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CAR-T Cell Therapy in Multiple Myeloma

Surbhi Sidana, MD
Stanford University

Disclosures

Consulting Fees: Magenta Therapeutics, BMS, Janssen, Sanofi, Oncopeptides

Contracted Research: Magenta Therapeutics, BMS, Allogene, Janssen

I will be discussing non-FDA approved indications during my presentation

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Objectives

1. Review BCMA CAR-T: FDA approved and advanced clinical development (ide-cel, cilta-cel)
2. Other BCMA targeted CAR-T therapies in US
3. Non-BCMA targets in development

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Triple Class and Penta Refractory MM: Poor Outcomes

MAMMOTH study	Median OS
Triple Class Refractory (PI, IMiD, anti-CD38)	**8.6 months**
Penta Refractory (2 PIs, 2 IMiDs, anti-CD38)	**5.6 months**

MAMMOTH study: Outcomes with next line treatment in triple class refractory MM

- **Overall response rate: 31%**
- **Median PFS: 3.4 months**
- **Median OS: 9.3 months**

Gandhi et al. *Leukemia*. 2019;33(9):2266-2275

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Recent FDA approved drugs in triple class refractory MM

	ORR	Median PFS	Median OS
Selinexor[1]	26%	3.7 months	8.6 months
Belantamab mafodotin[2,3]	31%	2.8 months	13.5 months
Melphalan flufenamide[4]	26%	4.2 months	11.2 months

1. Chari et al. NEJM 2019;381(8):727-738; 2. Lonial et al. *Lancet Oncol*. 2020;21(2):207-221; 3. Lonial et al. ASCO 2020 abstract 436, JCO 2020;38(15_suppl):8536; 4. Richardson et al. JCO. 2021;39(7):757-767.

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Targets for CAR-T in MM

BCMA (several constructs)

- Ide-cel
- Cilta-cel
- Others

In early development

- CS1 (SLAMF7)
- CD138
- CD38
- GPRC5D
- Others

Sidana and Shah. *Blood Adv*. 2019;3(21):3473-348

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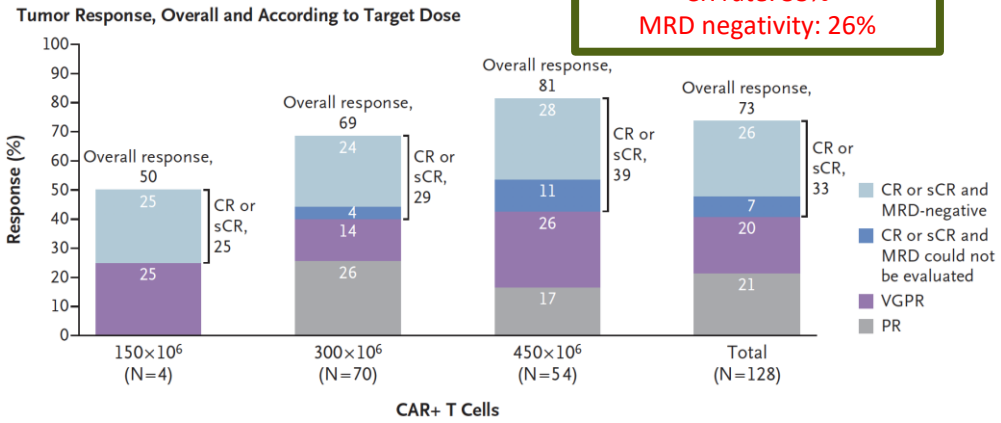
Idecabtagene Vicleucel (Ide-cel): FDA Approved March 2021

Baseline Characteristics	N=128
Median age	61 years
Target dose	300-450 million
Median Prior Lines	6
Triple Class Refractory	84%
Penta Refractory	26%
Bridging Therapy	88%

Overall response rate: 73%
CR rate: 33%
MRD negativity: 26%



Munshi et al. NEJM 2021;384(8):705-716

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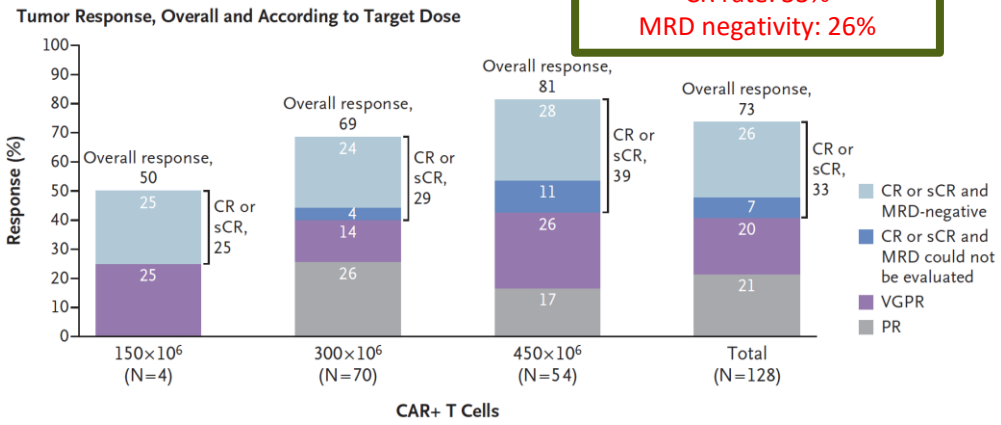

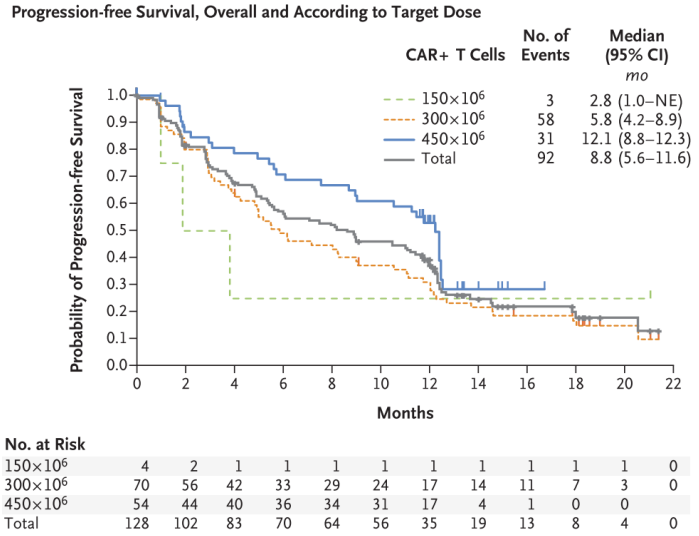

Survival Outcomes	
Median PFS	8.8 months
Median PFS in CR	20.2 months
Median OS	19.4 months

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Munshi et al. NEJM 2021;384(8):705-716

Ide-cel:Safety

Adverse Events	
CRS (all; grade 3 or 4)	84% (5%)
Median time to onset of CRS	1 day
ICANS (all; grade 3 or 4)	18% (3%)
Infections (all; grade 3 or 4)	69% (22%)
Grade 3 or 4 neutropenia > 1 month	41%
Grade 3 or 4 thrombocytopenia > 1 month	48%

* Long term cytopenias:> 1 month post-CAR-T

Munshi et al. NEJM 2021;384(8):705-716

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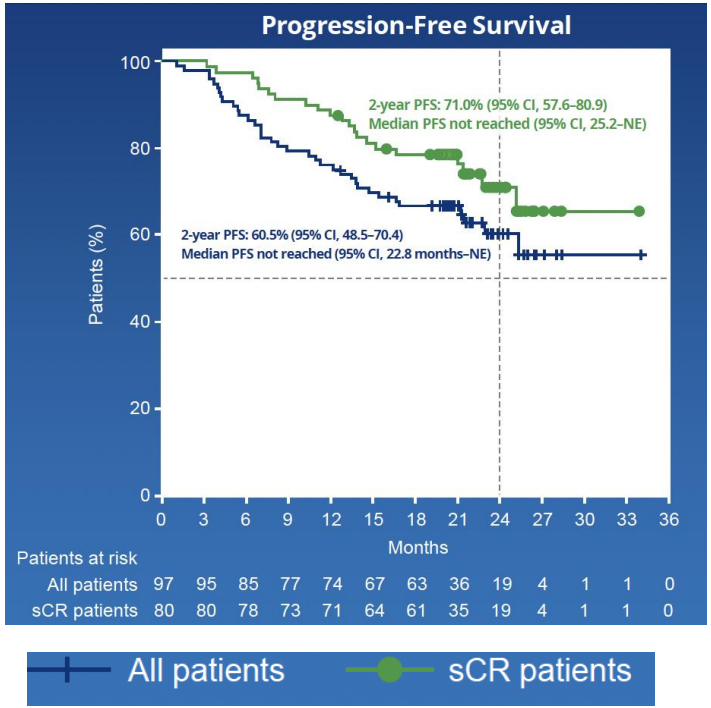
Ciltacabtagene Autoleucel (Cilta-cel)

Baseline Features	
N	97
Target CAR-T Dose	0.75 million/kg
Median age	61 years
Median prior lines	6
Triple Class Refractory	88%
Penta Refractory	42%

Efficacy	
ORR	98%
sCR rate	83%
MRD negative rate (10^{-5})	58%[2]
PFS	2 year: 61%, median NR
OS	2 year: 74%, median NR



1. Martin et al. ASH 2021
2. Usmani et al ASCO 2021

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Cilta-Cel: Safety

Adverse Events	
CRS (all; grade 3 or 4)	95% (5%)
Median onset of CRS	**7 days**
ICANS (all; grade 3 or 4)	17% (2%)
Infections (all; grade 3 or 4)	58% (20%)
Grade 3 or 4 neutropenia > 1 month*	10%
Grade 3 or 4 thrombocytopenia > 1 month*	25%
Delayed neurotoxicity (all; grade 3 or 4)	**12% (9%)**

* Long term cytopenias: > 1 month from onset of cytopenias

1. Martin et al. ASH 2021; 2. Usmani et al ASCO 2021 abstract 8005; 3. Madduri et al ASH 2020 abstract 177

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Delayed Neurotoxicity with Cilta-cel[1,2]

- All grade: 12%, grade 3: 9%
- Median onset: 27 days (range: 11-108)
    1. Movement/Neurocognitive Changes: 5
    2. Nerve palsy, peripheral motor neuropathy: 7
- Mechanism of delayed neurotoxicity: unclear
- Risk Factors: high-tumor burden, CRS/ICANS, high CAR expansion.
- No further events after mitigation strategies
- No delayed neurotoxicity reported in ide-cel KarMMa-1 trial, package insert of ide-cel notes incidence of grade 3 parkinsonism and grade 3 myelitis in another trial

1. Madduri et al ASH 2020 abstract 177; 2. Usmani et al ASCO 2021 abstract 8005

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Cilta-cel vs Ide-Cel

Baseline Features	Cilta-cel[1]	Ide-cel[3]
N	97	128
Target CAR-T Dose	0.75 million/kg	300-450 million
Median age	61 years	61 years
Median prior lines	6	6
Triple Class Refractory	88%	84%
Penta Refractory	42%	26%

Comparable treatment history, but…

Differences in patients difficult to appreciate with this rudimentary comparison of baseline variables

- Trajectory of relapse/aggressiveness of disease
- T-cell health
- Co-morbidities/marrow reserve

1. Martin et al ASH 2021; 2. Usmani et al ASCO 2021abstract 8005; 3. Munshi et al. NEJM 2021;384(8):705-716;

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Cilta-cel vs Ide-Cel

Comparable toxicity, except timing of CRS and delayed neurotoxicity with cilta-cel

Toxicity	Cilta-cel[1,2]	Ide-cel[3]
CRS (all; grade 3 or 4)	95% (5%)	84% (5%)
Median onset of CRS	**7** days	**1** day
ICANS (all; grade 3 or 4)	17% (2%)	18% (3%)
Infections (all; grade 3 or 4)	58% (20%)	69% (22%)
Grade 3 or 4 neutropenia > 1 month*	10%	41%
Grade 3 or 4 thrombocytopenia > 1 month*	25%	48%
Delayed neurotoxicity (all; grade 3 or 4)	12% (9%)	None**

* Long term cytopenias: Cilta-cel: > 1 month from onset of cytopenias, Ide-cel: > 1 month post-CAR-T ; ** In package insert: grade 3 parkinsonism and grade 3 myelitis in another ide-cel trial

1. Madduri et al ASH 2020 abstract 177; 2. Usmani et al ASCO 2021abstract 8005; 3. Munshi et al. NEJM 2021;384(8):705-716;

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Cilta-cel vs Ide-Cel

Current efficacy data: Interpret with caution as hard to appreciate true differences in patient population

Efficacy	Cilta-cel[1]	Ide-cel[2]
ORR; CR rate	98%;83%	73%;33%
MRD negativity rate (10^{-5})	58%	26%
PFS	2 year: 61%, median NR	Median: 8.8 months
OS	2 year: 74%, median NR	Median: 19 months

1. Martin et al ASH 2021; 2. Munshi et al. NEJM 2021;384(8):705-716;

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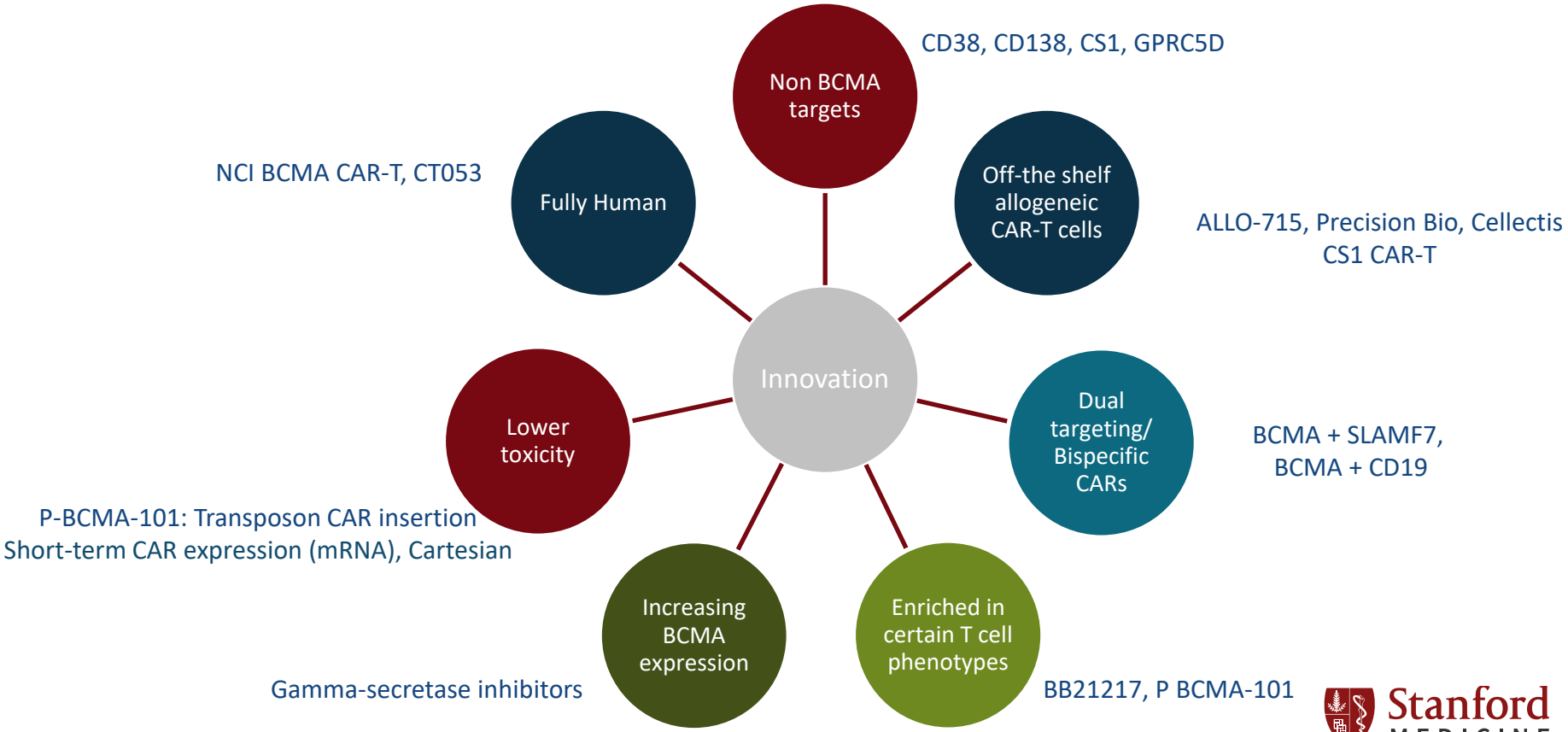
Innovation: Investigational Constructs



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Select BCMA Constructs in Early Clinical Development in US: Preliminary Data

69%	Uniqueness	Phase	N	CRS %: All (≥3)	ICANS %: All (≥3)	ORR
CT053/ CARSGen[1]	Fully Human	1b	20	75% (0)	15% (5)	94%
CART-ddBCMA/ Arcellx[2]	Computational designed synthetic binding domain, non-scFv	1	12	92% (0)	17% (8)	100%
BB21217/ Celgene[3]	PI3Ki co-culture, enrich memory phenotype	1a/b	72	75% (4)	15% (4)	69%
P-BCMA/ Posseida[4]	Transposon based, less AE, enriched for stem cell memory phenotype	1	53	17% (0)	4% (4)	44-75%
ALLO-715/ Allogene [5]	Off the shelf, additional LD with antiCD52	1	43	63% (2)	14% (0)	71% @ 320m with FCA
BCMA+GSI/ Fred Hutch & Juno[6]	FCARH143 BCMA CAR+ Gamma secretase inhibition JSMD-194	1	18	94% (28)	66%	89%

1. Kumar et al. ASH 2020; 2: Friggault et al. ASCO 2021; 3: Raje et al. ASH 2021; 4. Costello et al. ASH 2020; 5. Mailankody ASH 2021; 6. Cowan et al. ASH 2021.

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Use of BCMA CAR-T in Earlier Lines

Being investigated in clinical trials

- Early Relapse, randomized trials: CARTITUDE-4, KarMMa-3
- Earlier lines, including front line (BMT-CTN 1902, KarMMa-4, CARTITUDE-2, CARTITUDE-5)

Benefits:

- Better T cell health → potential for higher efficacy and duration of response
- Earlier treatment free interval

Concerns:

- Toxicity (long-term cytopenias and infections; longer term neurotox)

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CARTITUDE-2: Cilta-Cel in RRMM and 1-3 Prior Lines of Therapy

	N=20
Triple class refractory	40%
Previous lines of therapy	2 (1-3)
High-risk cytogenetics	35%
CRS, all (≥ 3)	85% (10%)
ICANS, all (≥3)	20% (0%)
ORR/CR	95% (85%)
6 and 12 month PFS	95% and 84%

Cohen et al. ASH 2021

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CARTITUDE-2: Cilta-Cel after 1 Prior Line of Therapy (PI and IMiD)

	N=19
High-risk cytogenetics	16%
CRS, all (≥ 3)	84% (5%)
ICANS, all (≥3)	5% (0%)
ORR/CR	95% (79%)
6 and 12 month PFS	90% and 84%

One patient with grade 3 movement and neurocognitive AE (delayed neurotoxicity at 38 days)

Van de Donk et al. ASH 2021

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Non BCMA CAR-T in Clinical Development in US

Target	CT Phase	NCT Number	Sponsor(s)
CD38	1	NCT03464916	Sorrento
CD138	1	NCT03672318	UNC Linenberger
BCMA+CD19	1	NCT03549442	Upenn/Novartis
GPRC5D (MCARH109)	1	NCT04555551	MSKCC
CS1/SLAMF7	1	NCT03710421	NCI; City of Hope
CS1 Allogeneic (MELANI-01)	1	NCT04142619	Cellectis

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GPRC5D targeted CAR-T cells: First Phase 1 Human Trial

Baseline Features	N=17
Median age	60 years
Median prior lines	6
Triple Class Refractory	94%
Prior BCMA	59%
Prior CAR-T	47%

Adverse Events	N=17
CRS (all; grade 3 or 4)	93% (7%)
ICANS (all; grade 3 or 4)	7% (7%)
Infections	19%
Grade 1 nail changes	56%
Grade 1 rash	19%
Grade 1 dysgeusia	6%

Efficacy	N=16
ORR	69%
CR rate	25%
MRD negative rate (10^{-5})	50%
ORR, Prior BCMA	80%
ORR, Prior CAR-T	75%

Mailankody et al. ASH 2021

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Summary

- CAR-T therapy: Unprecedented response rates/PFS in triple class refractory MM.
- CRS and ICANS are manageable.
- Cytopenias and infections are common, can be long term in a subset of patients.
- Delayed neurotoxicity can occur. Further study is need.
- Unmet need in special populations: Renal dysfunction, CNS involvement and plasma cell leukemia – excluded from clinical trials.
- New unmet need: Relapse after BCMA therapies
- Non-BCMA targets have shown promising early activity.
- Access to CAR-T remains an issue
- Understand & address quality of life and other late side effects with these newer treatments.

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Discussion