Does Precision Medicine Have A Role In MM In The Era Of Immune Therapies?

Absolutely YES!!

Madhav Dhodapkar, MD

Emory University

Me

Biology on MY SIDE

Thank you, Dr. Dhodapkar!
Of note, Dr. Hofmeister sent me the following message:
Patti

Thanks so much for the invitation.
Am I the YES or the No?
If it goes to whomever emails you first, I win. I vote **NO**.

Craig

What is New in the Era of Immune Therapies?: Available Approved Multiple Myeloma Therapies in 2022

IMIDs	PIs	Naked antibodies	XPO inhibitor	ADC	CART	Chemotherapeutic agents
Thalidomide	Bortezomib	Daratumumab (anti-CD38)	Selinexor	Belantamab (anti-BCMA + MMAF)	Ide-cel	Cyclophosphamide
Lenalidomide	Carfilzomib	Isatuximab (anti-CD38)			Cilta-cel	VDCEP, VDT-PACE
Pomalidomide	Ixazomib	Elotuzumab (anti-CS1/SLAMF7)				Melphalan

Steroids: prednisone, dexamethasone

Conventional chemotherapeutic agents: melphalan, cyclophosphamide, doxorubicin, bendamustine, combos (DCEP, VDT-PACE)

Belantamab: US and EU approval in 2020
Ide-Cel: US and EU approval in 2021
Cilta-cel: US and EU approval in 2022

Currently Approved CAR-Ts represent the ultimate form of highly personalized / precision therapy--- each product is tailor made for the individual patient.

CAR-T as an example of ultimate precision medicine

Because this is a highly specialized, highly personalized treatment, CAR T-cell therapy is available at a limited number of cancer centers with specialized expertise in cellular

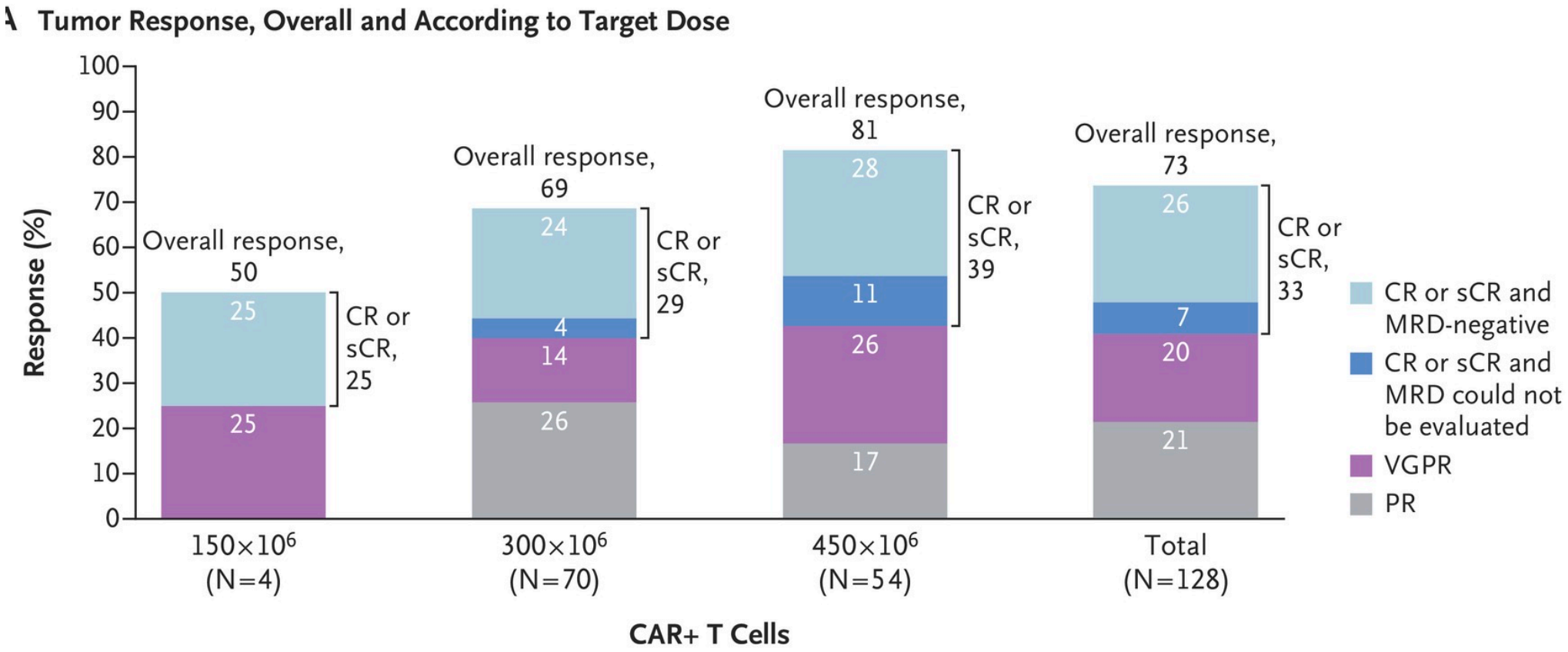
Websites

DFCI, Penn, NCI, Winship

CAR-T Therapy Ushering in a New Era of Precision Medicine for Patients With Chronic Lymphocytic Leukemia

Melenhorst JJ, Chen GM, June CH, et al. Decade-long leukaemia remissions with persistence of CD4+ CAR T cells. *Nature*. 2022; 602:503-509. doi:10.1038/s41586-021-04390-6

Ide-Cel in Relapsed MM



Ide-cel FDA Approved in 2021

Munshi et al NEJM 2022

Ciltacabtagene Autoleucel Approval Marks Second CAR T-Cell Therapy for Multiple Myeloma

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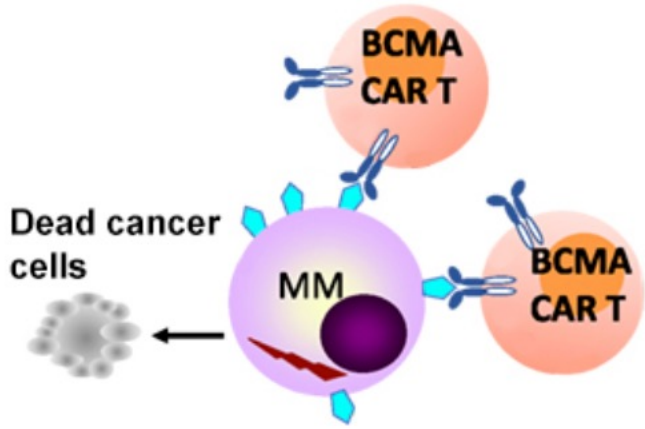
March 30, 2022, by NCI Staff

Patients with advanced multiple myeloma now have a second option for CAR T-cell therapy, a type of personalized immunotherapy. On February 28, the Food and Drug Administration (FDA) approved ciltacabtagene autoleucel for adults with multiple myeloma that is not responding to treatment (refractory) or has returned after treatment (relapsed).

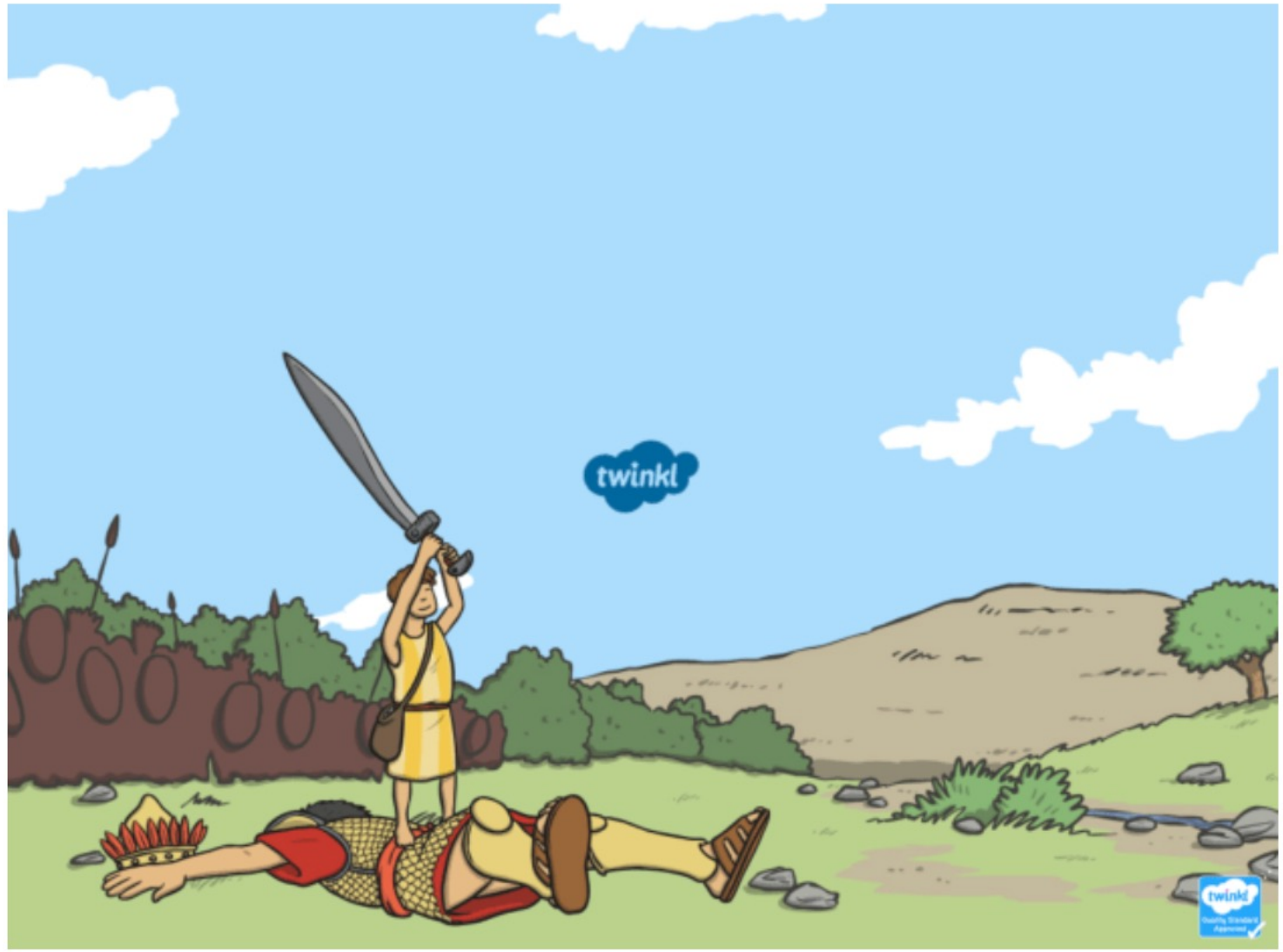


The two CAR T-cell therapies approved by the FDA for treating multiple myeloma bind to the BCMA protein on the surface of myeloma cells

Do CARTs ~~Does Precision Medicine~~ Have A Role In MM In The Era Of Immune Therapies?

Absolutely YES!!

Show of Hands please– If you believe Current CAR-Ts have NO Role in MM

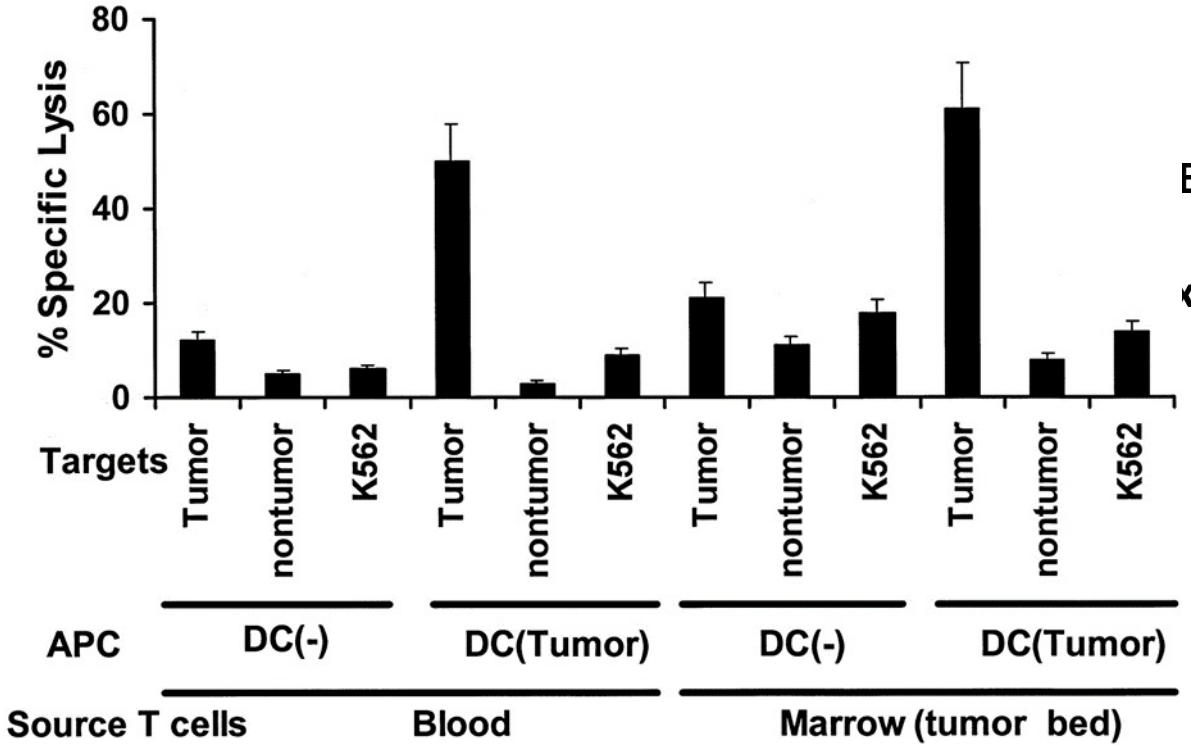

twinkl

Some Reasons Why Immunotherapy is An Attractive Option in Cancer

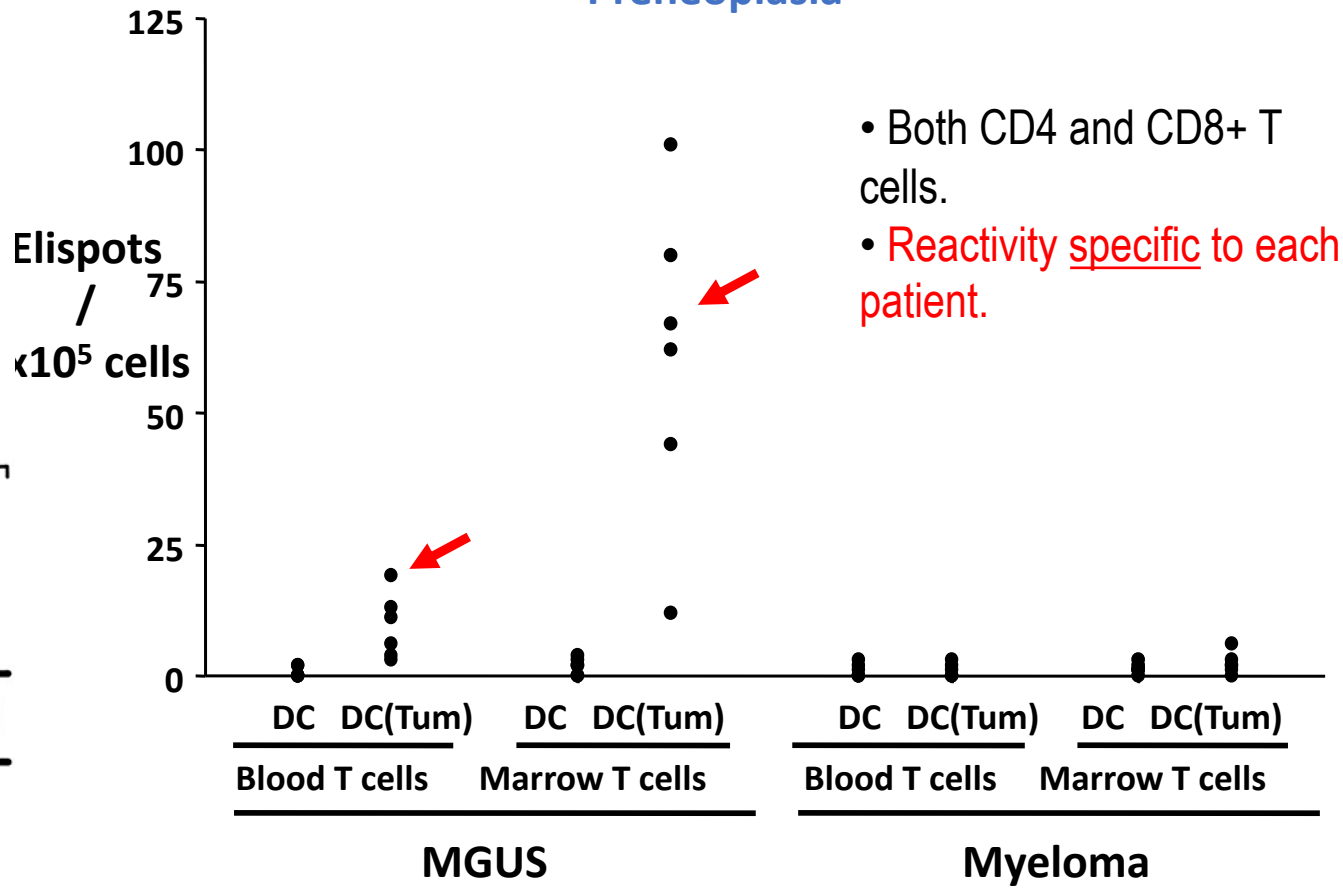
- Specificity…e.g. Flu vaccine does not protect against COVID
- Memory / Durability
- Ability to Evolve….Living Therapy

Immune System as a Potent and SPECIFIC Weapon against MM

NDMM and RRMM



Preneoplasia

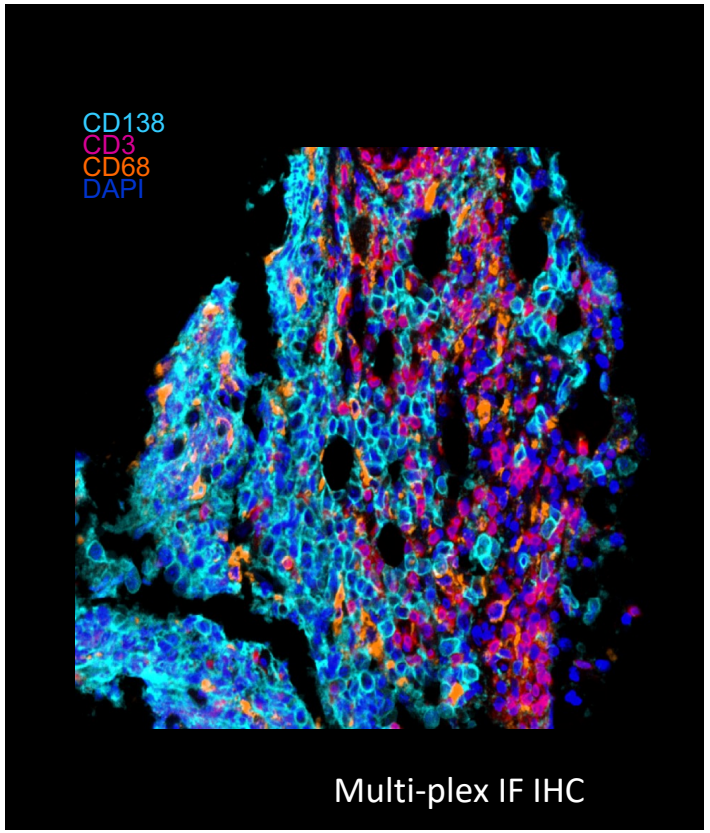


- Both CD4 and CD8+ T cells.
- Reactivity specific to each patient.

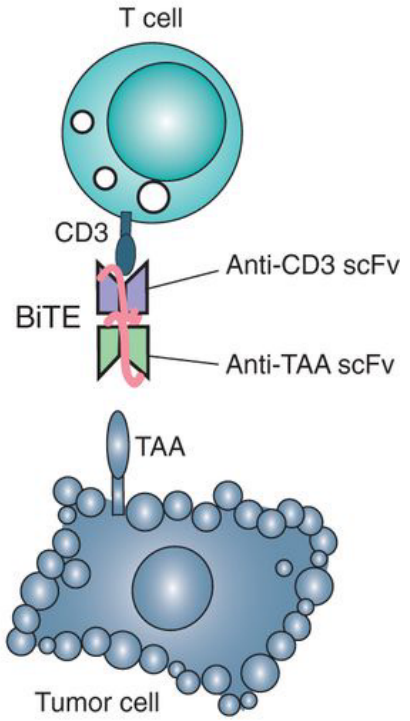
Dhodapkar et al. PNAS 2002
Dhodapkar et al. JEM 2003

Immune System Is impacted by Spatial Heterogeneity…but amenable to Redirection

Spatial Heterogeneity



T-cell Redirection



Slaney et al. Cancer Disc 2018

Dhodapkar et al. Unpublished

Promise and Challenges of CAR-Ts in MM

- High Response Rates….including against high-risk MM.
- One and done--- positive impact on QOL.

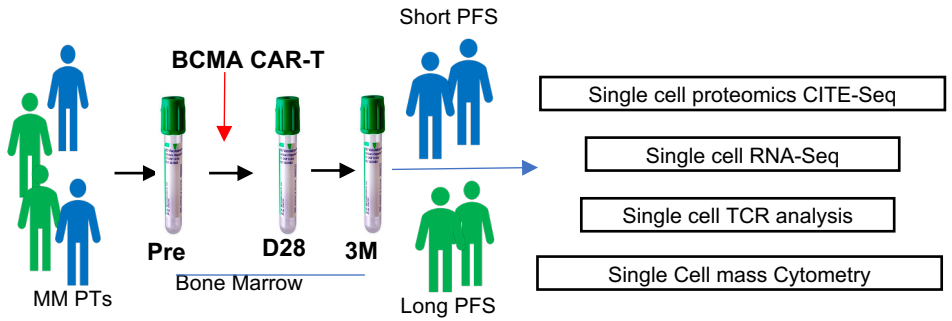
But:

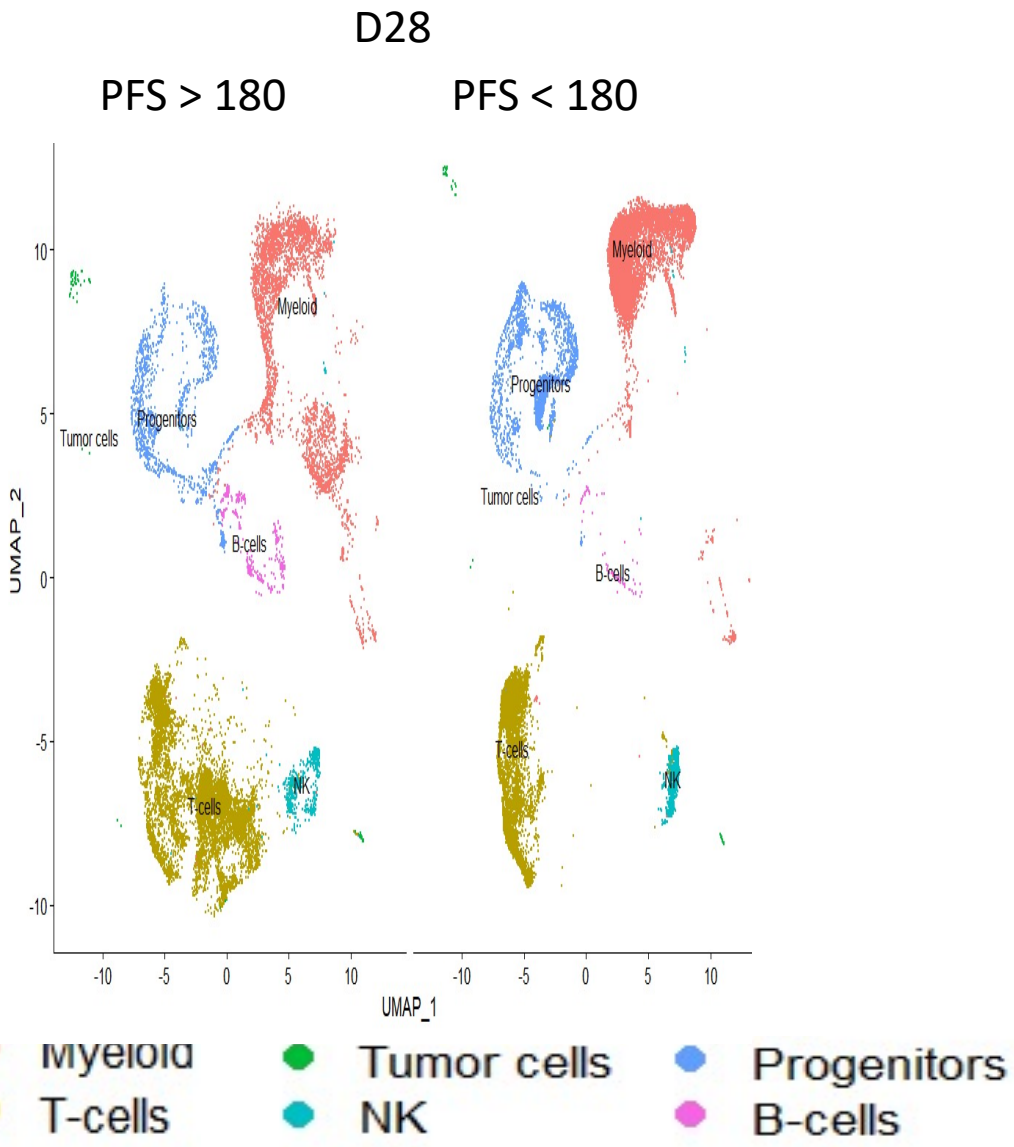
Durability seems limited….no flattening of PFS/OS curve

Cost and Access

Plenty of Opportunity for Improvement

Properties of Endogenous Immune Response Impacts Durability of PFS Following BCMA CARTs.





Blood Cancer Disc 2022 in press

Emerging approaches…some examples

- **Off the shelf CARTs**
  - **Allogeneic or Universal CARTs**
  - **Innate CARTs (NK or NK-T)**
- **In vivo CART manufacturing**
- **Advanced Engineering**
- Non-BCMA targets
  - GPRC5D, CS1, MM3, CD38….
- Improved manufacturing, cheaper, better product
- ……

No Two Patients Are Immunologically the Same

<u>Tumor- Associated</u>
Tumor-induced immune suppression
T cell dysfunction
Hypogammaglobulinemia
Chronic inflammation
Cytopenias
….

<u>Host</u>
Age
Thymic function
Metabolic disorders
Microbiome
….

<u>Threats</u>
Seasonal / Opportunistic pathogens
Pandemics
Viral reactivation
….
Residual Tumor
Tumor Evolution/Immune Evasion

Immunologic Diversity Leads to Distinct Product as well as Response to the product in each pt.

Dhodapkar M. ASCO 2022

…but What About Bispecifics ?

Advantages:

- Off the shelf.
- Rapid access--- for patients requiring immediate Rx.
- Does not require prior lymphodepletion.

But---

- Not yet approved….as of July 23, 2022.
- Will likely require ongoing Rx / multiple doses.
- Less optimal for QOL.
- Long term effects on T cell function due to chronic activation….risk of atypical infections.

…..what about other MM therapies….

- **Remember – even current Rxs have immunologic mechanisms…**
  - E.g. Bortezomib- immunogenic cell death; IMiD- Ikaros depletion, Dara- CD38 depletion; SCT- induction of new immune responses in mouse models.

- ….we will need to revisit current front-line therapies in the future as immune therapies improve….

ClinicalTrials.gov

Personalized Autologous Transplant for Multiple Myeloma

ClinicalTrials.gov Identifier: NCT04483206

Recruitment Status : Recruiting
First Posted : July 23, 2020
Last Update Posted : March 14, 2022

See **Contacts and Locations**

Sponsor:
Emory University

Collaborators:
National Cancer Institute (NCI)
Gateway for Cancer Research

Information provided by (Responsible Party):
Craig Hofmeister, Emory University

Warning– stay away from distracting arguments…not relevant to current debate (e.g.)

T11:14, Bellini

T4:14, MMSET

MyDRUG

Fake news

…even more precision may be in the future

- Choosing combinations of CARTs and/or bispecifics based on target expression….and preexisting immunity
- Specific remodeling of TME based on HLA and neoantigens.
- Improved and more personalized “bi / tri- multi-”-specifics
- Advanced synthetic immunity

….we do need to address cost, access and disparities…..to realize the promise of precision medicine

Cost vs Value

Underlining the promise of precision therapies, especially CAR T-cell immunotherapy, is their considerable cost—$475,000 for tisagenlecleucel and $373,000 for axicabtagene ciloleucel—vs their value. A panel discussion at the briefing, moderated by **Richard L. Schilsky, MD, FACP, FASCO**, ASCO's Senior Vice President and Chief Medical Officer, explored the challenges to realizing the full potential of precision medicine in cancer care. Dr. Schilsky asked panel member **Robert W. Dubois, MD, PhD**, Chief Science Officer and Executive Vice President of the National Pharmaceutical Council, to explain "how the precision medicine approach potentially creates value even in the face of what are acknowledged to be very expensive treatments."

Conclusions

- CAR-Ts and other precision immune approaches will not only have a role but may become the mainstay of MM therapy

- We will need to better understand how to make these responses durable

- Thank you for your attention….

- …and thanks to my esteemed colleague for being Wrong (for a change).