Clinical Development of Adoptive Cell Therapy

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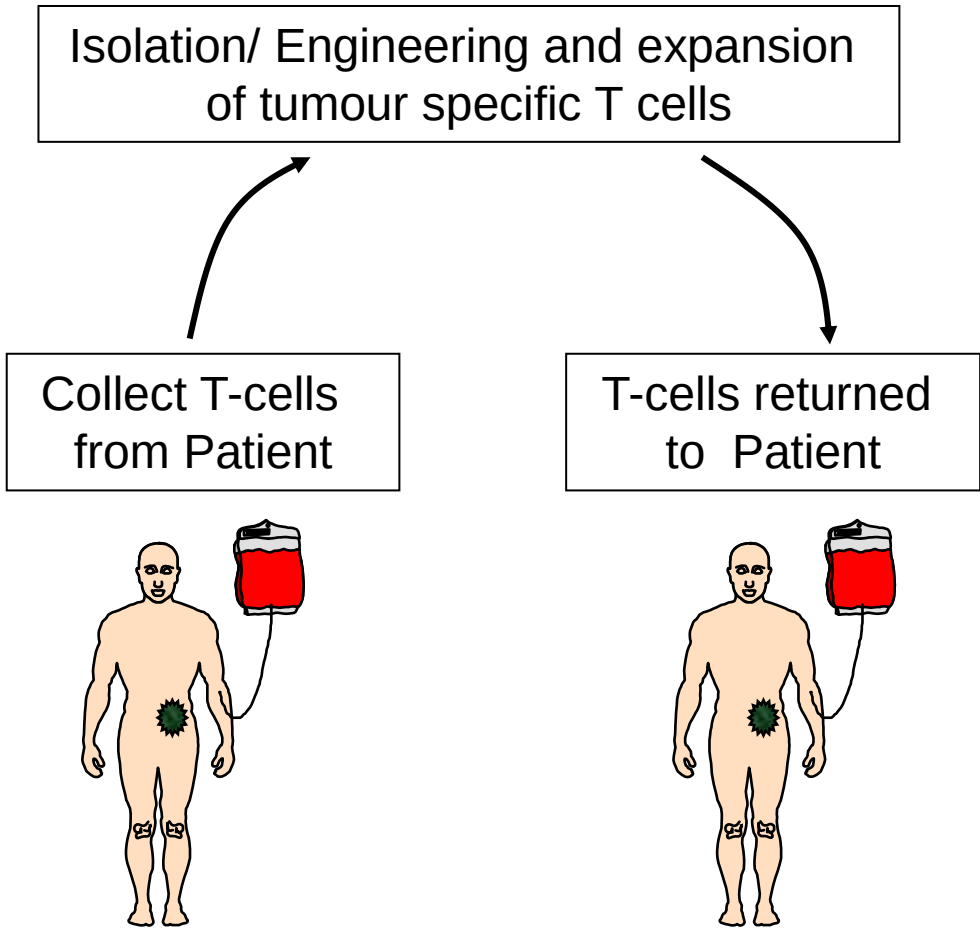
Adoptive Cell Therapy

- Two basic approaches
  - Natural T cells
    - Isolated from blood
    - Isolated from tumour
  - Genetically Engineered T cells
    - Engineered from blood lymphocytes
      - TCR based receptors
      - Antibody based chimeric receptor



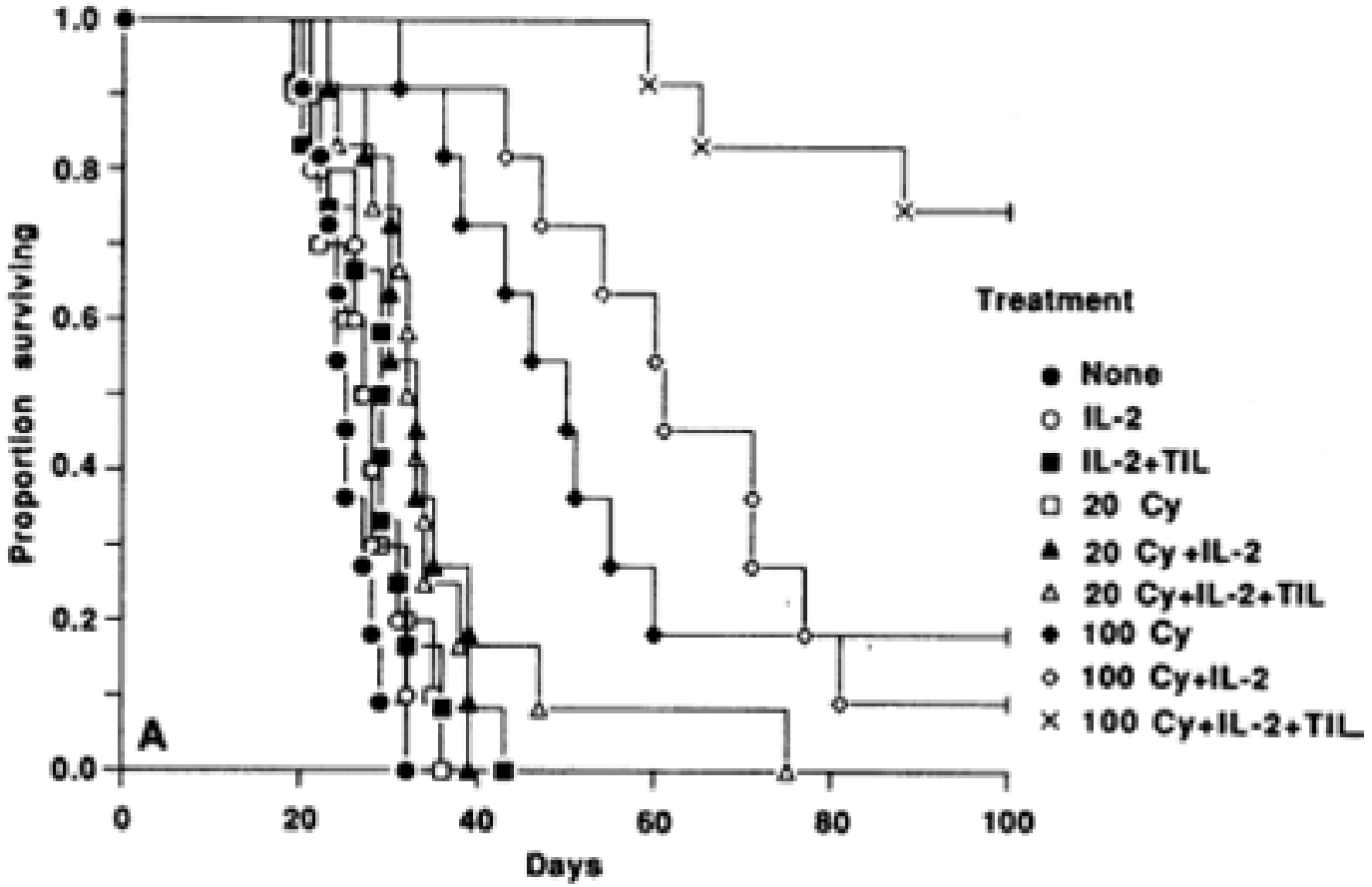
Considerations for Clinical Delivery of ACT

- Complex/Personalised so the efficacy bar will be high
- Need to comply with EU GMP regulations
- Main attractions
  - Short-term treatment
  - Long-term benefit
- Main Drawbacks
  - Complex/Costly
  - Toxicity of supportive therapy
    - Pre-conditioning chemotherapy
    - Supporting Cytokines
- Practical Challenges
  - How to role out to multiple centers

Overview

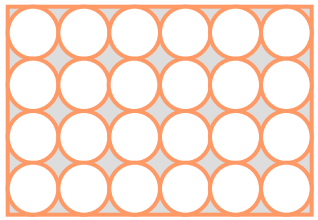
- Overview of Adoptive Cell Therapy
- Setting up a GMP unit for ACT
- Developing TIL therapy for Melanoma in UK
  - Planned Trials
- Engineered T-cell Trials in Manchester
  - CEA
  - CD19
- EU FP7 ATTACK – Trials targeting NY-ESO-1

Pre-clinical Evidence for TIL Therapy

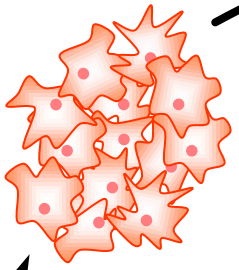


Rosenberg SA, et al., A new approach to the adoptive immunotherapy of cancer with tumor-infiltrating lymphocytes. Science. 1986 Sep 19;233(4770):1318-21.

TIL Treatment

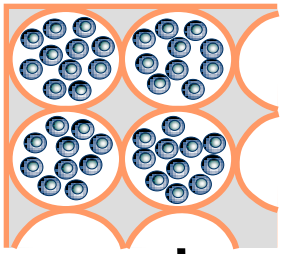


2. Cut Excised Tumour into 2-3 mm pieces

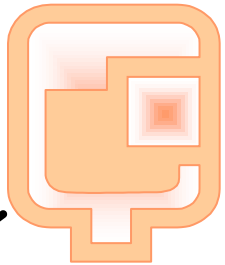


3. Culture bulk tumour in plates + IL-2

4. T cells Expand 2-3 weeks



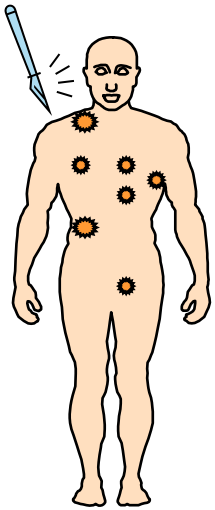
TIL Product



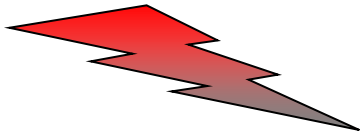
5. Rapid Expansion Protocol – 2 weeks

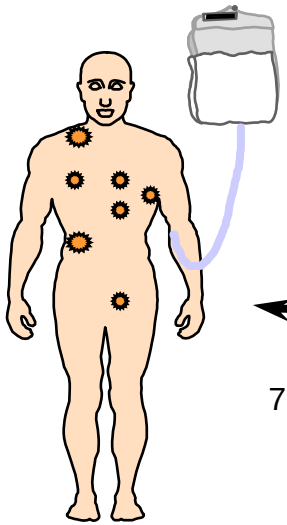
7. Safety and Numbers analysed *in vitro* *Cells Concentrated*

1. Surgery to remove tumour sample



6. “Pre-conditioning Therapy” with Cyclophosphamide and Fludarabine





Patient with Melanoma

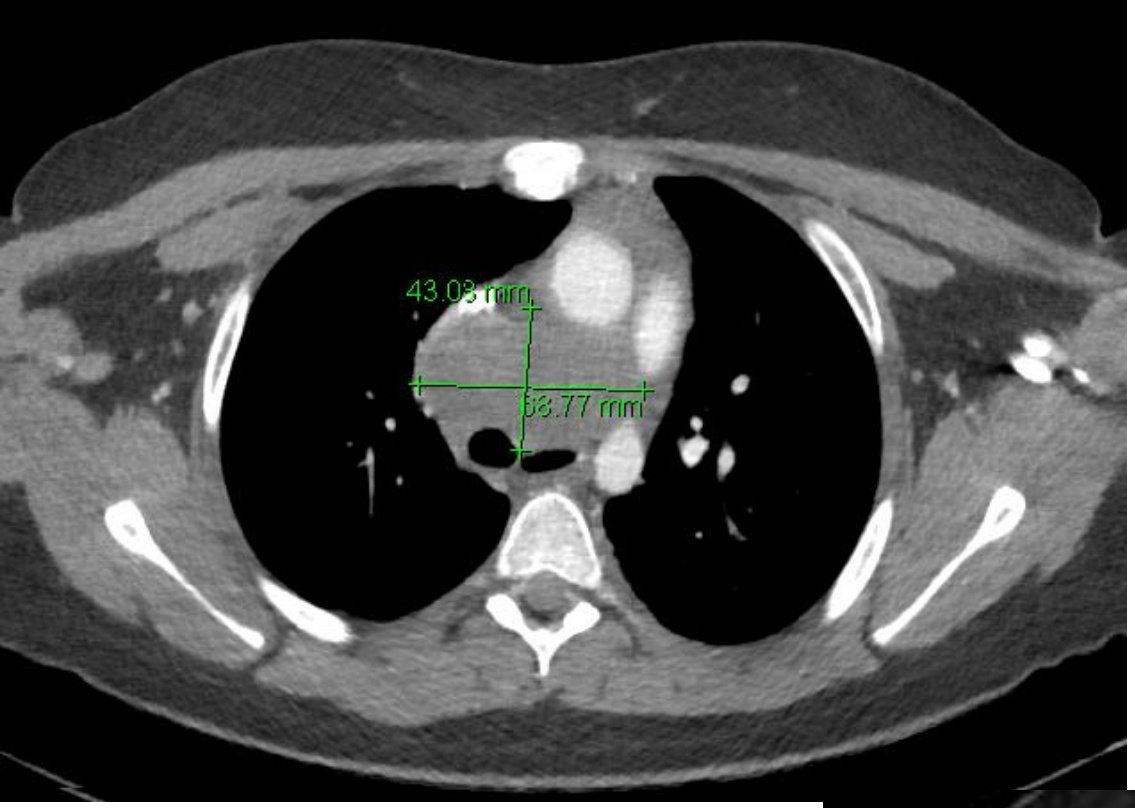
8. Return cells to patient + supportive therapy with IL2

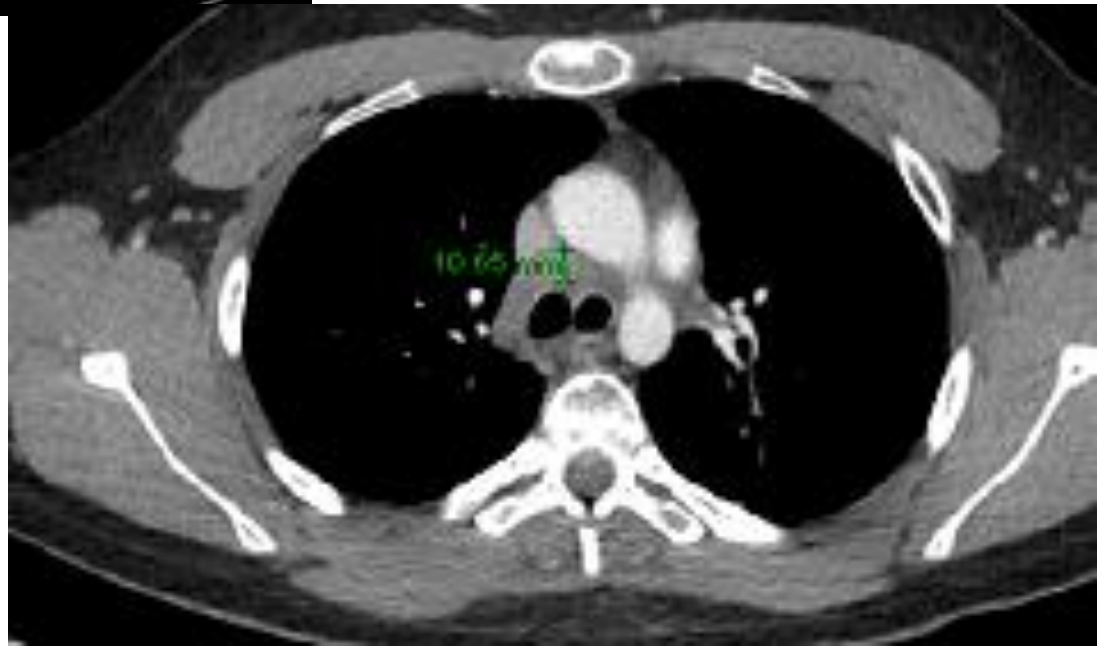
Setting This Up in Manchester

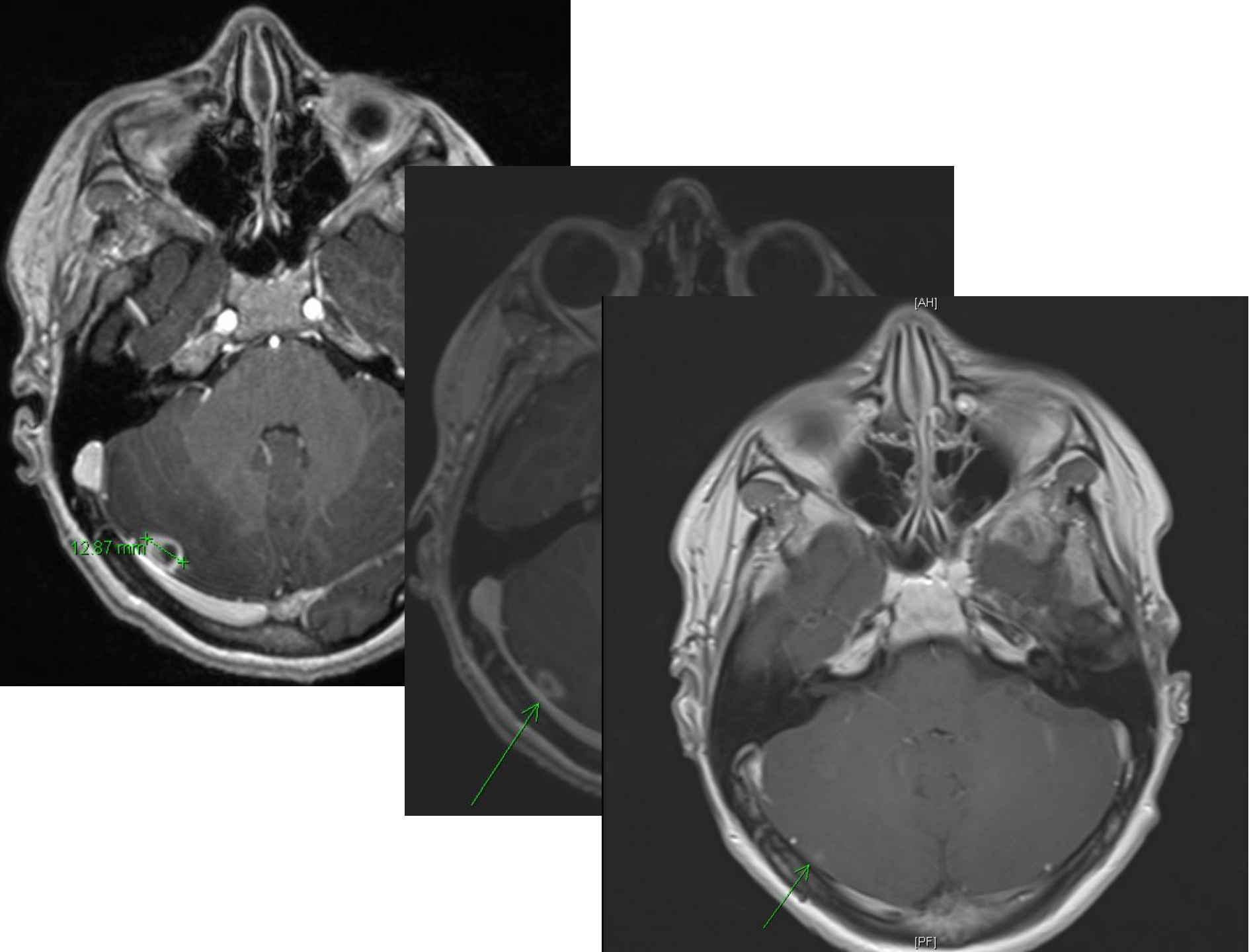
Cellular Therapeutics Unit (CTU)

- Move away from classical clean rooms
- Provides a controlled sterile environment
- Protects patients cells from infection or contamination
- Allows rapid decontamination with vaporised hydrogen peroxide
- Allows multi product processing
- Closed Systems outside isolators
- REP entirely in WAVE bioreactors

MANCHESTER 1824
The University of Manchester


43.03 mm
38.77 mm




12.87 mm
[AH]
[PF]

Where are we going with TIL ?

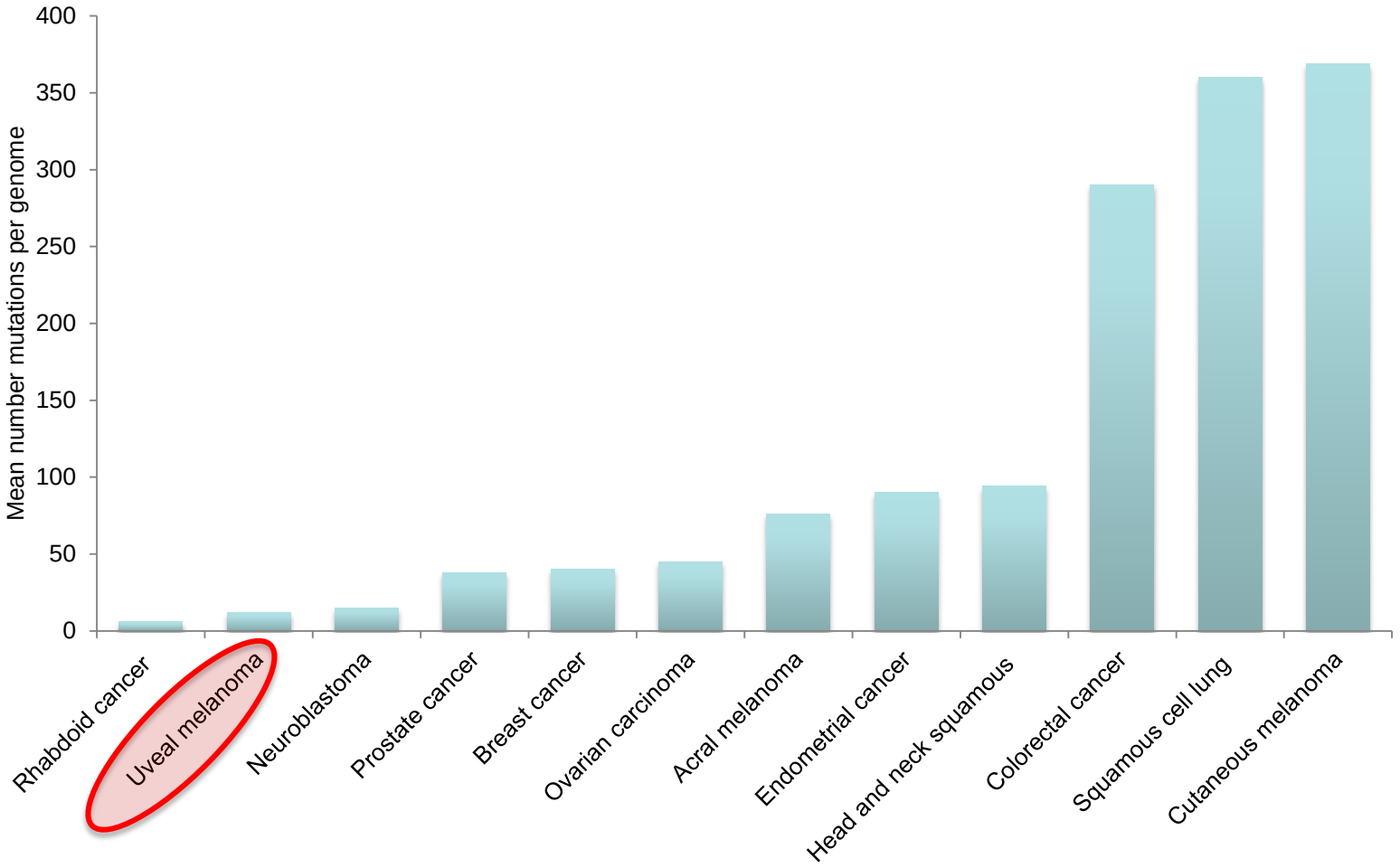
Trials with TIL

- Randomized Phase II trial
  - Salvage Therapy in Melanoma
  - High-Dose IL2 vs LD IL2
  - Single Centre UK Study
- Phase III Trial (PI John Haanen)
  - Randomized Trial vs Ipilimumab
  - Three Centre European Study

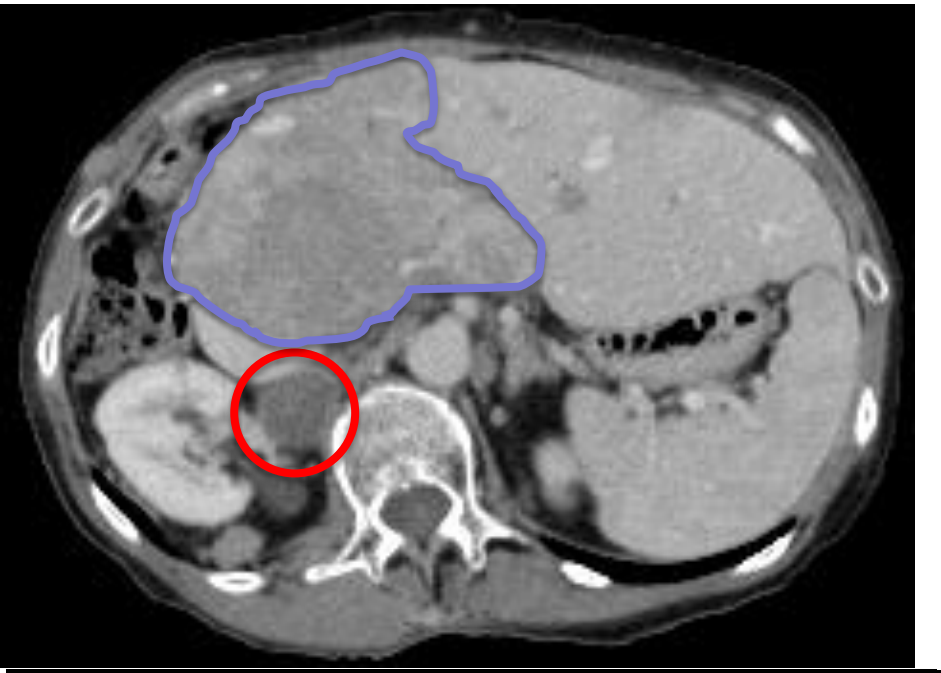
  (Amsterdam, Copenhagen, Manchester)

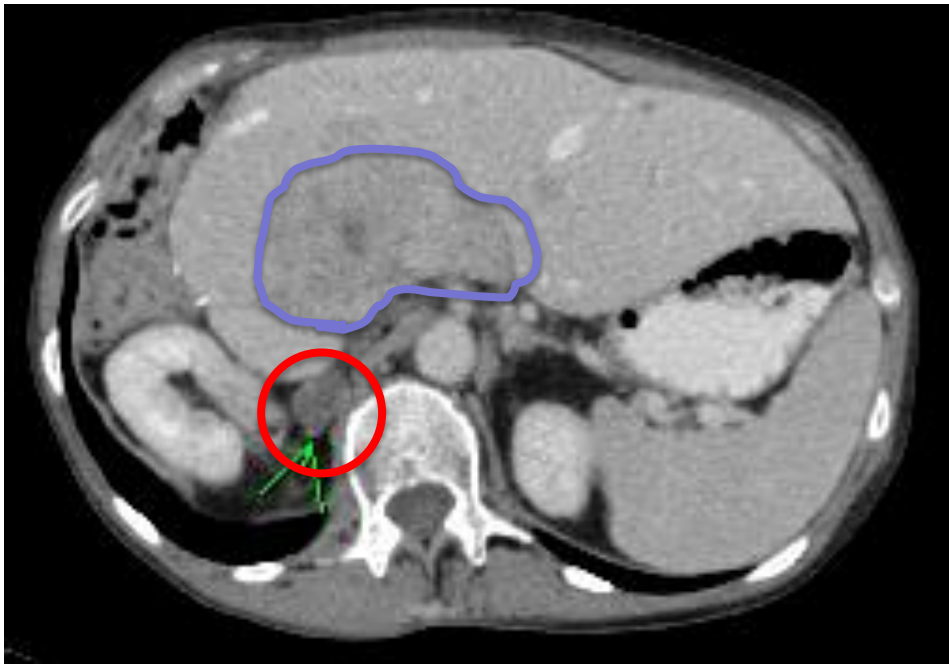
What is Special About Melanoma Biology?

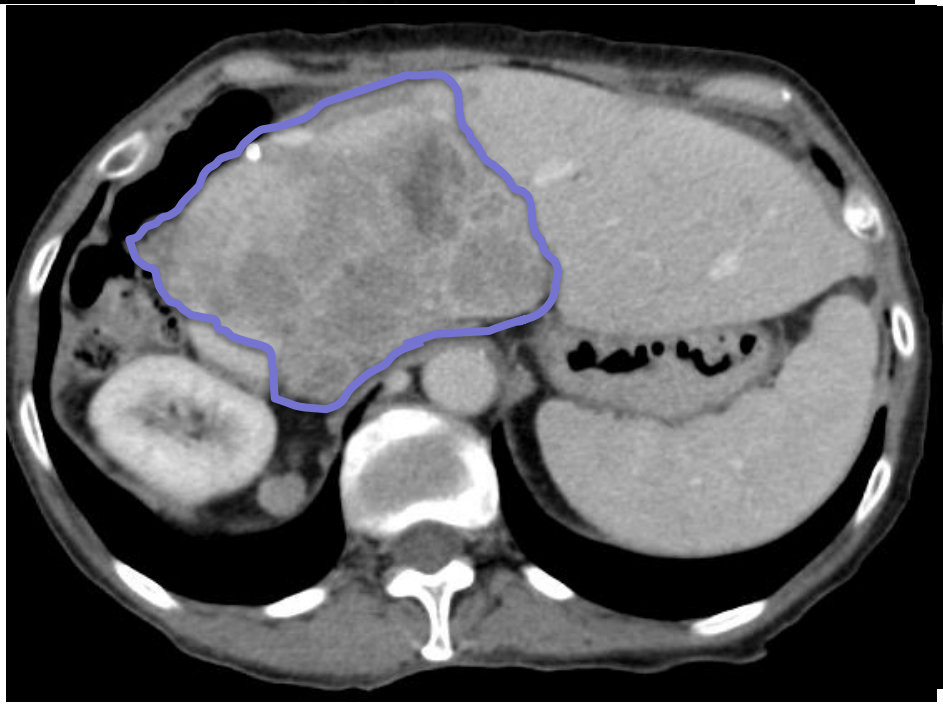
Many tumour types have correlation of outcome with T-cell infiltration

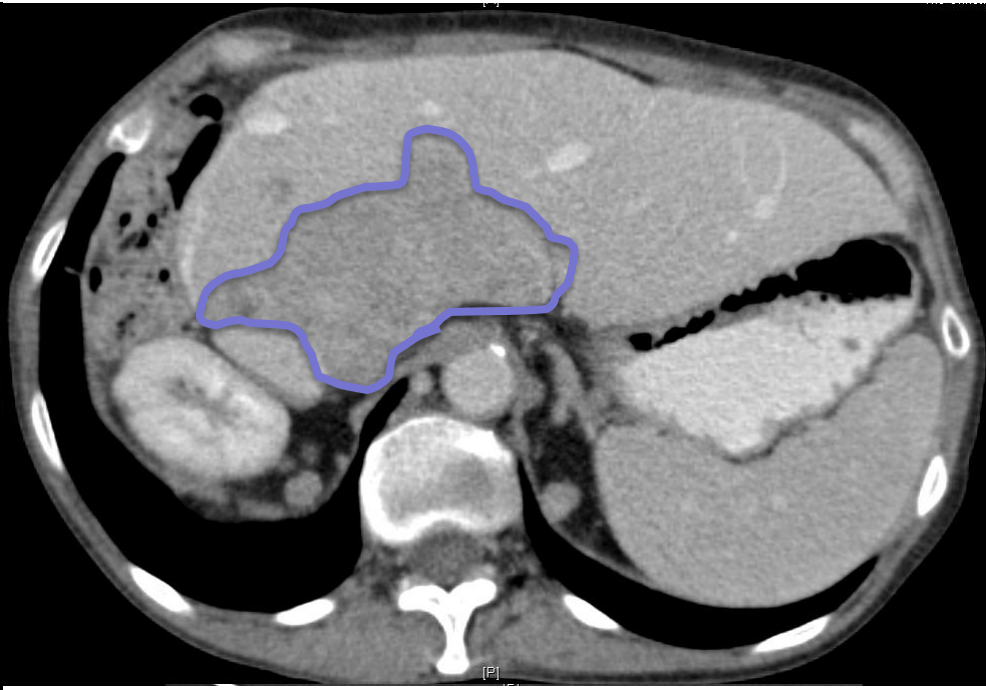


Non-Synonomous Coding Mutations in Exome Sequences



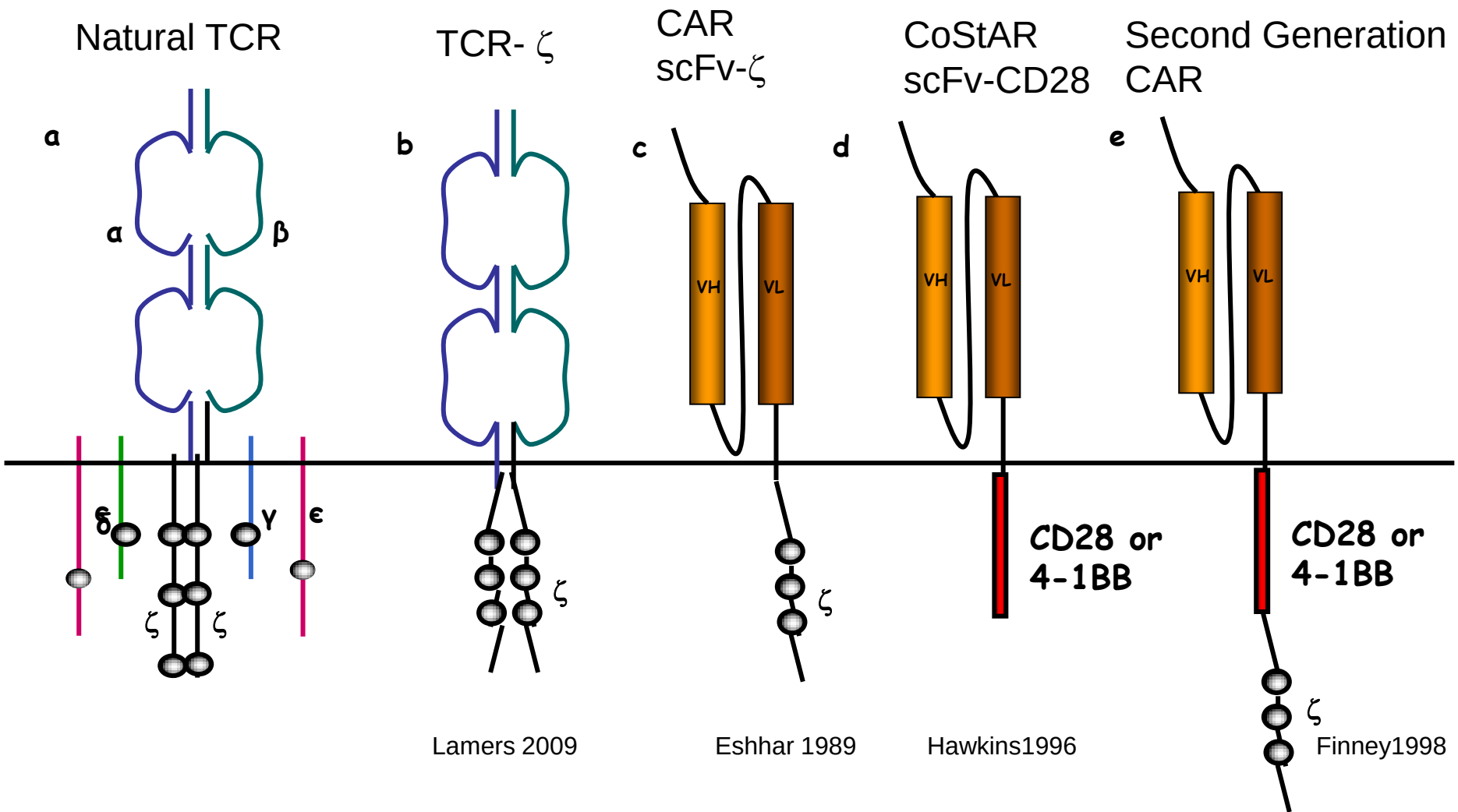






Extending Cell Therapy to Other Diseases?

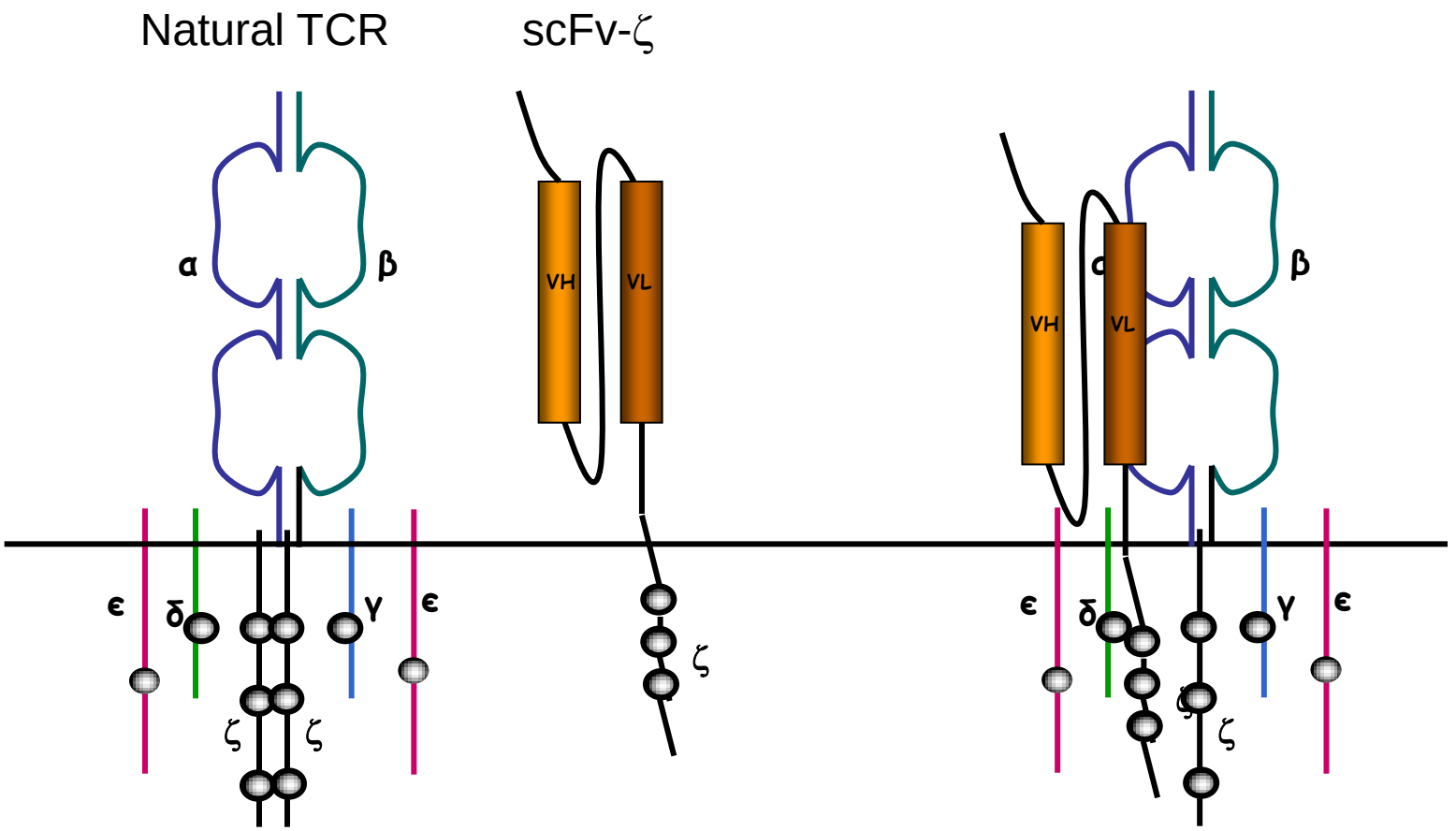
Engineered T cells Receptor Development



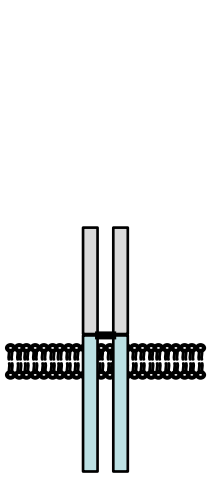
Why do use first generation CAR?

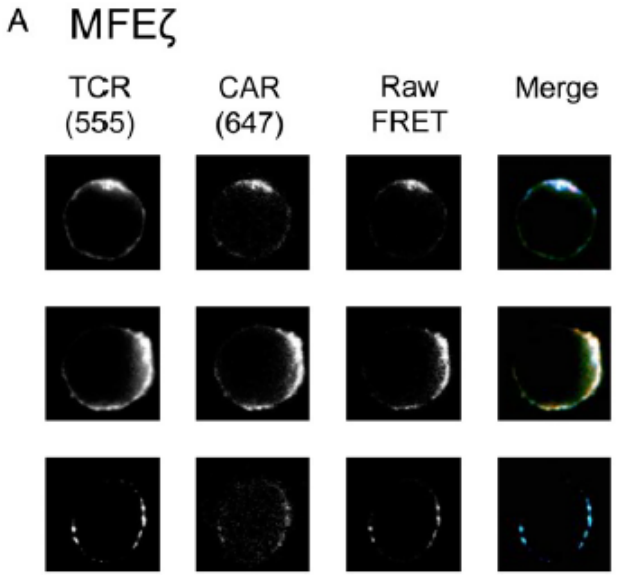
- TIL can be very effective
- Optimized 1st generation CAR
- No benefit in animal models of 2nd generation CAR in CD19 models
- Toxicity seen with second generation CAR in in CD19 models
- Potentially important to ensure target safe before moving to enhanced receptors

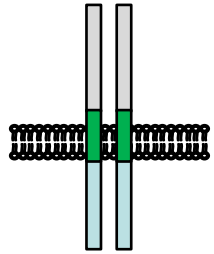
Does CAR Interact with TCR?*and is it important for function?*

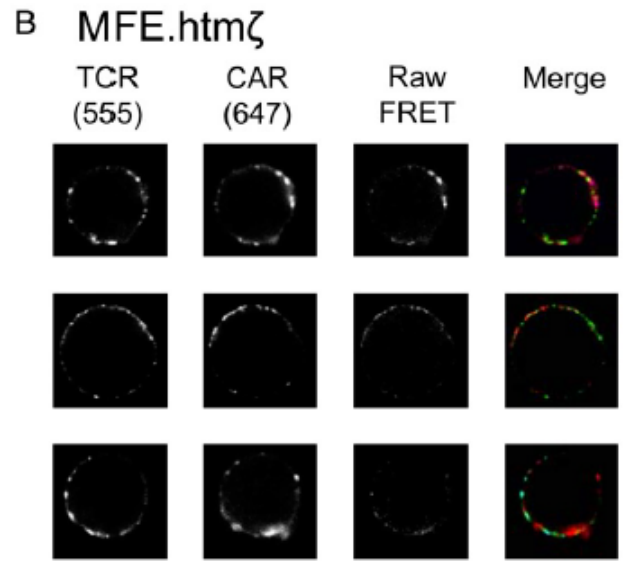


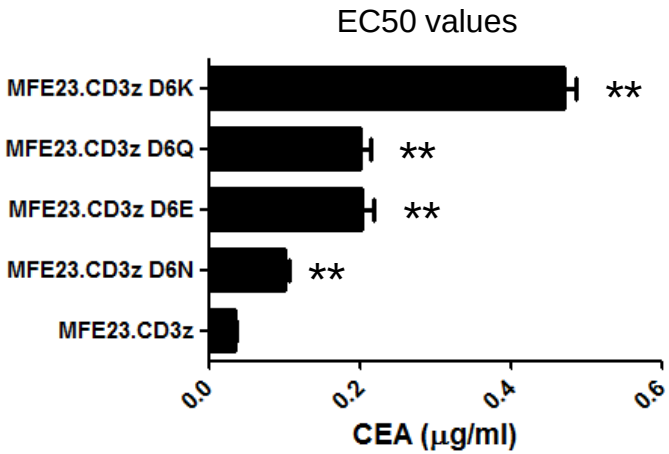
CARs with CD3ζ-transmembrane domain *can integrate into the endogenous TCR complex*

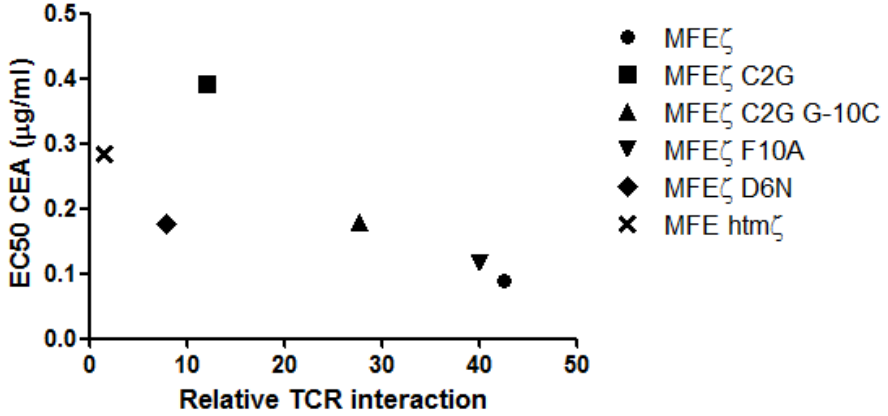








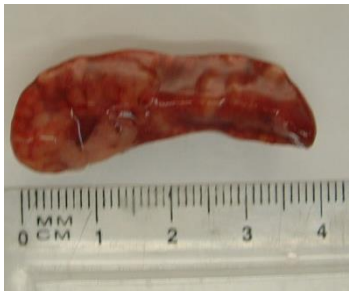


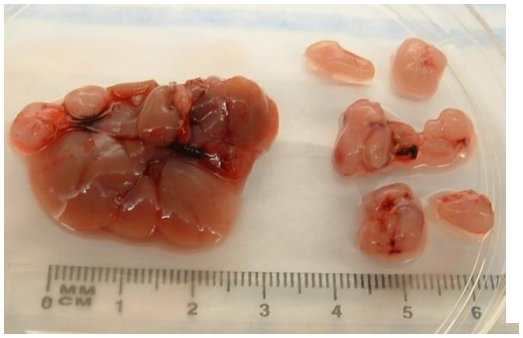


Bridgeman, J.S. et al. J. Immunol. (2010) 184(12):6938-49

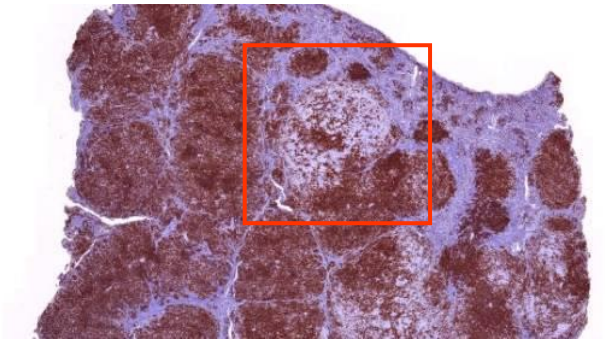
Symptomatic Lympho-proliferation

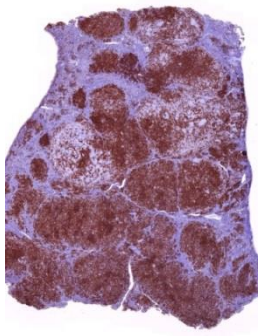
Fully Autologous Mouse Model of CD19-CAR Therapy

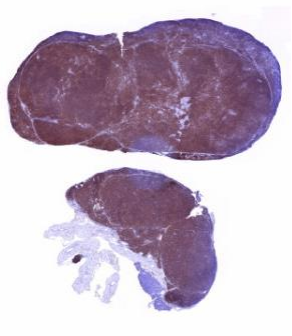


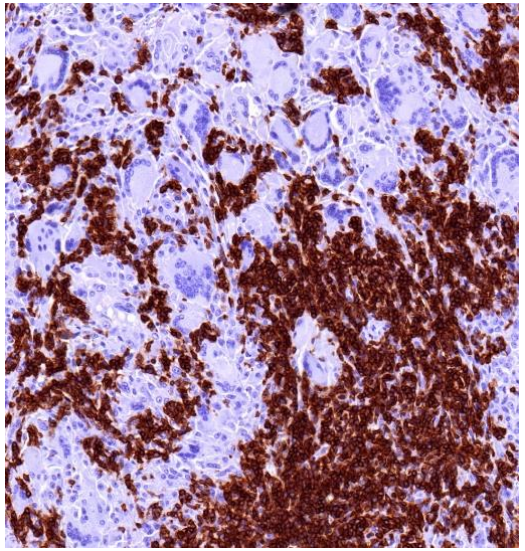


CD34 (CAR marker)





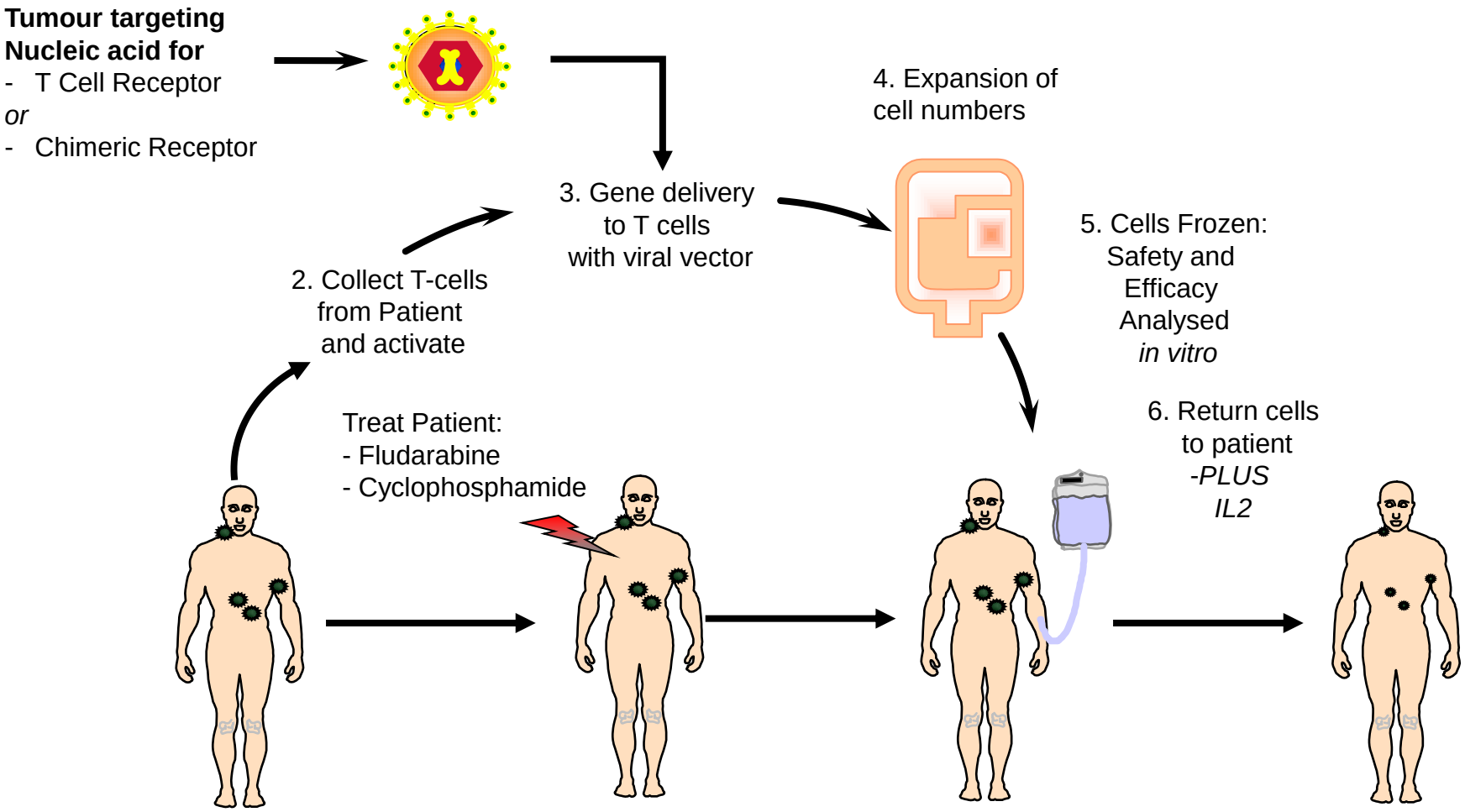




- Lympho-proliferation is largely CD4+ transduced cells

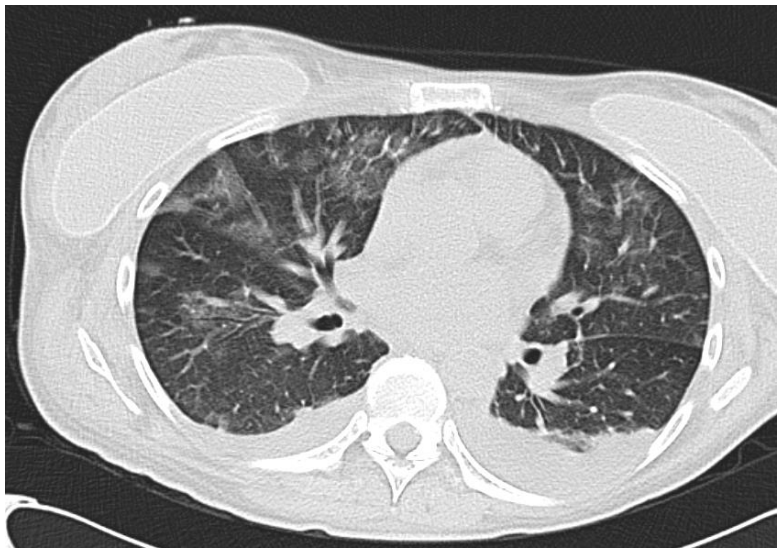
Cheadle EJ, et al., Differential role of Th1 and Th2 cytokines in autotoxicity driven by CD19-specific second-generation chimeric antigen receptor T cells in a mouse model. J Immunol. 2014 Apr 15;192(8):3654-65.

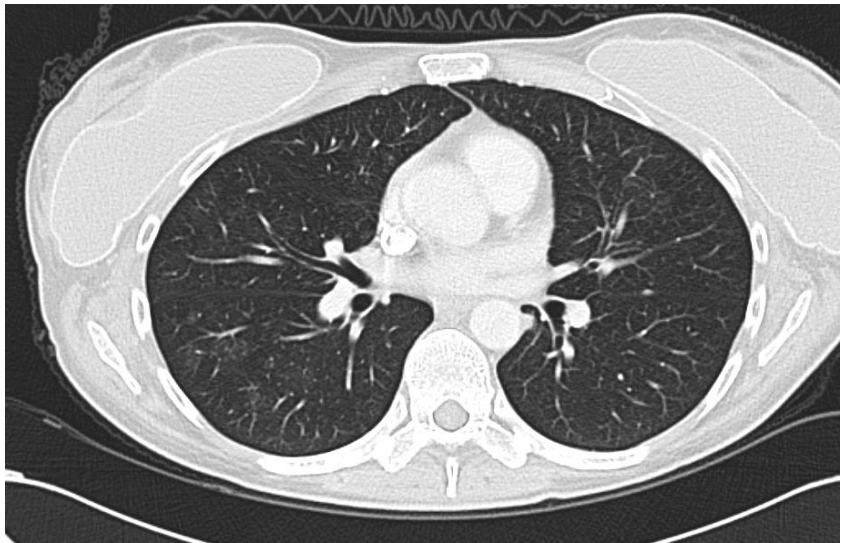
Clinical Trial Design : Based on other trials - TIL



Phase I : 1st Generation CEA CAR T-cell Trial

- 14 patients treated
- Indication of biological and possible clinical activity
- T cell survival limited but some tumour localisation
- Only occurred with full pre-conditioning and high dose cells
- Coincided with maximum cytokine release
- Reversible Lung toxicity – ? Cross reacting antigen / low level CEA in lung
- No major responses (although one patient alive > 5 years)
- Trial halted



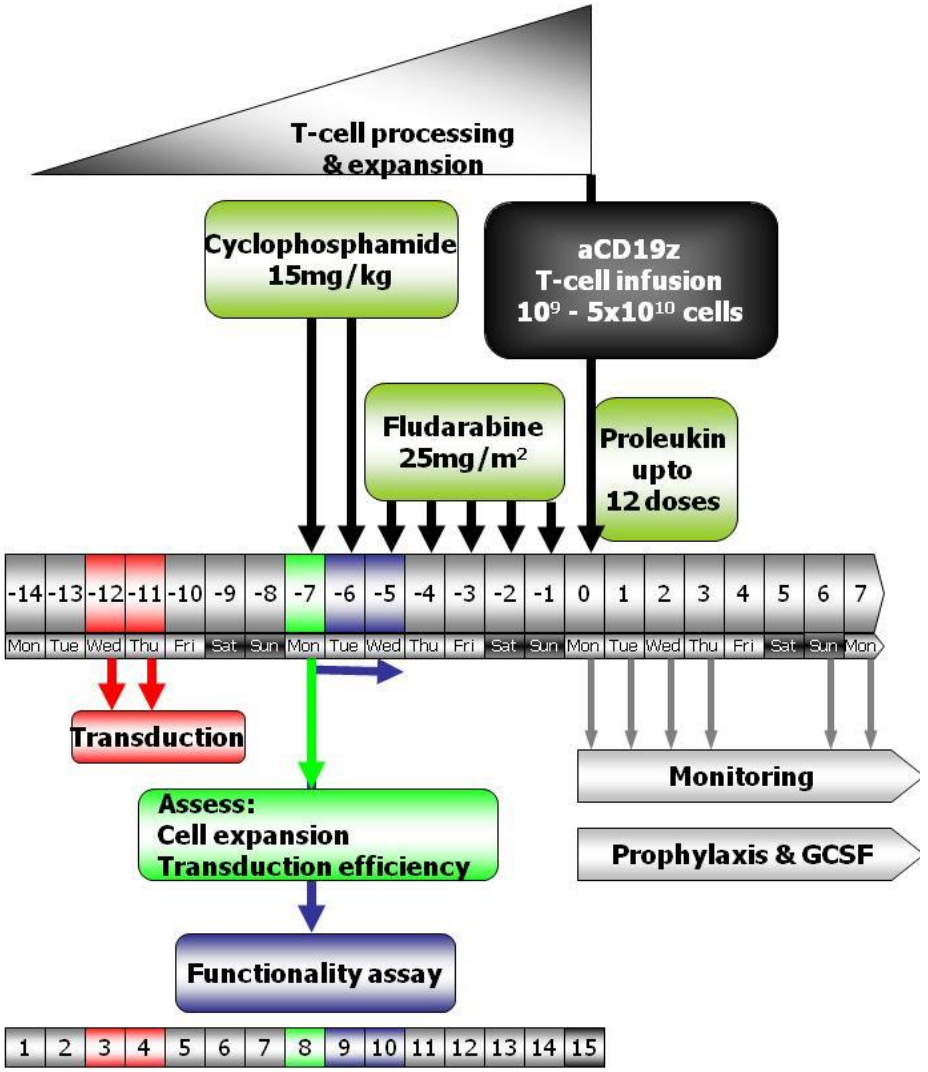


Overview of CD19 CAR Trial

CD19 Trials
HD37 – 1st Generation CAR

Low Dose Cyclophosphamide
Low Dose IL2

Dose Escalation Cells

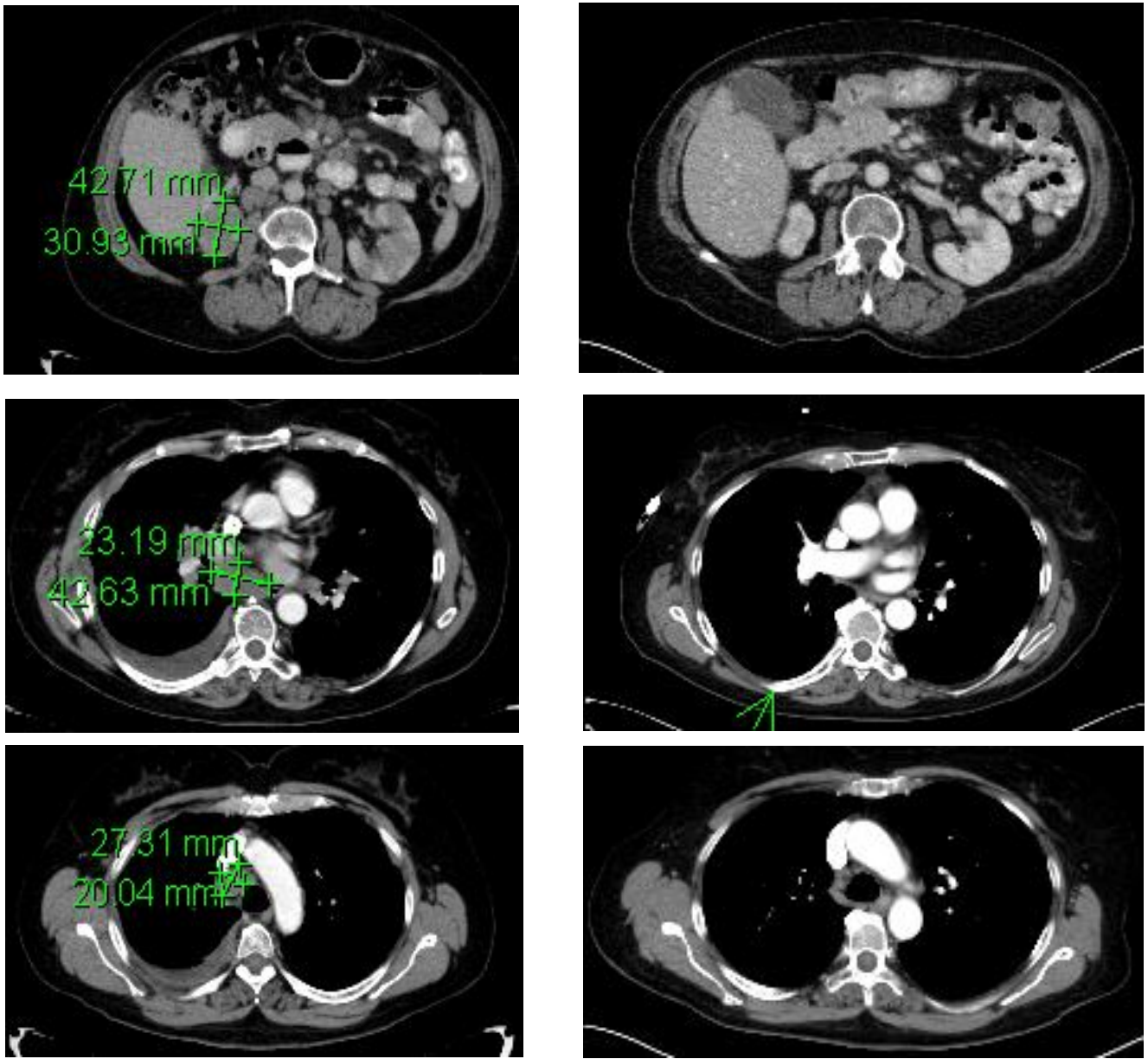


Summary of Patient characteristics

Patient number	Age	Malignancy	Number of previous therapies	Number of T-cells infused (% transduced)
002	54	DLBCL	3	$1x10^9$ (25.7)
005	58	MCL	7	$1x10^9$ (31.5)
006	57	MCL	4	$1x10^9$ (54.6)
012	74	DLBCL from CLL	3	$1x10^9$ (22.0)
013	62	DLBCL	2	$1x10^{10}$ (20.5)
015	61	MZL	3	$1x10^{10}$ (21.7)
016	52	DLBCL from FL	3	$6x10^9$ (20.9)

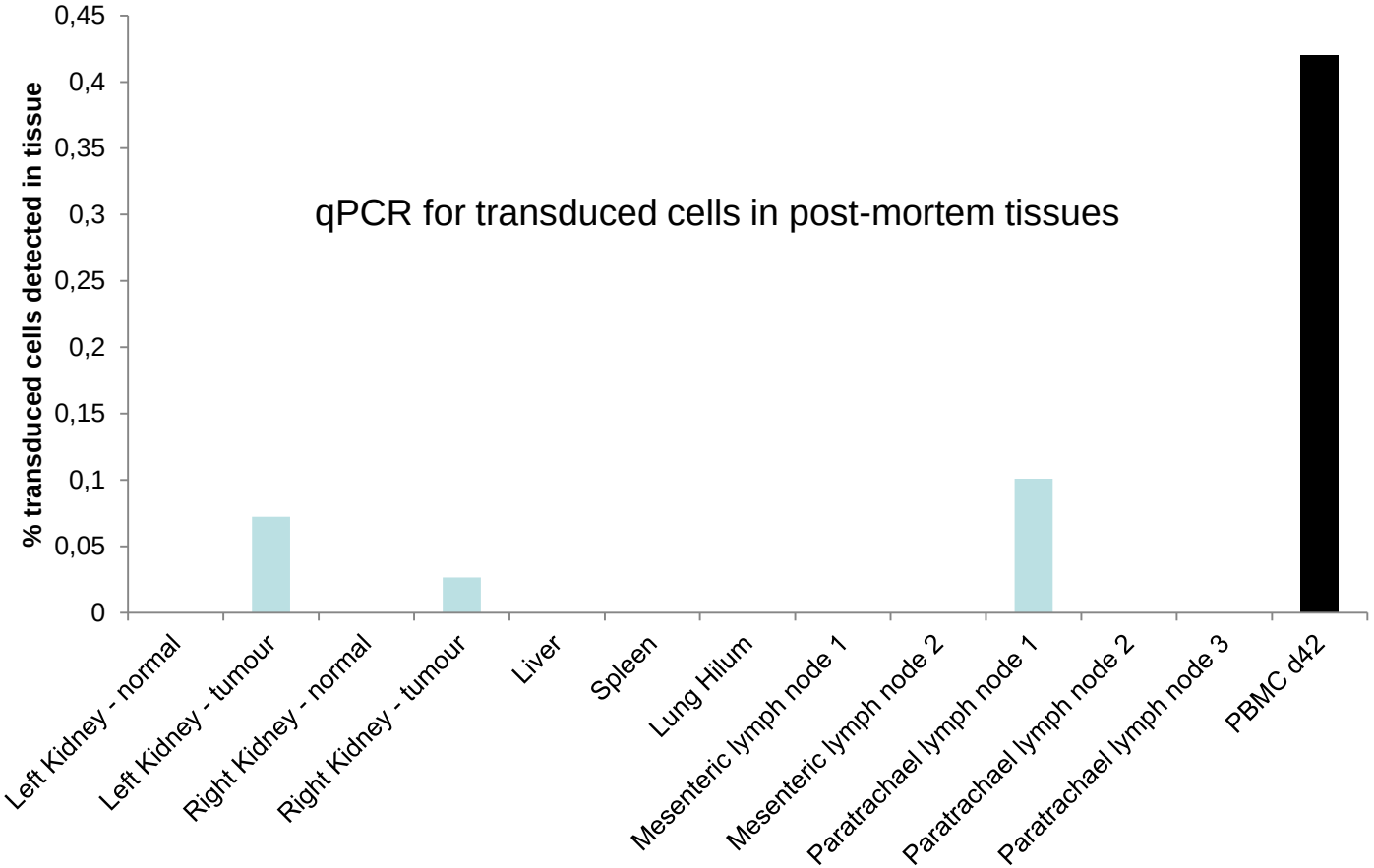
Dose Escalation 10^9 to 10^{10} cells

Rapid Response to Higher Dose CAR T-cells



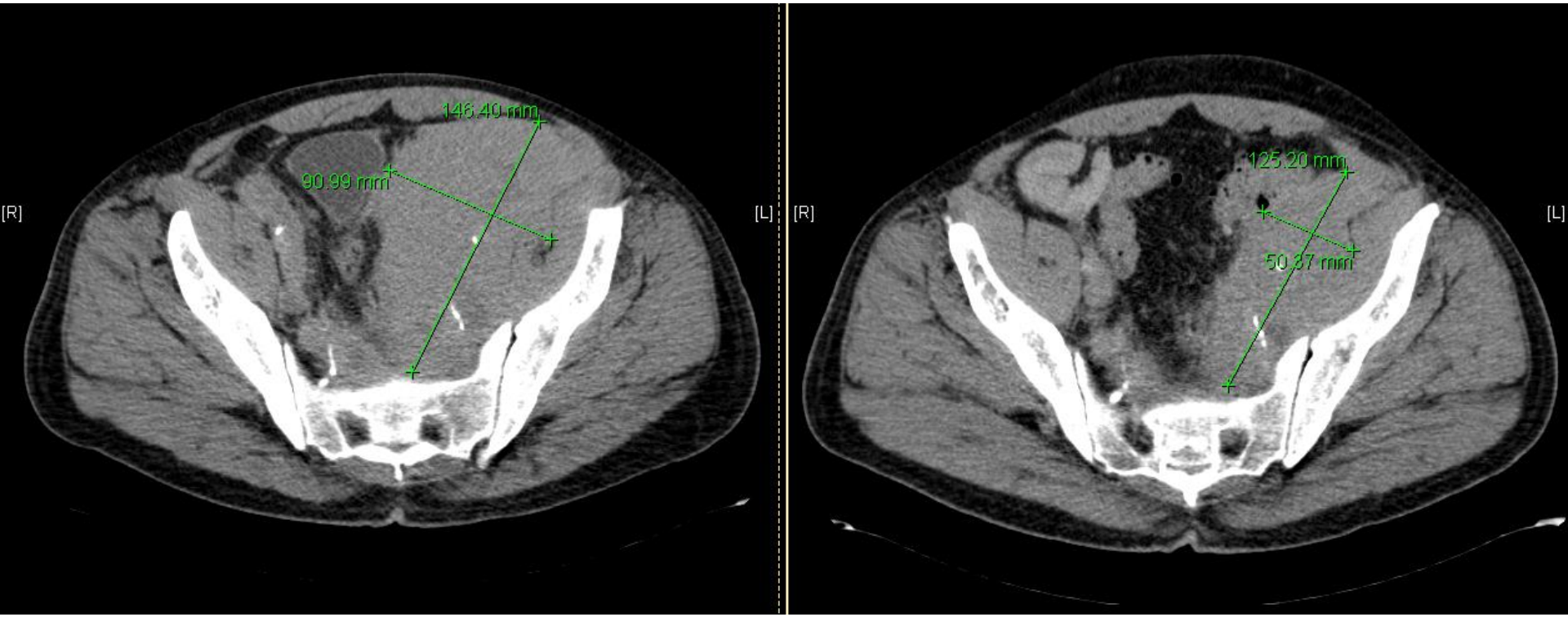
CD19-013 - Course

- Developed Lymphomatous Meningitis
  - 50 Lymphoma : 1 CAR-T-cell in CSF
- Post Mortem Minimal Disease outside CNS



CD19-015 clinical results

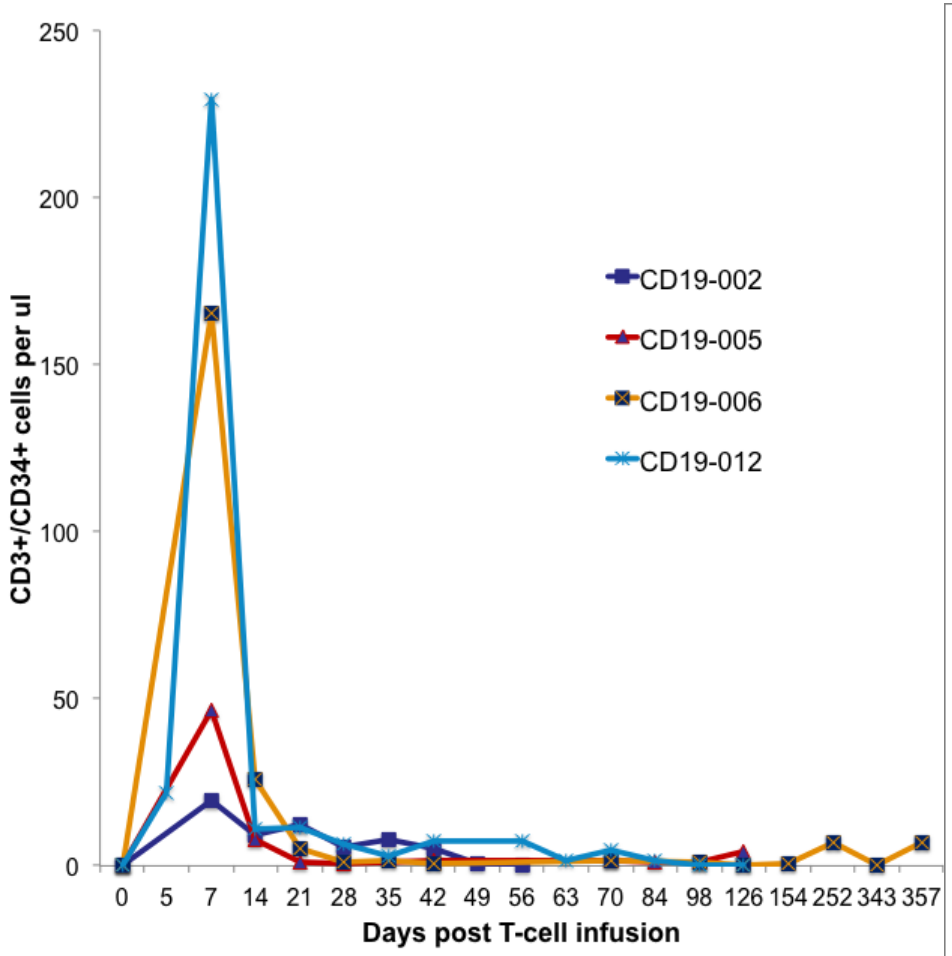
Marginal zone lymphoma

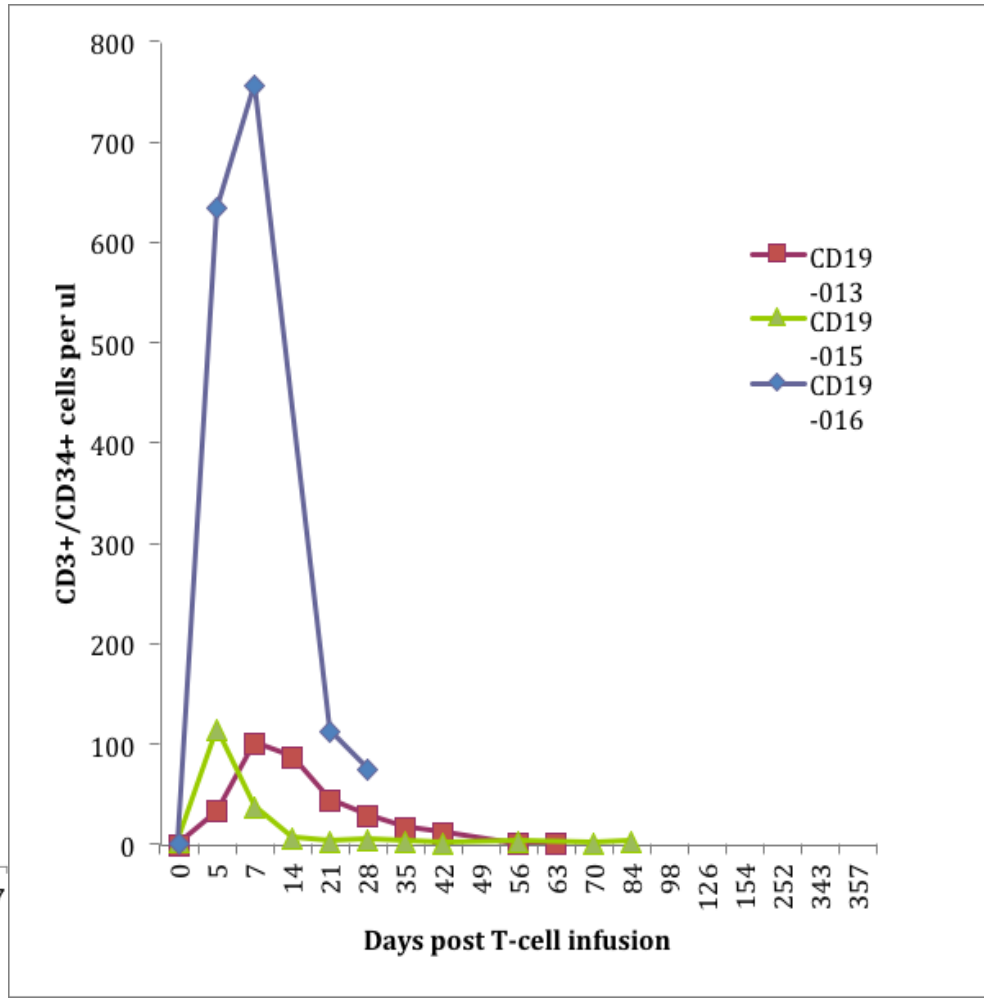


Pre-treatment

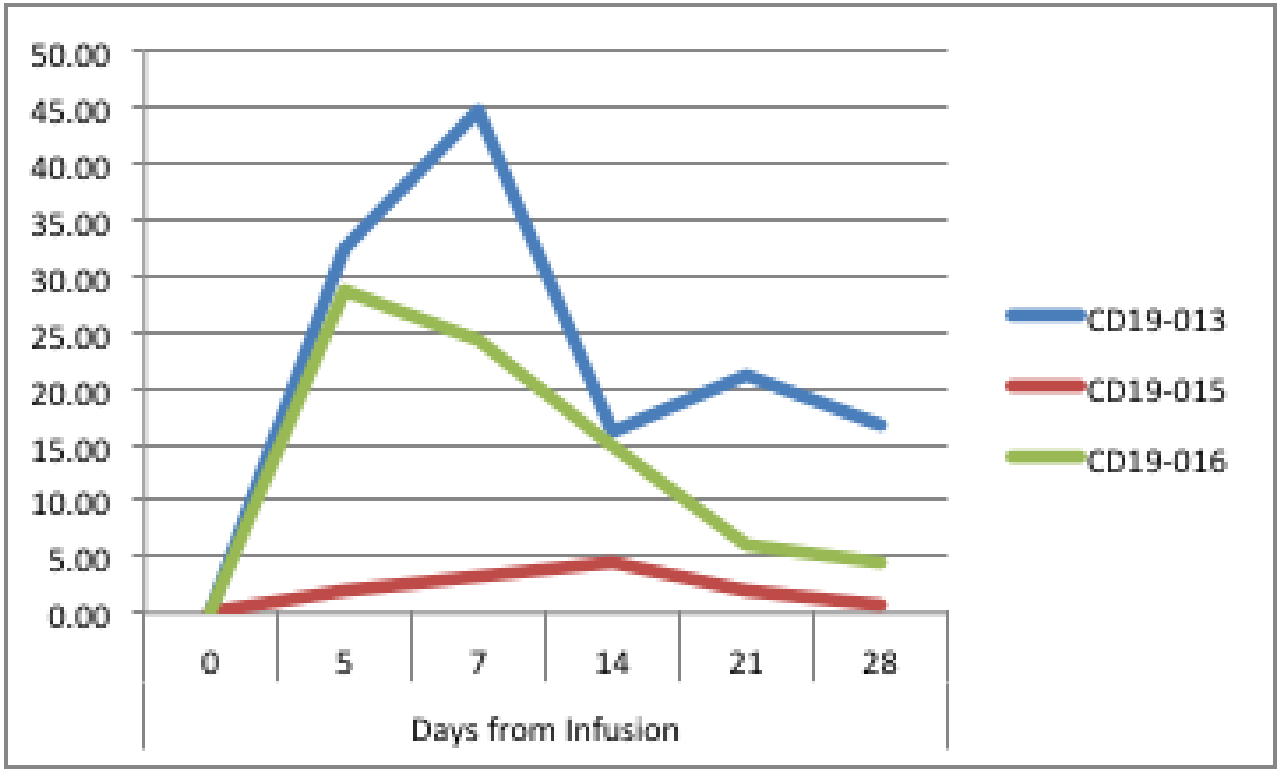
Week 12 post infusion

CD3+/CD34+ cells over time





T-cell Survival / Biology



- T-cell survival better than CEA trial
- Evidence of Positive Selection in some patients
- ? Persistence better in DLBCL
  - Known to have strongest B7 Expression

Engineered T-cells Targeting CD19

- First Generation Receptor
- Low dose chemotherapy
- Low dose IL2
- Dose Escalation of Cells
  - Cohort 1 : 2/4 PR
  - Cohort 2: 3/3 PR*
  - Good Persistence of CD19 T-cells - ? selection
- Generally Low Toxicity
  - transient neurotoxicity - ? mechanism
- Potential to combine earlier in treatment

EU FP7 ATTACK(2)

ATTACK
ADOPTIVE ENGINEERED T CELL TRIALS TO ACHIEVE CANCER KILLING

Background

- Several CAR / TCR shown on target toxicity
- 1G4 TCR Targets HLA-A2 SLLMWITQC
  - Found in NY-ESO-1 and LAGE-1
  - Study at NCI found high response rate *
    - 4/6 in synovial sarcoma
    - 5/11 in melanoma
  - No On-target Toxicity
- Adaptimmune Developed Lentiviral Vector based on optimised TCR
  - Active in Sarcoma, Myeloma

Two key objectives

- Test Efficacy of ACT targeting NY-ESO-1 in Oesophagogastric cancer
- Test improved methods of cell transduction/expansion
  - Selecting CD62L + cells , expanding in IL7&/IL15

ADAPTIMMUNE
transforming T cell therapy

* Robbins et al. J Clin Oncol, 2011: 29; 917-924

ATTACK: Trials

- OG Phase II
  - Up to 28 patients
  - Designed to establish RR in common solid Tumour
  - Opened November 2014
- Melanoma Phase II
  - Up to 34 patients
  - Designed to compare optimised production with Central Memory Type T-cells with Standard production
- Both Centralised Production
    - Manchester & Amsterdam

Key Strategic Objective:

To establish feasibility of multi-centre international trials with centralized production

Conclusions

- Cell Therapy has potential for wide range of cancers
  - Can be extremely effective and produce *durable* benefits
  - ***May*** be so effective because they target mutated antigens (truly tumour specific)
    - Targeting multiple targets may also be important
  - It is relatively complex but processes becoming standardised
- Engineered Cell Therapy – key challenges
  - Potentially very effective
  - Risk of “on-target” toxicity
  - *Appropriate Clinical Targets need to be defined*
- Challenges with Deliverability remain
  - Centralised vs Automated “Bedside” Production
- Engineering T-cells further to enhance efficacy and improved deliverability may facilitate improved clinical processes

Acknowledgements

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