-CAR w/u initiated
 - Excellent KPS => Discussion and Plan BCMA CART **[Cilta-cel preferred]**



Case(s) #1: Presentation



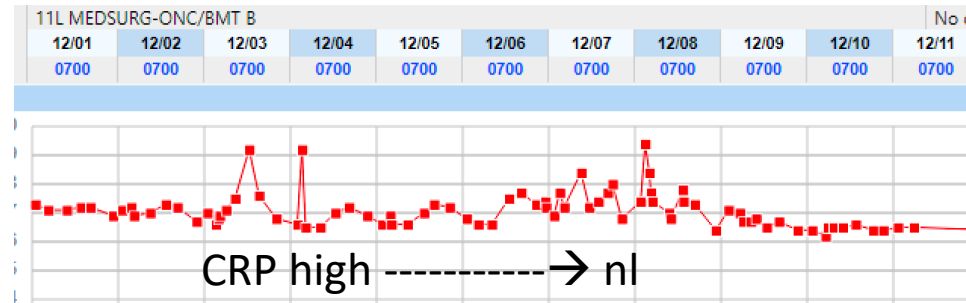
- Apheresis: 08/12/2024
 - 14 liter collection
 - ALC 0.31
 - Bridging Therapy:
 - KPd x 1 cycle
 - Response: **VGPR** – m-prot 0.3 gm, **BM 3%PCs**
 - Cells “ready”: ~10/02/24; Infused 11/30/24
 - Patient **proceeded to CAR**
- Brain to vein (6m – but getting treatment)
- Earlier time to CAR – less chance of OOS product

Case(s) #1: Presentation

- CAR Therapy:
 - LD - Flu/Cyt
 - Cilta-cel infused 11/30/2023: Cilta-cel infused: $0.7 \times 10^6/\text{kg}$

- Toxicity:

- **CRS:** Max Gr1
Toci x 2
- **ICANS:** None
12/7
 - ALC peak: 3.1 @14d
- **HLH/IEC-HS:** Max Ferritin ~6000. Fibrinogen 170
- Cytopenia: Resolve by Day 30
- Response: Day 90 sCR – MRD(-)



CRS
treated with

12/3 and
Dex 10 Q12 x6 doses x 2

Conclusions: *Cilta-Cel* and *Bispecific* therapy

- Amazing responses
 - Best patients do better with immunotherapies early
 - Earlier lines of therapy [patients want QOL NOW]
 - At UCSF prefer CAR for less heavily pretreated
- Early Relapse: CAR vs. Bispecific
 - Excellent response to CAR in early relapsed MM
 - *Is it better than late relapse; or do we “save for later”?*
- Late Relapse
 - Bispecifics may be best therapy for late relapse
 - May have lower responses with prior BCMA therapy
- Currently no maintenance after CAR therapy



Bring down costs!