LIVE PODCAST

T Cell Directed Therapy in Prostate Cancer

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T Cell Therapy in Prostate Cancer

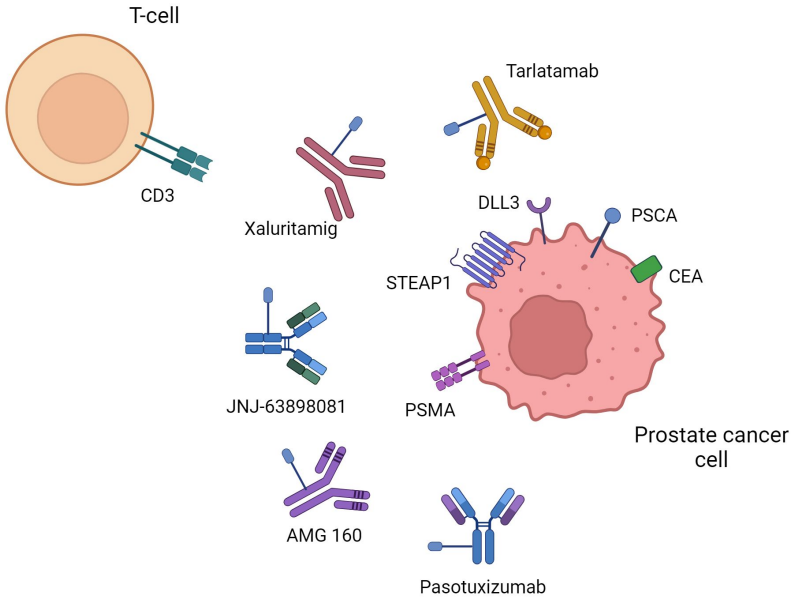
Table 1. TAAs and their expression in type of prostate cancer versus their normal distribution.

Tumor-associated antigen	Cell/tissue distribution
PSCA	**Prostate adenocarcinoma**, urothelial, skin, esophagus, neuronal, stomach
PSMA	**Prostate adenocarcinoma**, prostate acinar epithelium, proximal tubular cells, glial cells, jejunal brush border cells, salivary glandular cells
STEAP-1	**Prostate adenocarcinoma**, bladder, ovary, bone marrow, cardiac, respiratory
DLL3	**Neuroendocrine prostate cancer (NEPC)**, neurons, pancreatic islet cells, pituitary
CEA	**NEPC**, urogenital, respiratory, gastrointestinal

Dorff T et al. ***CCR***, 2022

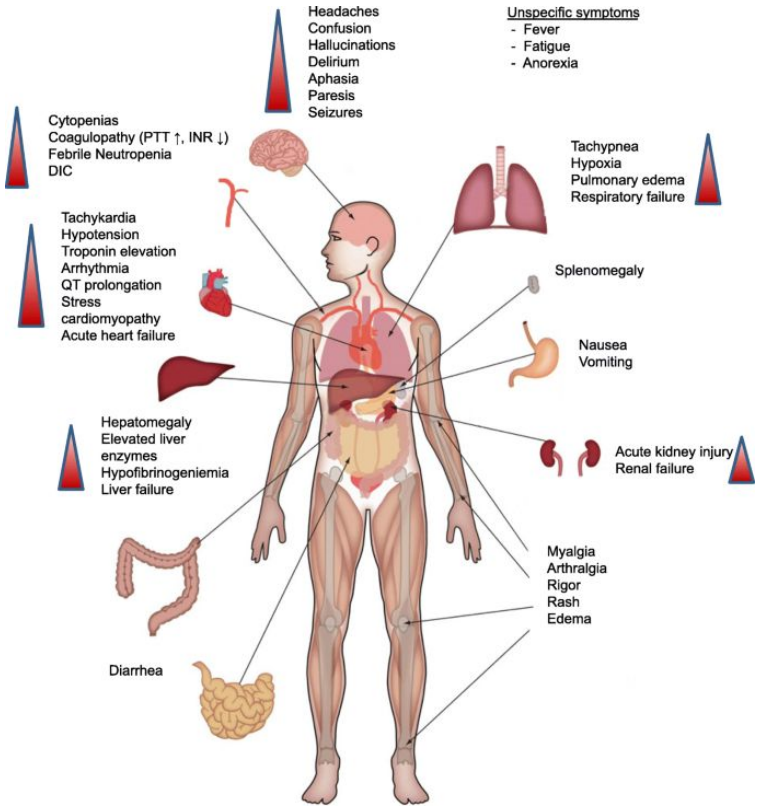
CEA, Carcinoembryonic Antigen; DLL3, Delta-like Ligand 3; PSCA, Prostate Stem Cell Antigen; PSMA, Prostate-specific Membrane Antigen; STEAP-1, Six-transmembrane Epithelial Antigen of the Prostate 1

TCEs bypass steps needed for MHC-TCR-dependent T-cell activation and engage CD3 on T-cells and a tumor-associated antigen, leading to T-cell mediated killing



Slide adapted from Neeraj Agarwal ESMO 2024

Cytokine Release Syndrome (CRS)

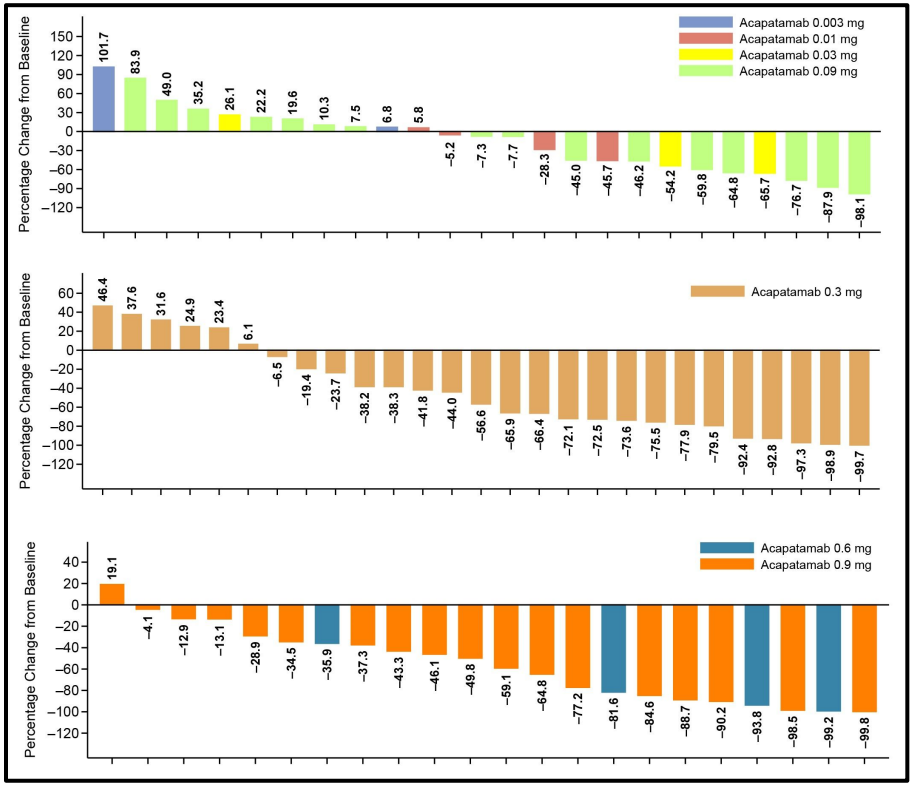


Grade 1	Grade 2	Grade 3	Grade 4
Fever, nausea, fatigue etc, requiring symptomatic treatment only	GR1 CRS sxs and • **IVF or low-dose vasopressor for hypotension, or** • **O2 requirement** < 40%, or • Grade 3 transaminitis	GR1 CRS sxs and • High dose or multiple vasopressor for hypotension, or • O2 requirement >= 40%, or • Grade 4 transaminitis	GR1 CRS sxs and • Requirement for ventilator, or • Grade 4 organ toxicity (excluding transaminitis)
Outpatient	Generally inpatient +/- ICU	ICU	ICU

Shimabukuro et al. *JITC*. 2018; Lee DW et al. *Biol Blood Marrow Transplant*. 2019

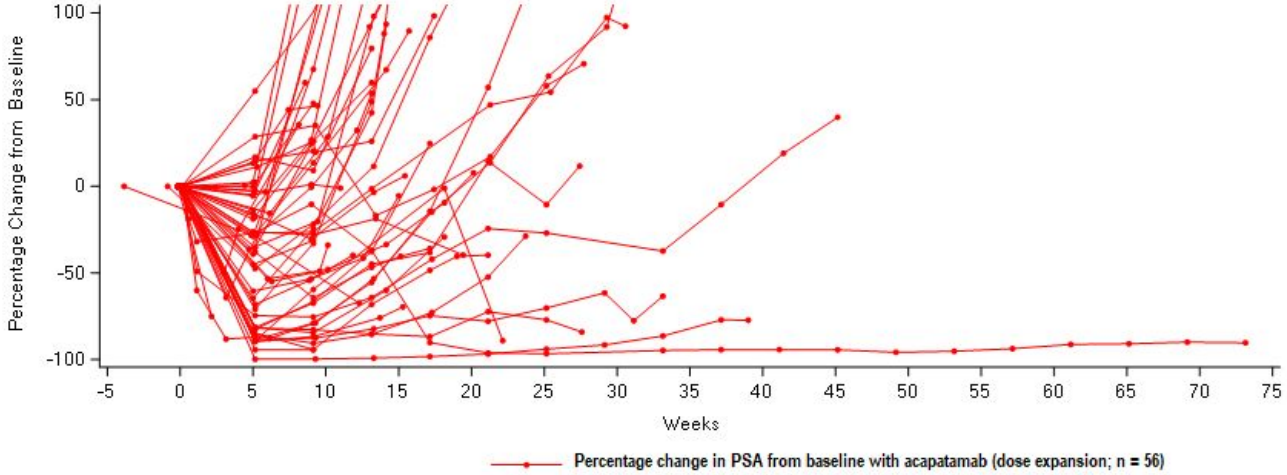
Acapatamab (AMG160) PSMA x CD3 Bispecific

- Ph1 trial mCRPC post ARPI + taxane, n=133
- Dose exploration (0.003-0.9mg) + expansion (0.3mg)
- Safety: CRS 97-98%; GR3 in 23% (exploration) and 16% (expansion)
- Efficacy in Expansion:
  - Confirmed PSA50 in 30.4% of patients
  - RECIST ORR 7.4%
  - rPFS 3.7mo (95%CI, 2.0-5.4)
- This agent is not being developed given the toxicity (CRS) and lack of durability



Dorff T et al. *CCR*. 2024

What does this tell us about T Cell Engagers?

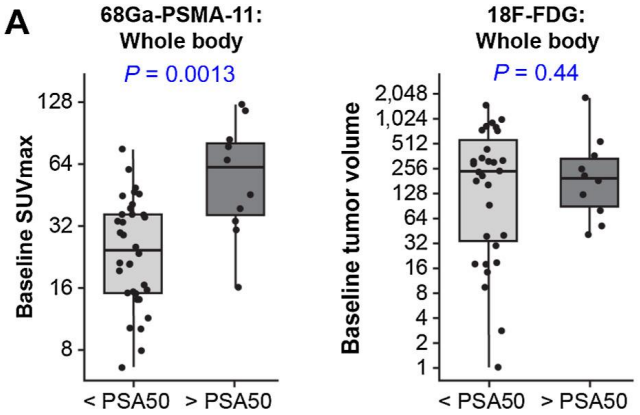


Dorff T et al. *CCR*. 2024

1. These agents CAN engage an immune response that correlates with EFFICACY
2. PSA declines happen EARLY
3. Challenge: for those who have initial PSA declines, DURABILITY is a problem, but we need to understand WHY – is it at the tumor level (expression), immune level? Is it a feature inherent to the drug itself/PK?

PSMA PET as a Biomarker for PSMA TCE

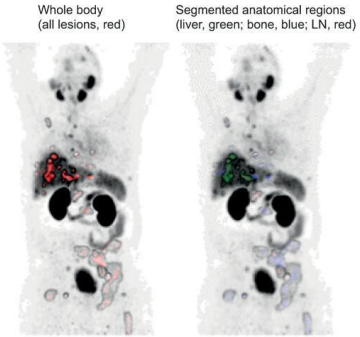
Higher PSMA SUVmax associated with longer rPFS and PSA 50 with Acapatamab



	Low PSMA expression (n=23)	High PSMA expression (n=22)
Median rPFS mo	1.97 (1.84, 3.78)	5.39 (1.97, 8.31)
Median fu mo	5.55 (5.55, NE)	3.25 (1.84, 8.31)

*Patients were classified as having high (SUV_{max} > 5.06) or low (SUV_{max} < 5.06) tumor PSMA expression by ^{68}Ga-PSMA-11 based PET/CT imaging. Dorff T et al. *CCR*. 2024

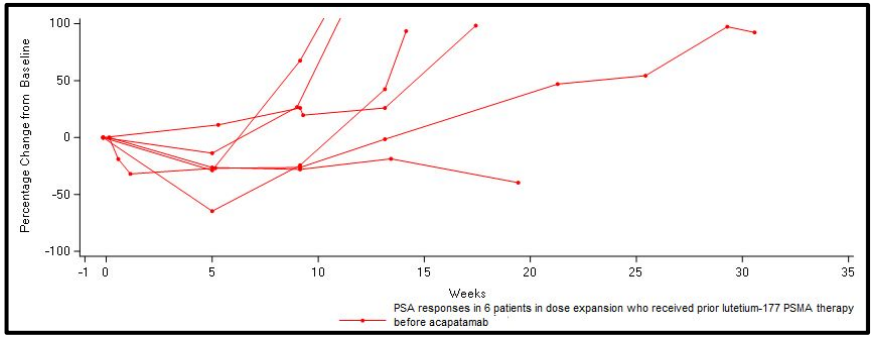
Quantitative ^{68}Ga-PSMA-11 PET and Clinical Outcomes in Metastatic Castration-resistant Prostate Cancer Following ^{177}Lu-PSMA-617 (VISION Trial)



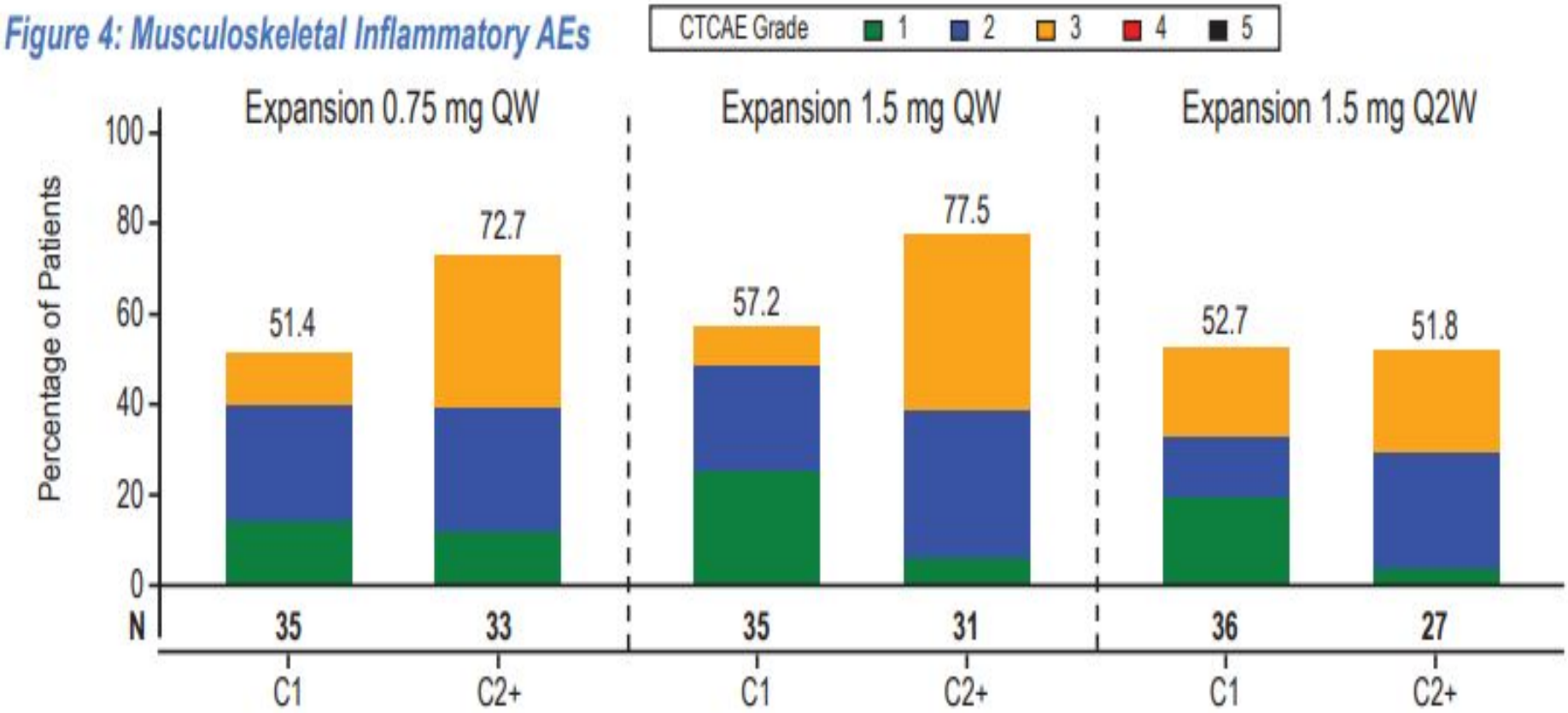
- Exploratory secondary analysis of the VISION trial including 826 randomized participants.
- Baseline ^{68}Ga PSMA-11 PET SUV_{mean} was strongly associated with improved outcomes following ^{177}Lu-PSMA-617 therapy vs controls (HR, 0.86–1.43).
- A 1-unit whole-body tumor SUV_{mean} increase was associated with a 12% or 10% decreased risk of radiographic progression or death, respectively.
- Higher PSMA-positive tumor volume was associated with worse overall survival (HR, 1.36–2.12).

Kuo PH and Morris MJ et al. Published: August 20, 2024
https://doi.org/10.1148/radiol.233460
Radiology

Acapatamab-induced PSA response in patients who received prior lutetium-PSMA therapy



Xaluritamig (AMG509) STEAP1 x CD3 Bispecific

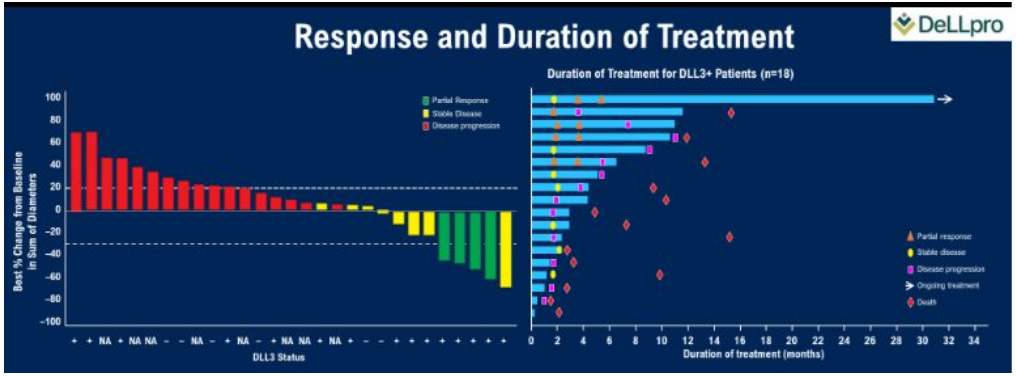


Kelly WK et al. *Cancer Discovery*. 2024; ESMO 2024

NCT#	Drug	Target/N	Rates of CRS	Discontinue/ Interrupt for Toxicity	Publication
NCT03792841 NCT04631601	Acapatamab (AMG 160)	PSMA N=133	*Exploration:* ANY: 97.4% GR3: 23.4% *Expansion:* ANY: 98.2% GR3: 16.1%	*CRS Leading to discontinuation:* ***0%*** *CRS Leading to Interruption:* ***11.3%***	Dorff, CCR, 2024
NCT05369000	LAVA-1207	PSMA x gamma-delta T cell N=20	ANY: 20% GR1:10% GR2: 10%	*Not reported*	Mehra, GU ASCO 2023
NCT05369000	JNJ-63898081	PSMA N=39	ANY: 66.7% GR1: 33.4% GR2: 33.3%	*Discontinuation:* ***5.1%***	Lim, Clin GU Cancers, 2023
NCT04702737	Tarlatamab (AMG 757)	DLL3 N=40	ANY: 75% GR1: 55% GR2: 17.5% GR3: 2.5%	*TRAE leading to discontinuation* ***7.5%*** *TRAE leading to interruption:* ***20%***	Aggarwal, ASCO 2024
NCT04221542	Xaluritamig (AMG 509)	STEAP1 N=97	ANY: 72% GR1: 26% GR2: 33% GR3: 2%	*TRAE leading to discontinuation:* ***19%*** *TRAE leading to interruption:* ***47%***	Kelly, Cancer Discovery, 2024

Tarlatamab in De novo or Treatment Emergent NEPC

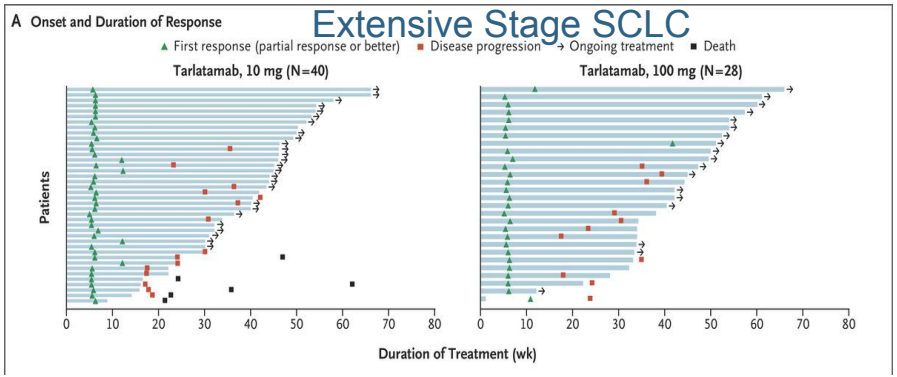
- Broad eligibility for inclusion of NEPC in ph1b; N=40
- Tarlatamab 100mg IV Q2wk
- Expected toxicity profile (CRS)
- Overall ORR: 10.5% (95% CI, 2.9 - 24.8mos)
- DLL3 + by IHC ORR: 22.2% (6.4 - 47.6mos)



Aggarwal R et al, ASCO 2024

Histological features*	Patients N = 37** (%)	DLL3+ x/X** (%)
Evaluated tumor samples for DLL3	32 (86)	18/32 (56)
Small cell (pure or mixed)	17 (46)	11/15 (73)
Adenocarcinoma with NE features†	15 (40)	7/14 (50)
Adenocarcinoma with genomic markers††	5 (14)	0/3 (0)

Extensive Stage SCLC



- SCLC: ORR 40% in the 10 mg cohort
- SCLC: DOR 12.3mos (94% CI, 6.6-14.9)

(N Engl J Med 2023;389:2063-75)

Audience Question

One or more T cell engager therapies will be FDA-approved in prostate cancer in the next 3-5 years

1. True
2. False

Benefits and Challenges for T Cell Engagers

Advantages

- Bypass TCR-MHC
- Off the shelf (scalability)
- High T:E ratio/Belief that less PSMA expression may be needed (compared to RLT?)
- Opportunity to target different TAA
- CRS is largely reversible and transient, as compared to cumulative toxicity with chemotherapy

Disadvantages

- Reliant on endogenous T cell effector function
- Requires frequent and ongoing dosing
- Development of ADAs
- Patient population (elderly, CAD)/toxicity
- Inpatient administration due to CRS/availability in community practice