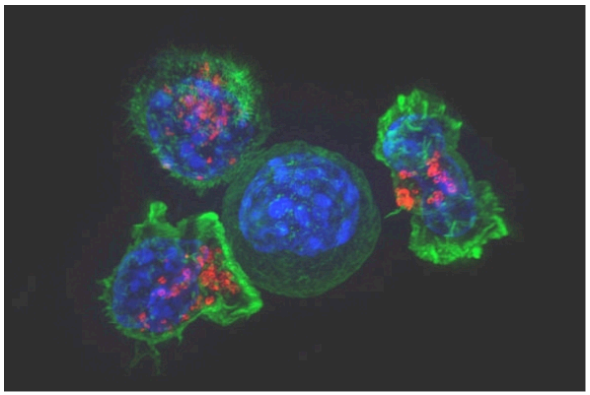
MANCHESTER 1824

Adoptive Cell Therapy For Melanoma:

A perspective on Tumour Infiltrating Lymphocyte Therapy

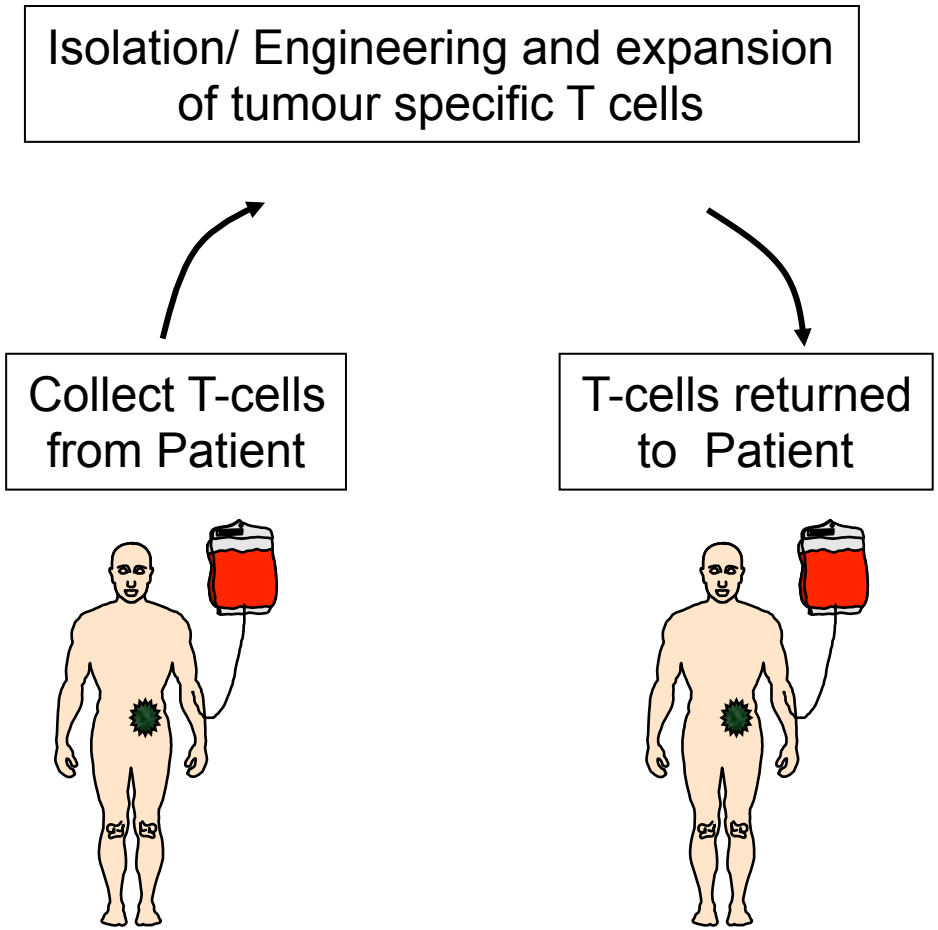
Robert Hawkins



The Christie NHS
NHS Foundation Trust

Adoptive Cell Therapy

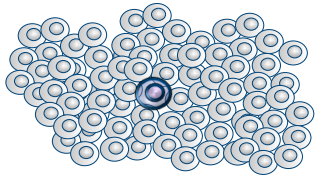
- Two basic approaches
  - Natural T cells
    - Isolated from blood
    - Isolated from tumour
  - Genetically Engineered T cells
    - Engineered from blood lymphocytes
      - TCR based receptors
      - Antibody based chimeric receptor



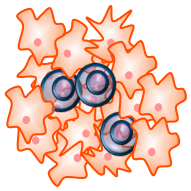
What is TIL therapy?

- Type of Adoptive Cell Therapy – TILs, CAR-T, TCR
- **T**umour **I**nfiltrating **L**ymphocytes – white blood cells (T cells, B cells, NK cells)
- Natural anti-tumour mechanism – to identify, infiltrate and attack solid tumours
- Highly potent & highly selective for cancerous tissue
- However, tumour microenvironment often 'switches off' natural tumour-killing function of TILs
- TIL therapy involves isolation and massive *ex-vivo* expansion of T cells from TILs before re-infusion into same patient
- Large influx of TIL derived T cells, plus pre- and post-conditioning therapy to dampen immunosuppressive environment and further expansion of TILs *in-vivo* results in significant and durable responses in melanoma patients:
  - ~ 50% overall responses of which many remain as durable responses
  - 10-25% probably "cured"

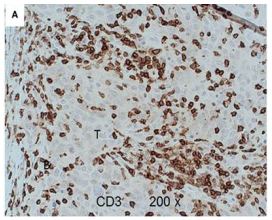
Blood – Cancer Specific T-cells are very rare



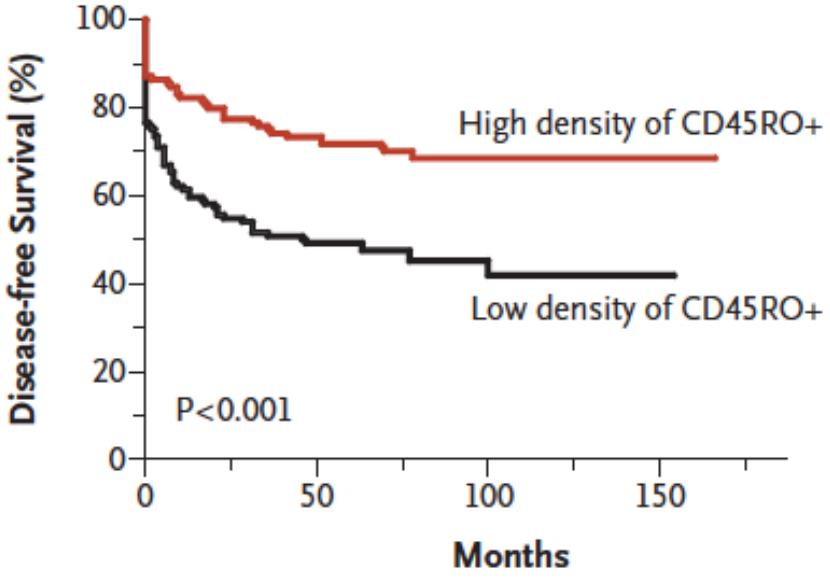
Tumour - Cancer Specific T-cells are enriched

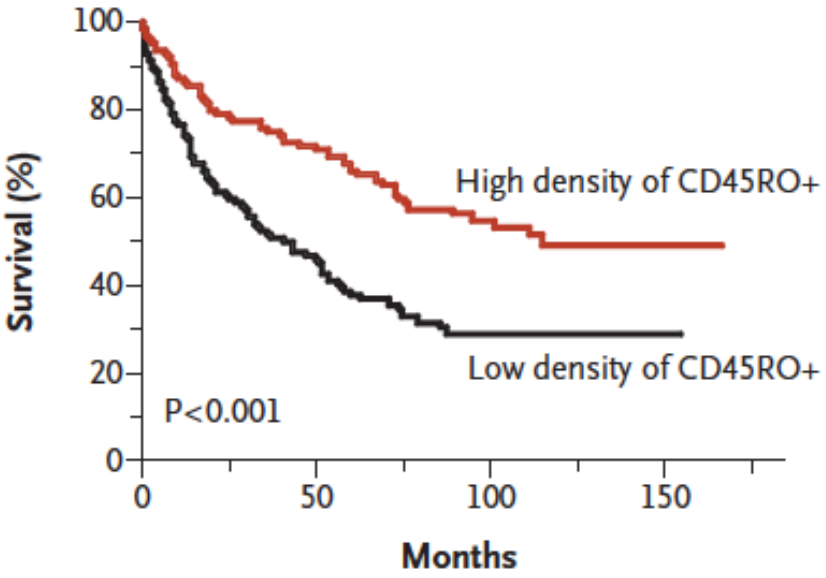


Tumour - stained to show high levels of T-cells (in brown)



Correlate of Immune Cells with Outcome



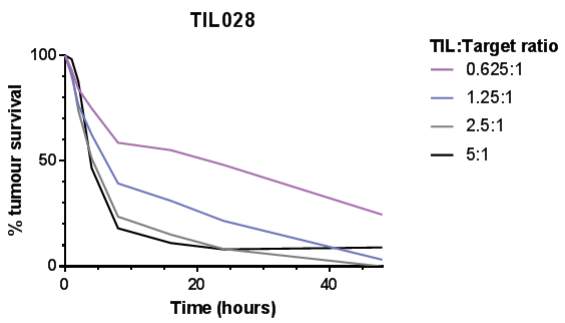


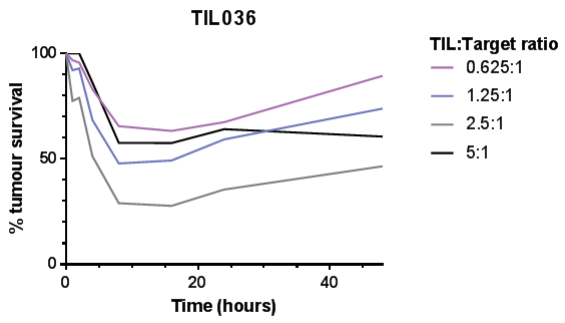
- Is is cause and effect?
- What are they recognising?

Franck Pagès et al. Effector Memory T Cells, Early Metastasis, and Survival in Colorectal Cancer. N Engl J Med 2005; 353:2654-2666

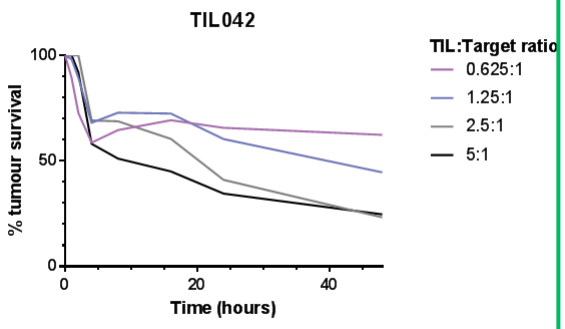
In Vitro Activity of TIL

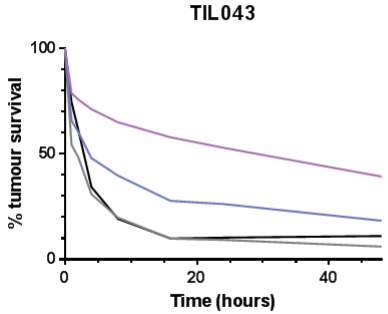
Acral Melanoma

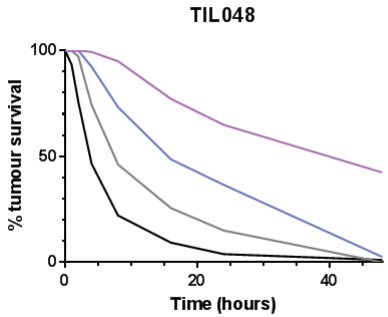


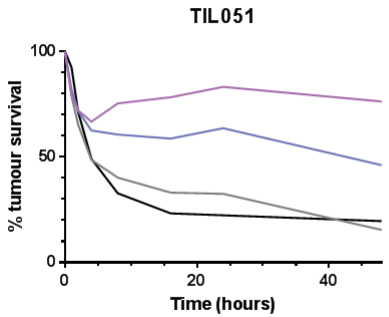


Uveal Melanoma





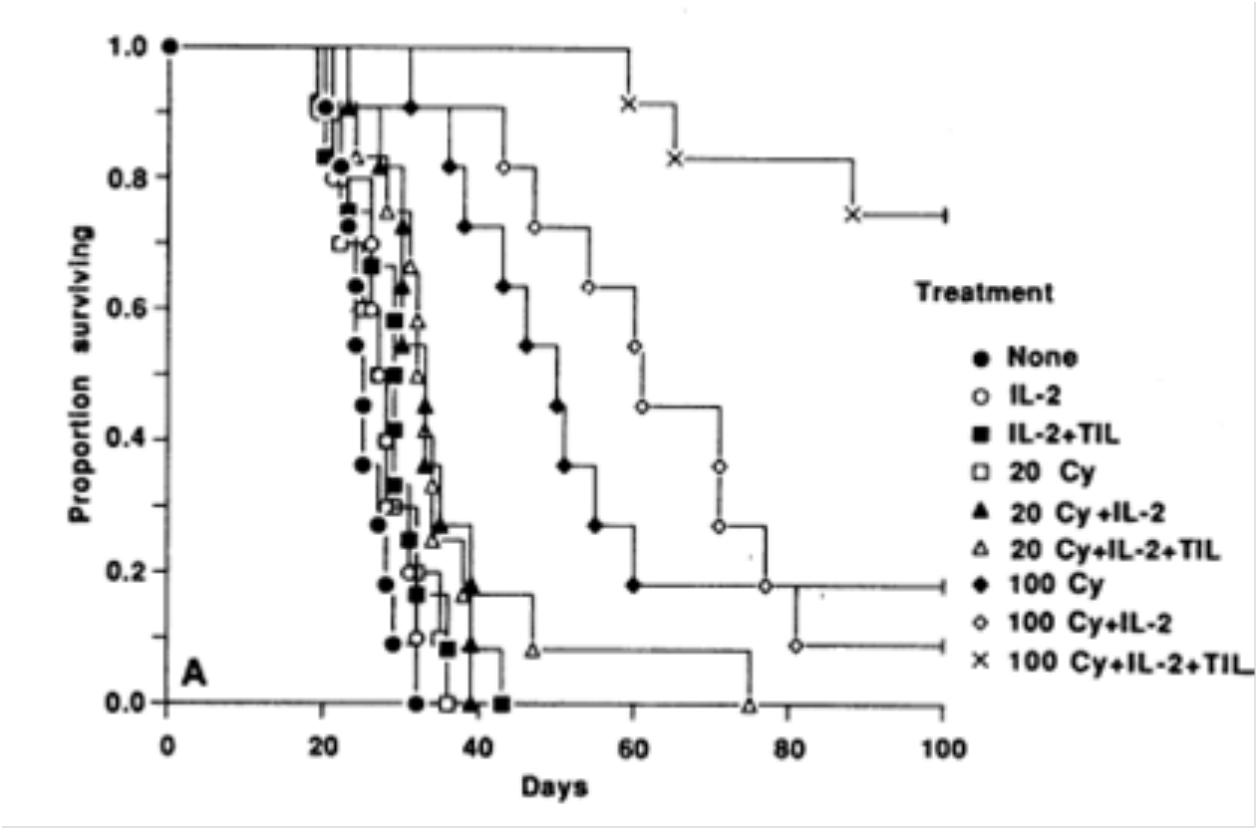




Cutaneous Melanoma

Overall 90% success rate in growing melanoma TIL

Pre-clinical Evidence for TIL Therapy

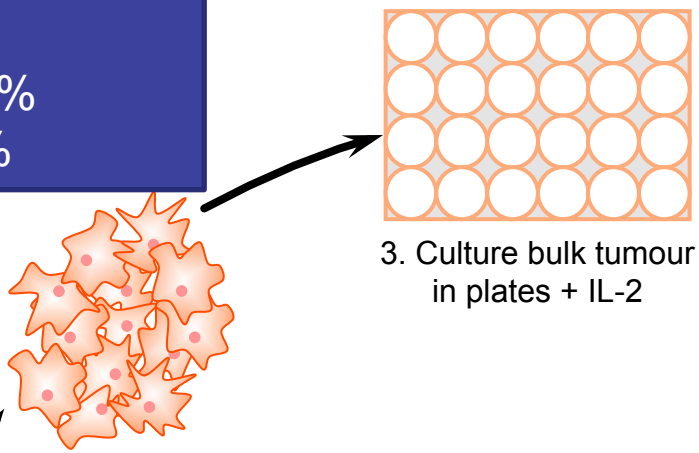


Rosenberg SA, et al., A new approach to the adoptive immunotherapy of cancer with tumor-infiltrating lymphocytes. Science. 1986 Sep 19;233(4770):1318-21.

TIL Treatment

Evolving Treatment

- RR 1990 20%
- RR 2010 50-75%
  - CR 20-25%



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

1. Surgery to remove tumour sample

6. "Pre-conditioning Therapy" with Cyclophosphamide and Fludarabine

5. Rapid Expansion Protocol – 2 weeks

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

Patient with Melanoma

8. Return cells to patient + supportive therapy with IL2

Historical TIL Studies

Indication	Publication	Year	Responses
Melanoma	Dillman et al	1991	OR = 29% CR = 5%
Melanoma	Rosenberg et al	1994	OR = 34% CR = 6%
Renal	Goedegebuure et al	1995	OR = 50% CR = 0%
Gastric	Xu et al	1995	OR = 35% CR = 13%
Renal	Figlin et al	1997	OR = 26% CR = 9%
Melanoma	Rosenberg et al	2011	OR = 56% CR = 22%
Cervical	Stevanovic et al	2015	OR = 33% CR = 22%

Considerations for Clinical Delivery of ACT

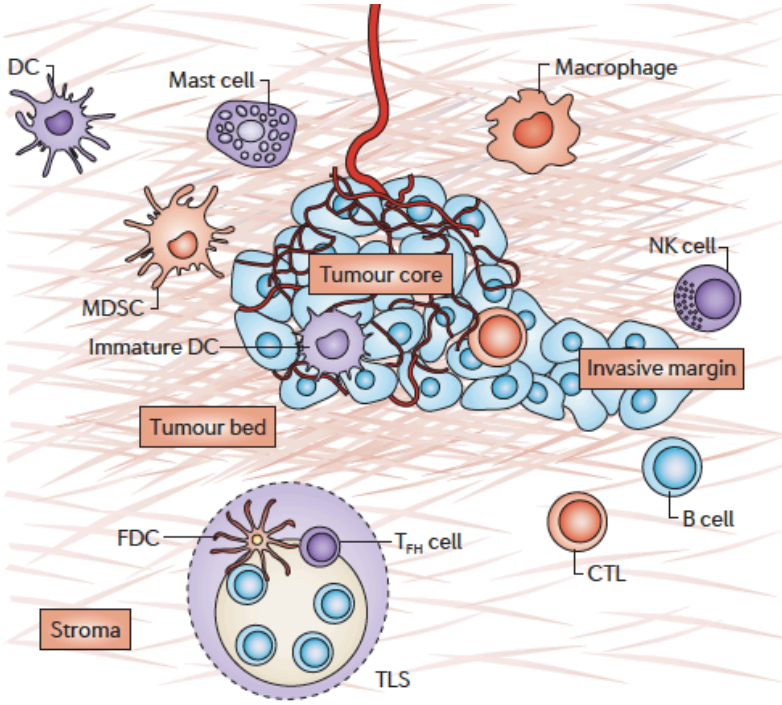
- Complex/Personalised so the efficacy bar will be high
- Need to comply with EU GMP regulations
- Main attractions
  - Manipulate cells outside body – free from immunological controls
  - Short-term treatment
  - Long-term benefit
- Main Drawbacks
  - Complex/Costly
  - Toxicity of supportive therapy
    - Pre-conditioning chemotherapy
    - Supporting Cytokines
  - Potential on-target toxicity
- Practical Challenges

Developing GMP Cell Therapy Manufacturing

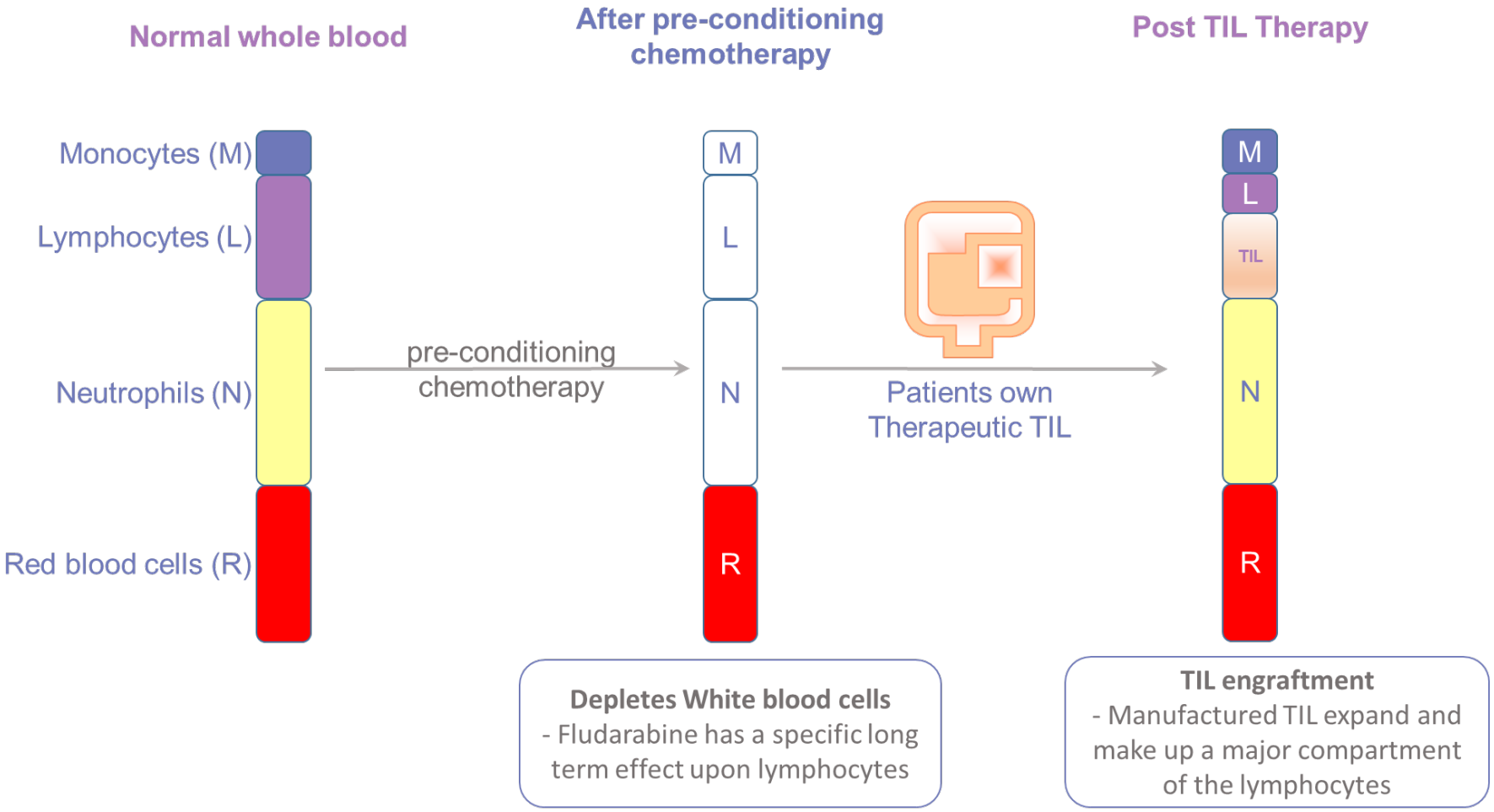
- Move away from classical clean rooms
- Provides a controlled sterile environment
- Protects patients cells from infection or contamination
- Allows rapid decontamination with vaporised hydrogen peroxide
- Allows multi product processing
- Closed Systems outside isolators
- REP entirely in WAVE bioreactors

Why Pre-Conditioning Chemotherapy?

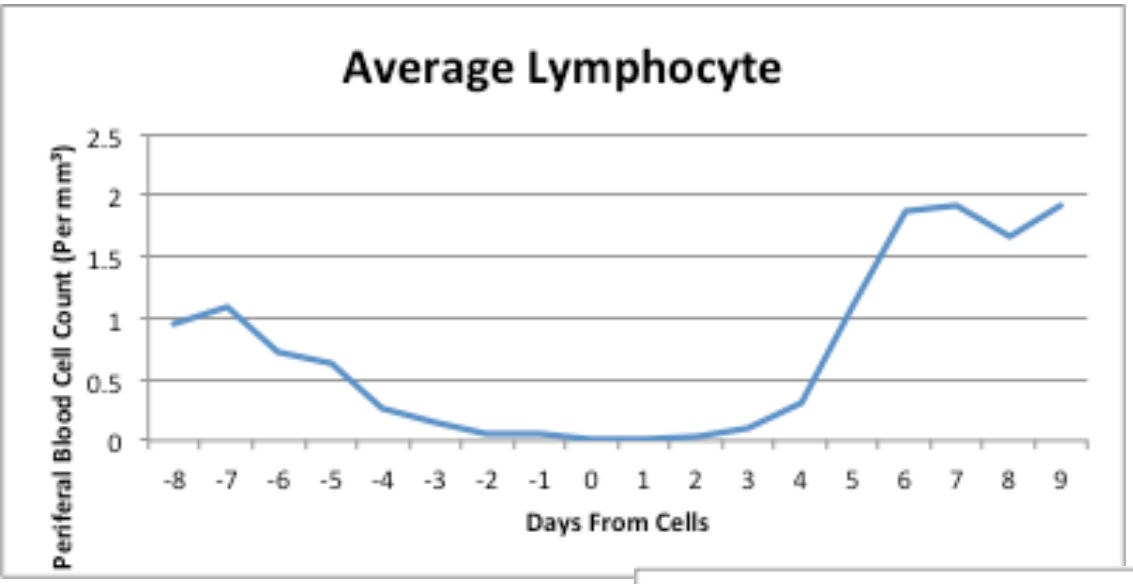
- Effects on Tumour Microenvironment
  - Elimination of immune-suppressive cells
  - *For example* Treg, MDSC
- Enhances T-cell Engraftment
  - Increases homeostatic cytokines (IL7/IL15)

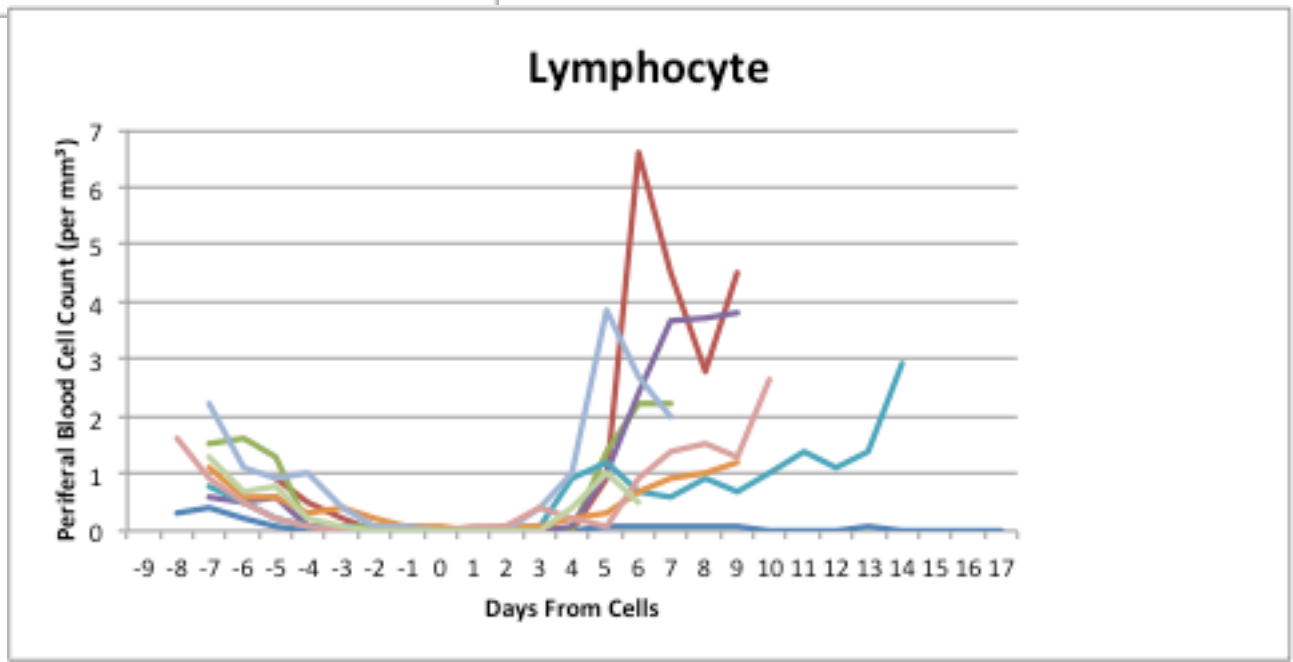


Schematic Representation of ACT process

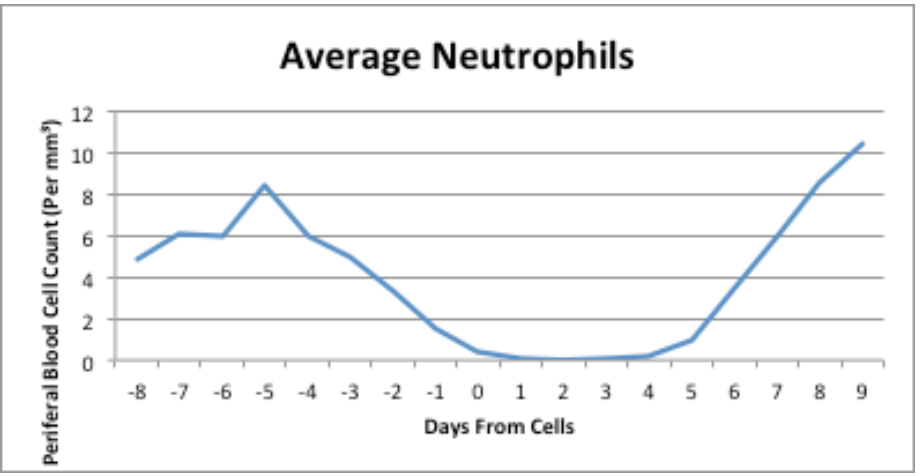


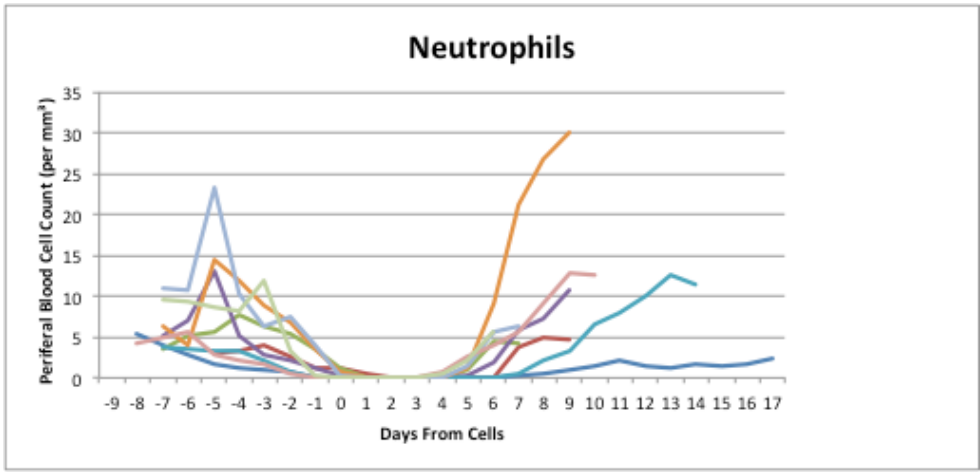
Lymphocyte Recovery

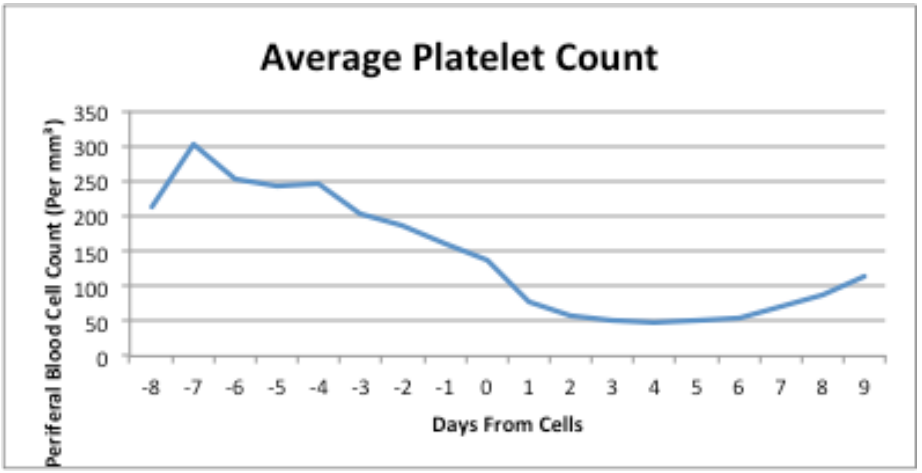


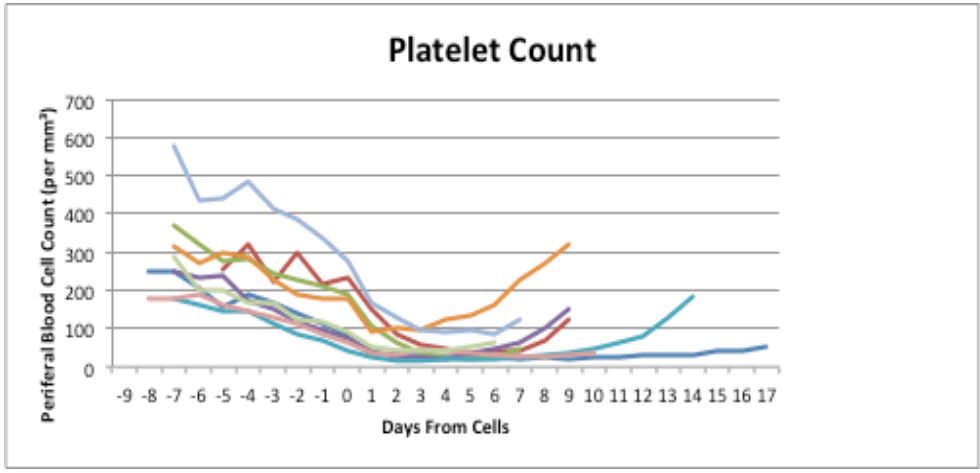


Practicalities of Therapy







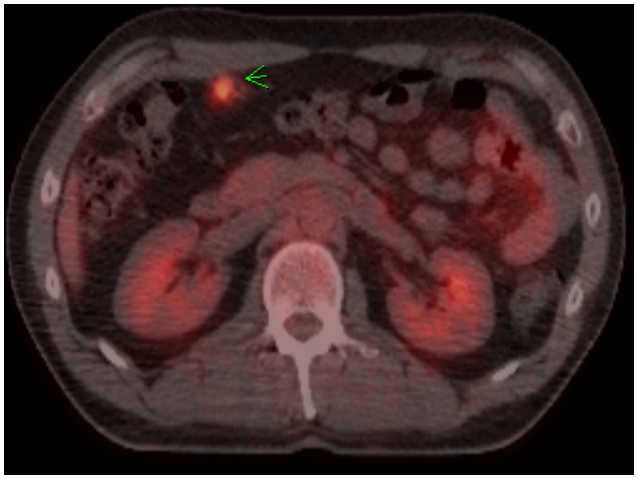


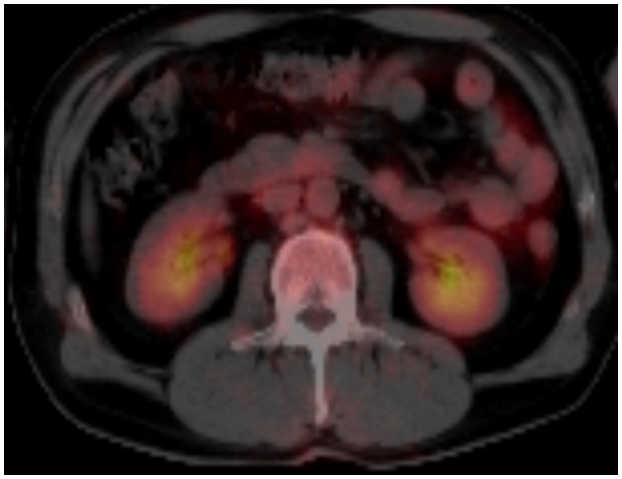
- Admission
  - Median16 days
  - Range 14 – 25
- On average 8 doses IL2 given

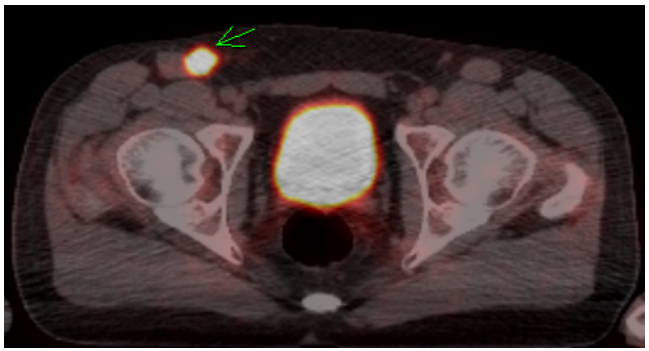
A straight forward case

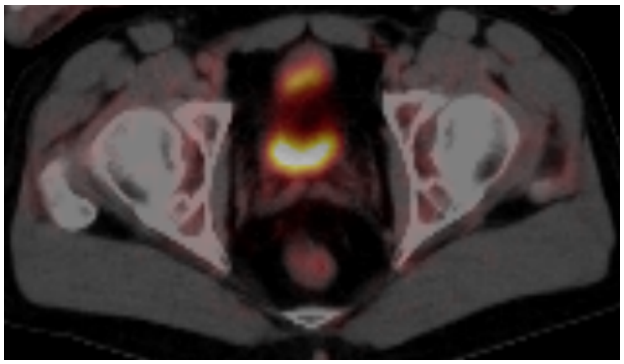
Pre- Treatment

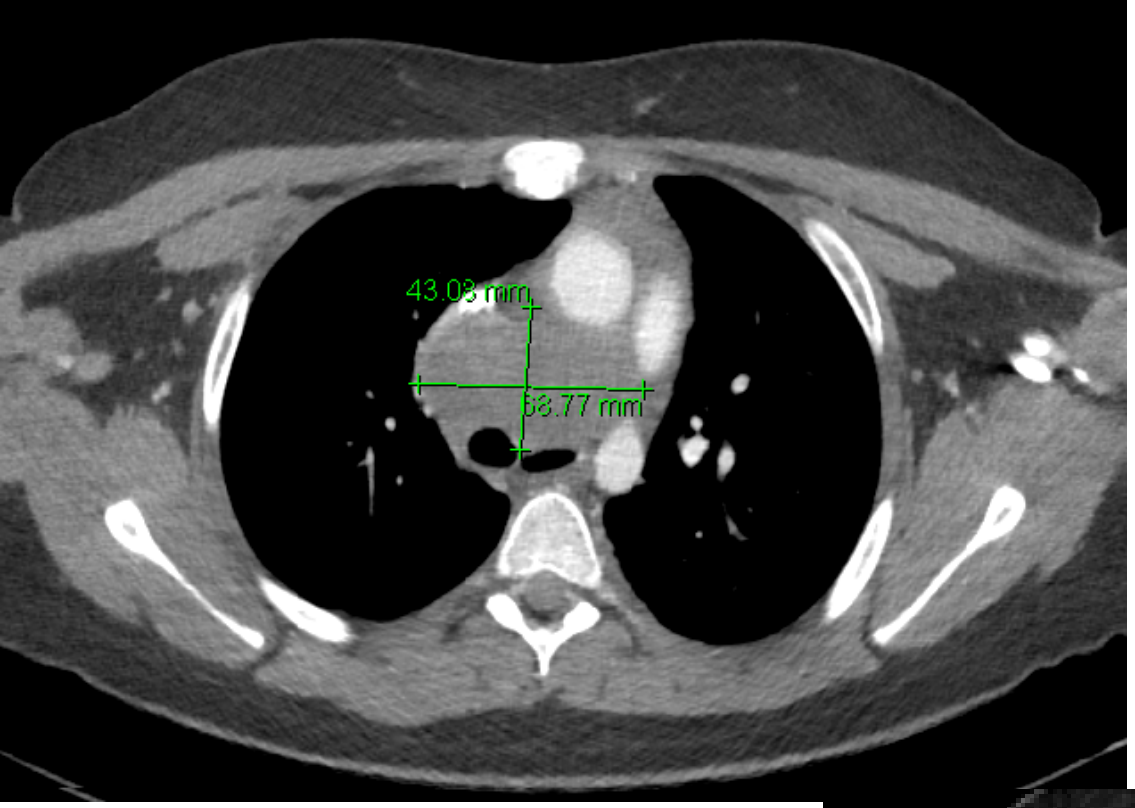
Post-Treatment

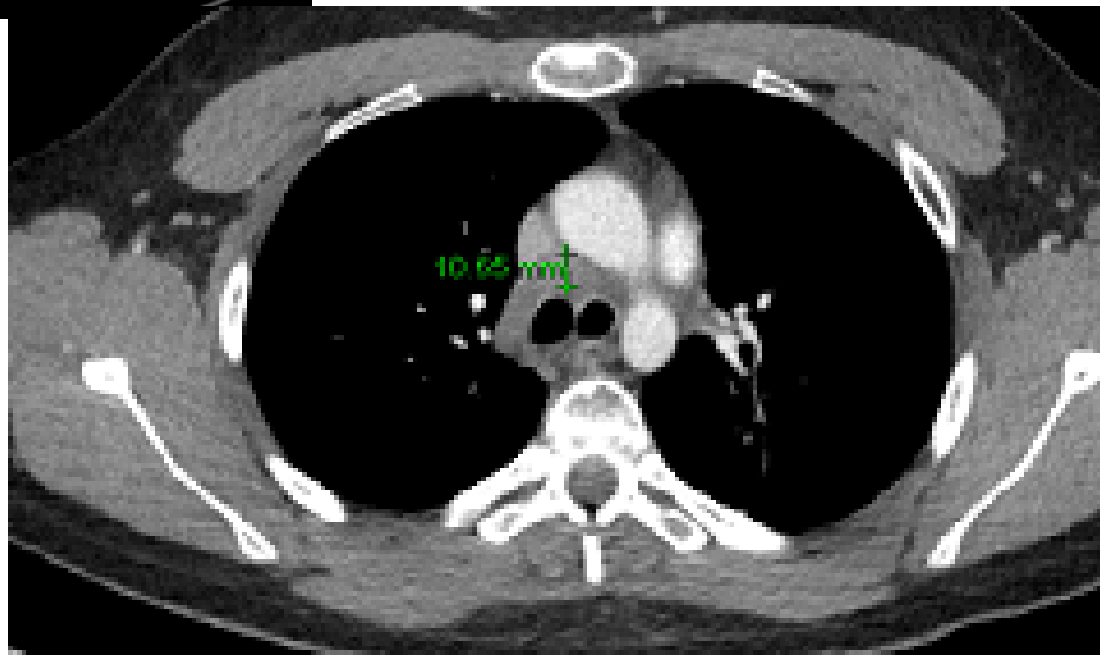


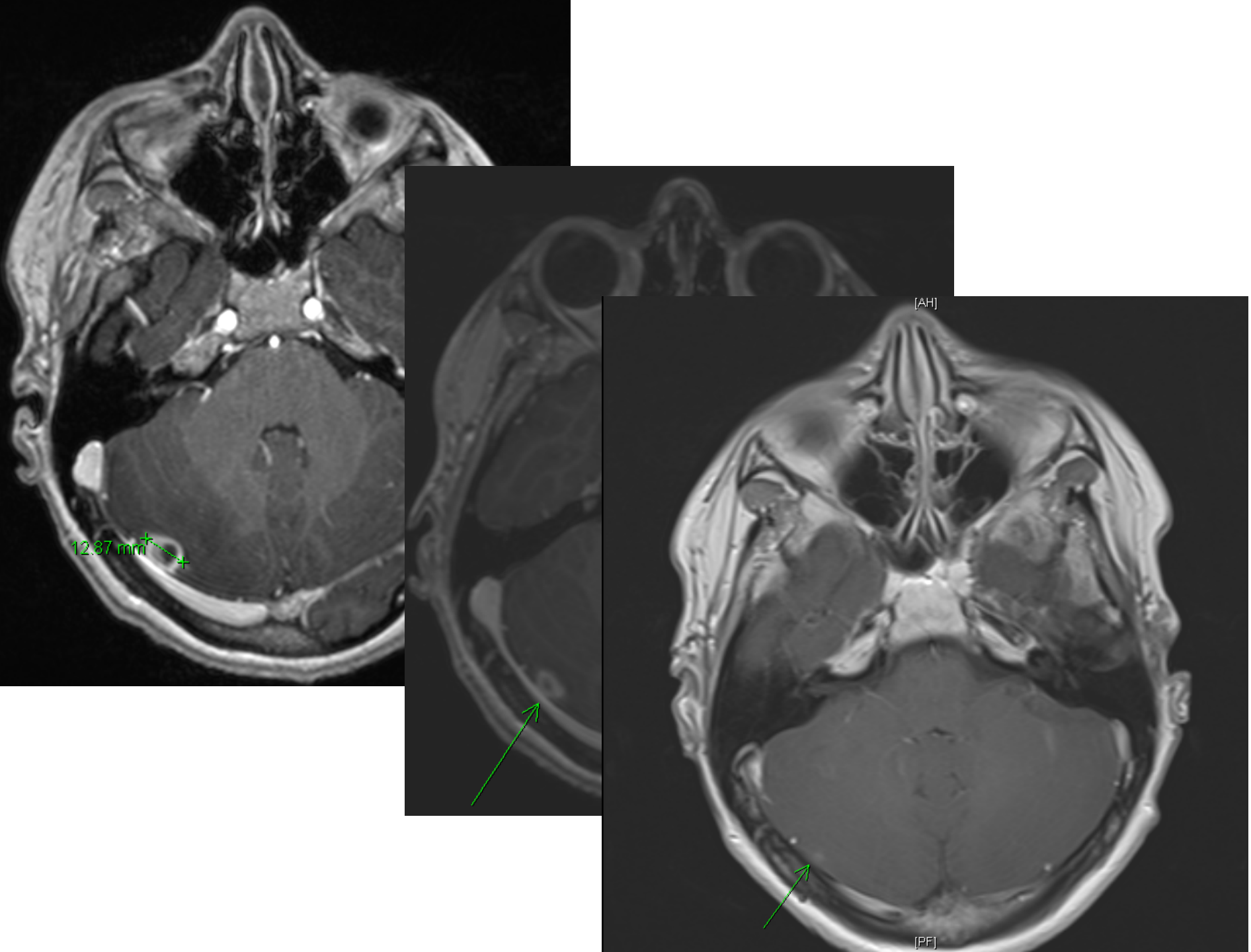




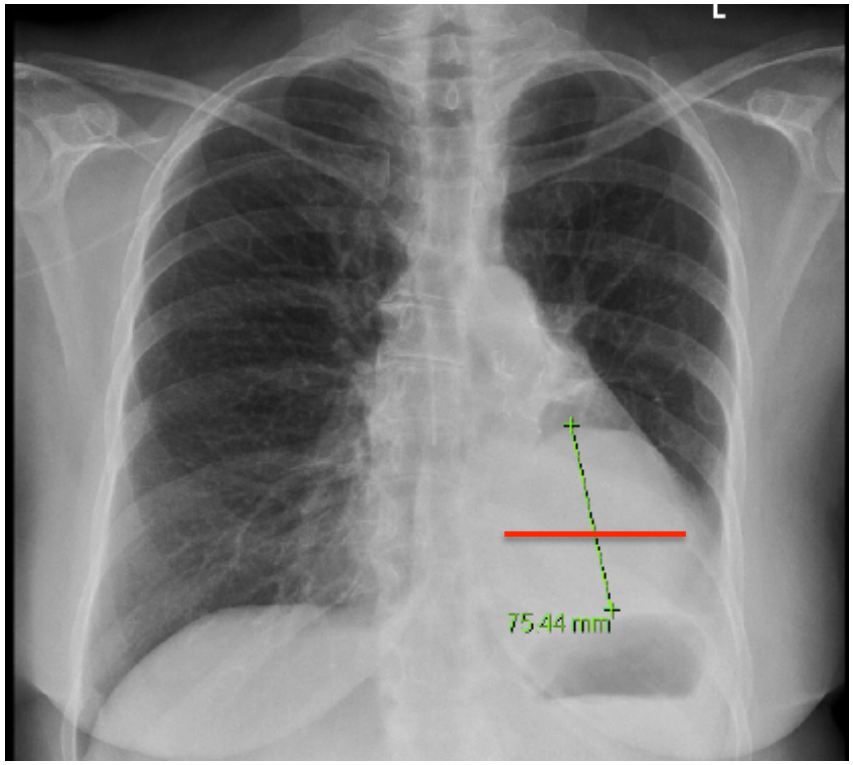



43.03 mm
68.77 mm


10.65 mm


12.87 mm
[AH]
[PF]

Patients on B-Raf Inhibitors



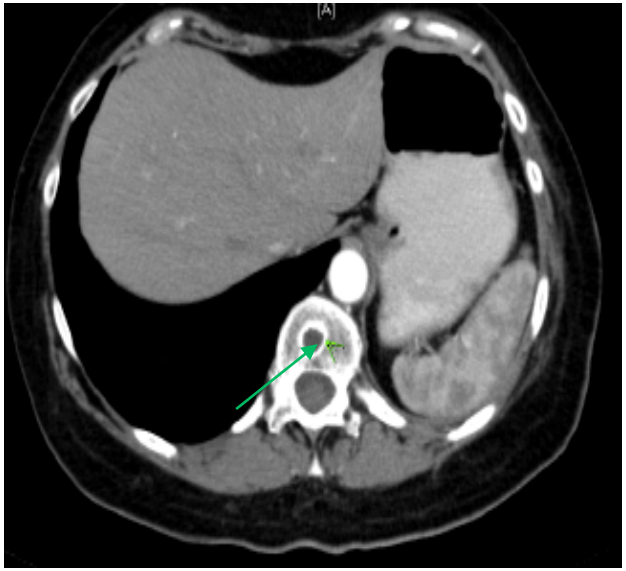
TIL with B-Raf Inhibitor

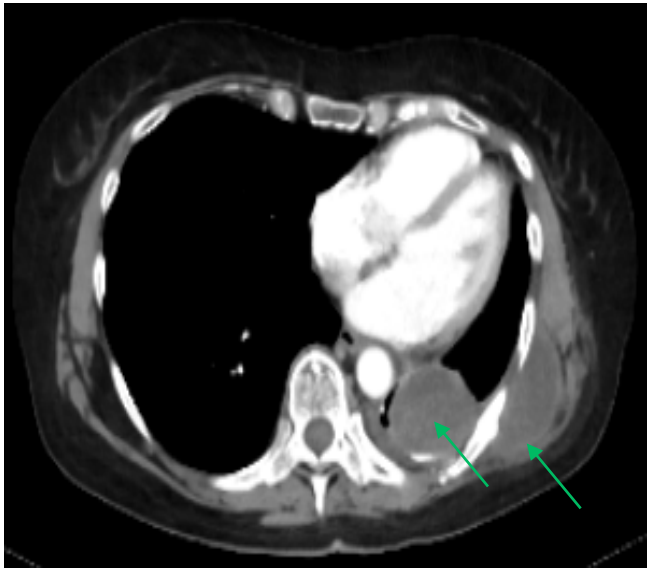
Female, 60 yr

Received $3.67x10^{10}$

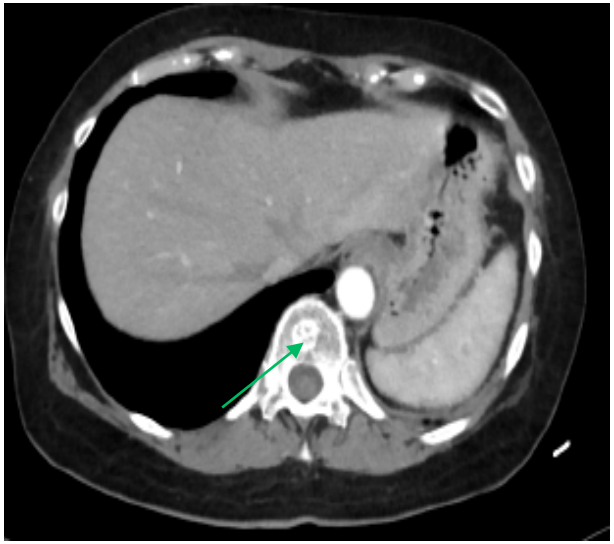
Previously failed B-raf inhibitors, anti-PD1 and Ipilimumab

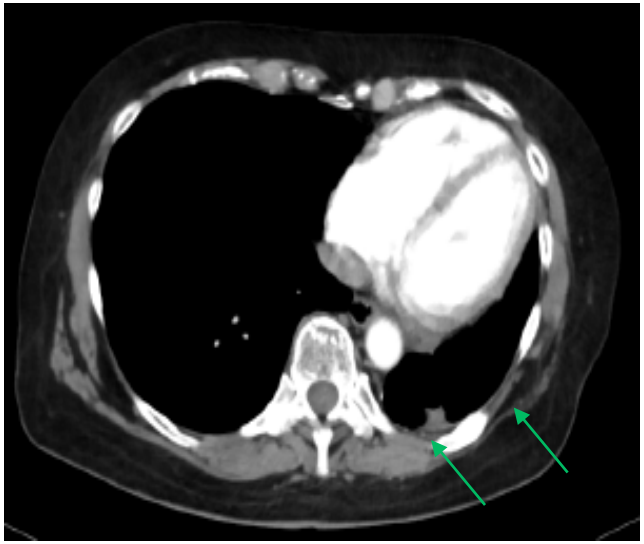
December 2014



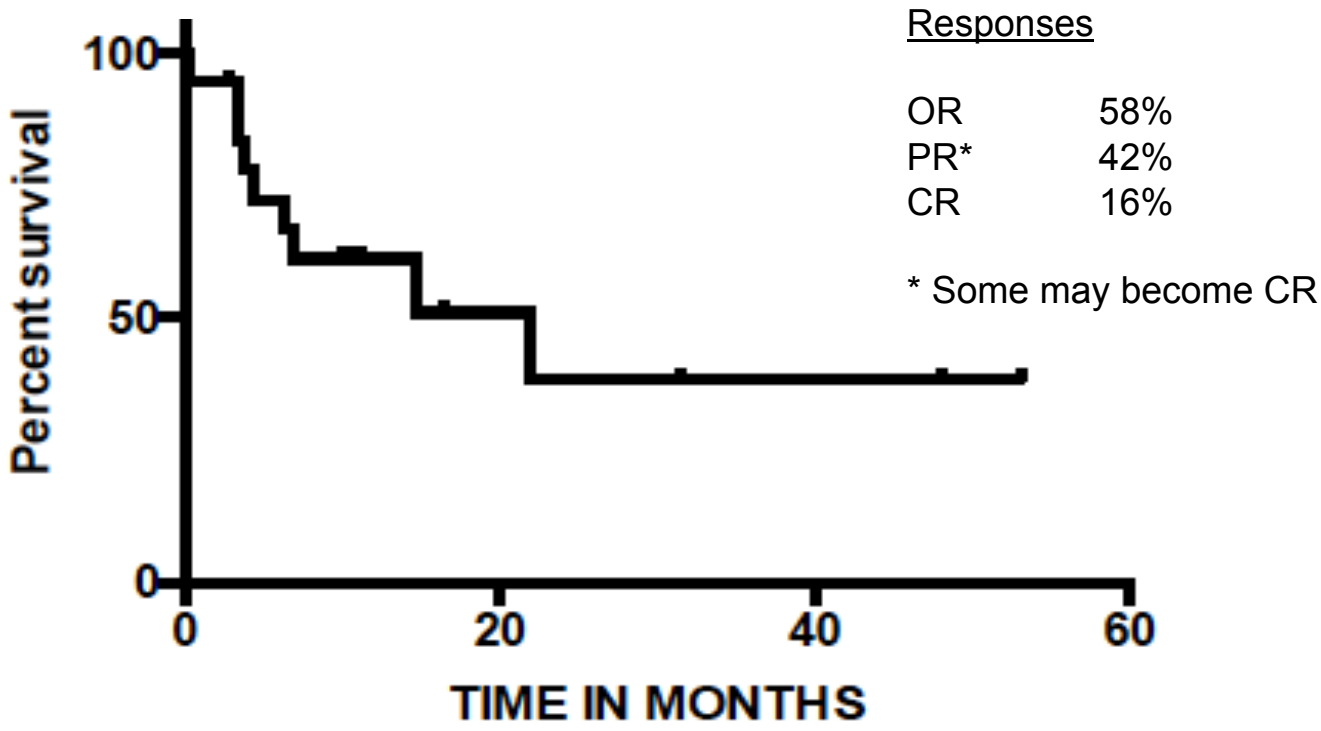


September 2015



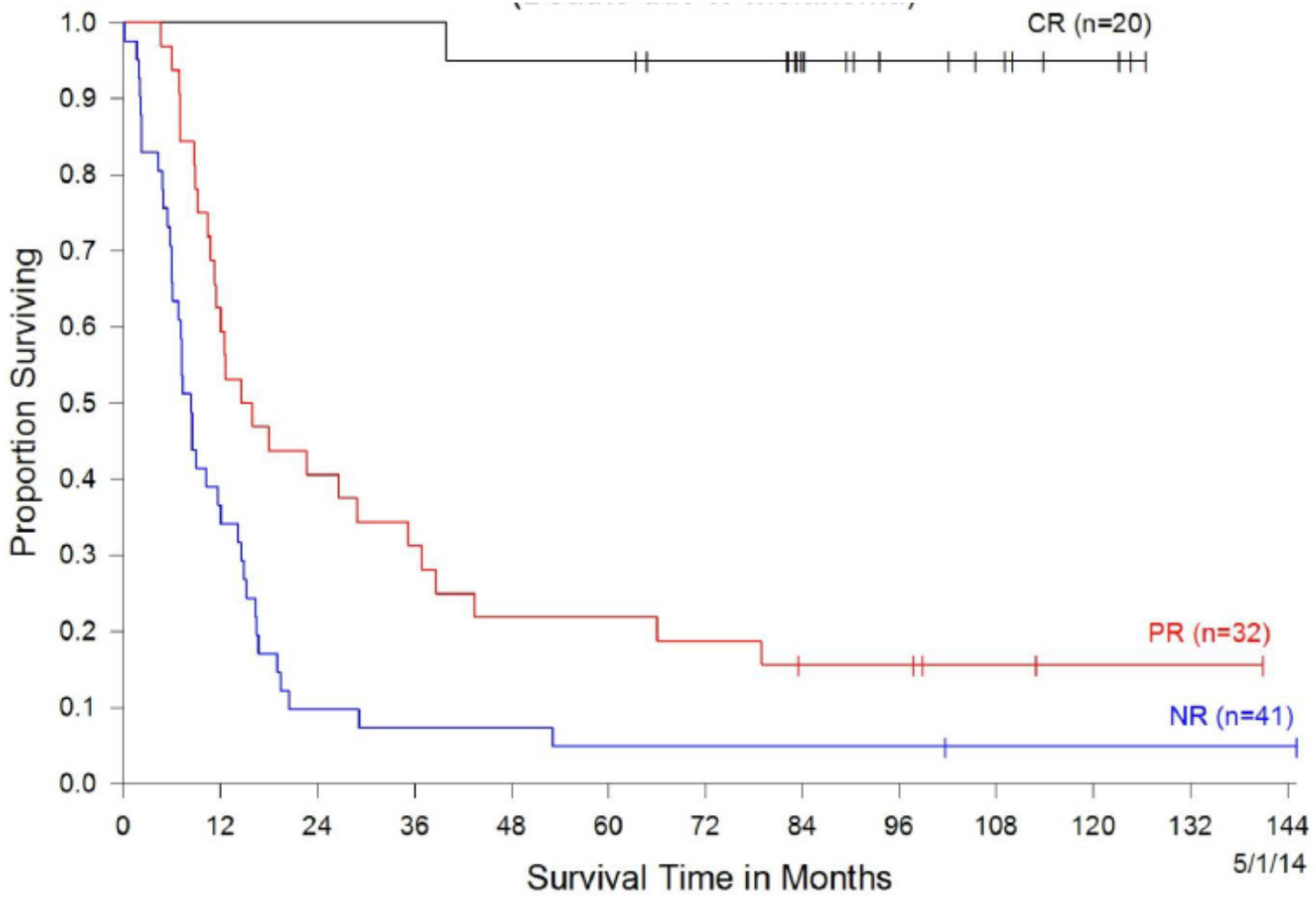


Long-term benefits in CTL TIL Therapy:
relapse/refractory melanoma



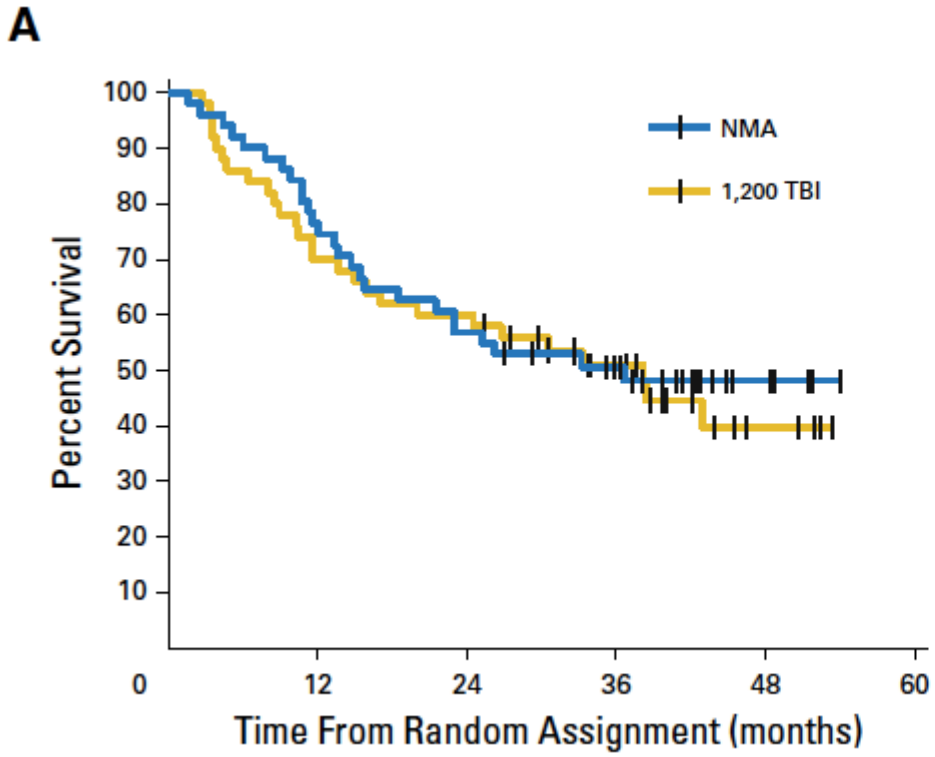
- Globally > 500 patients treated
  - RR 40-70%
  - CR 10-25% - almost all durable ? cures

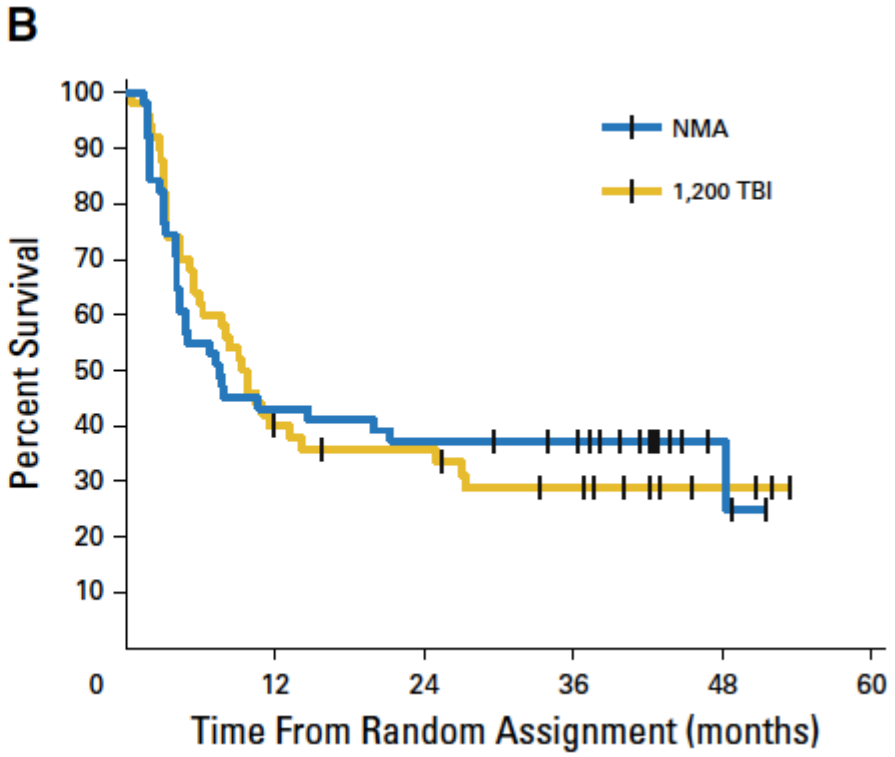
Key Outcome – Durable Responses



Rosenberg et al., *Clin Cancer Res July 1, 2011 17; 4550*

Is more intensive therapy better?





Overall Survival

Progression-Free Survival

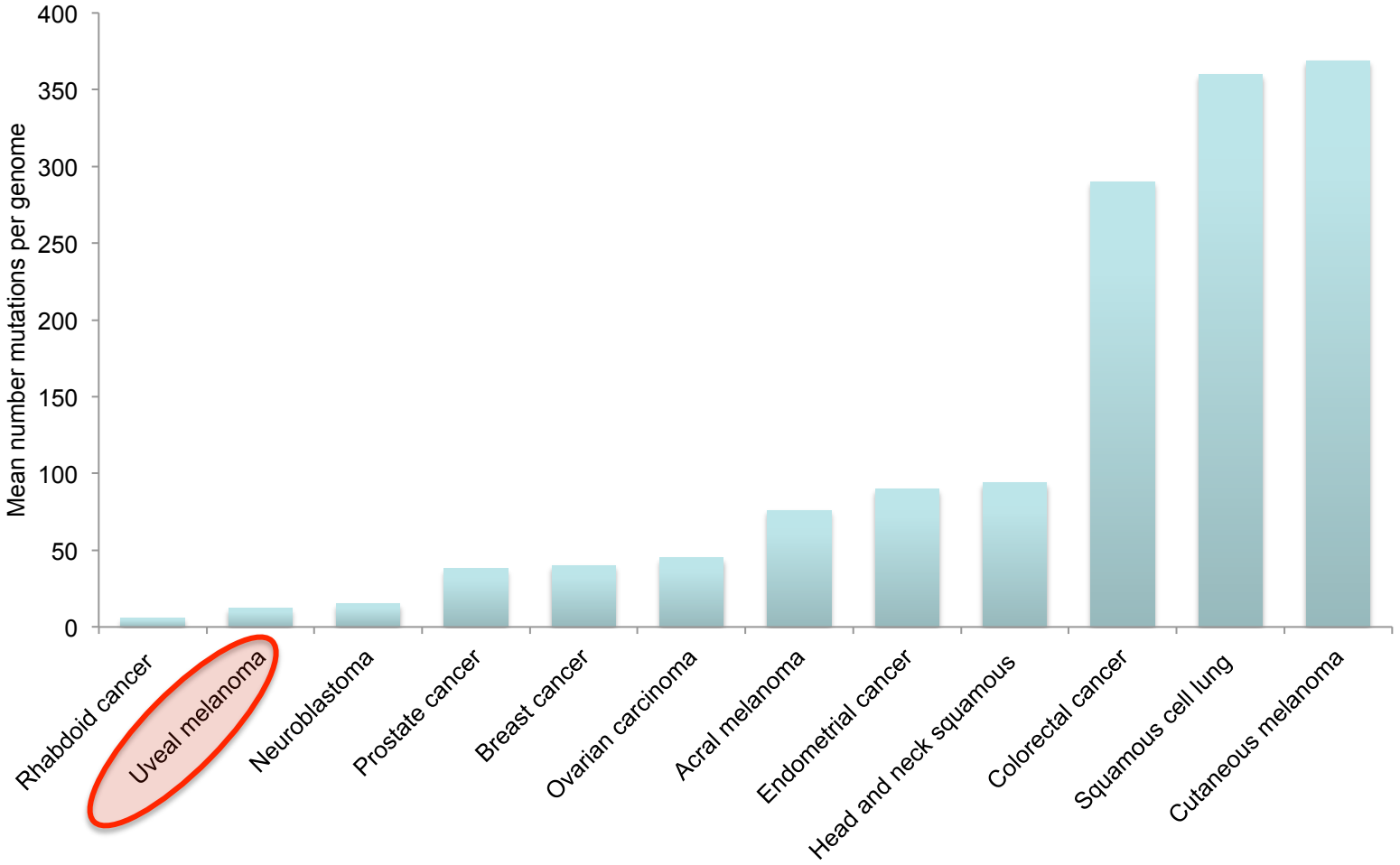
Response rate	45% vs 62%
Complete Response Rate	24% vs 24%

Goff et al., J Clin Oncol. 2016 Jul 10;34(20):2389-97

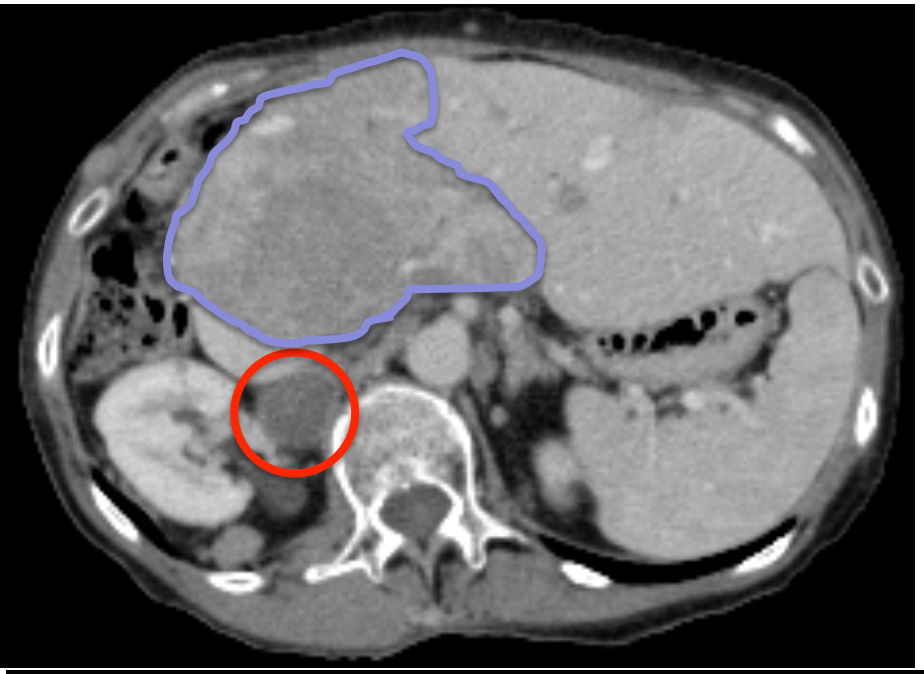
What is happening in TIL Therapy?

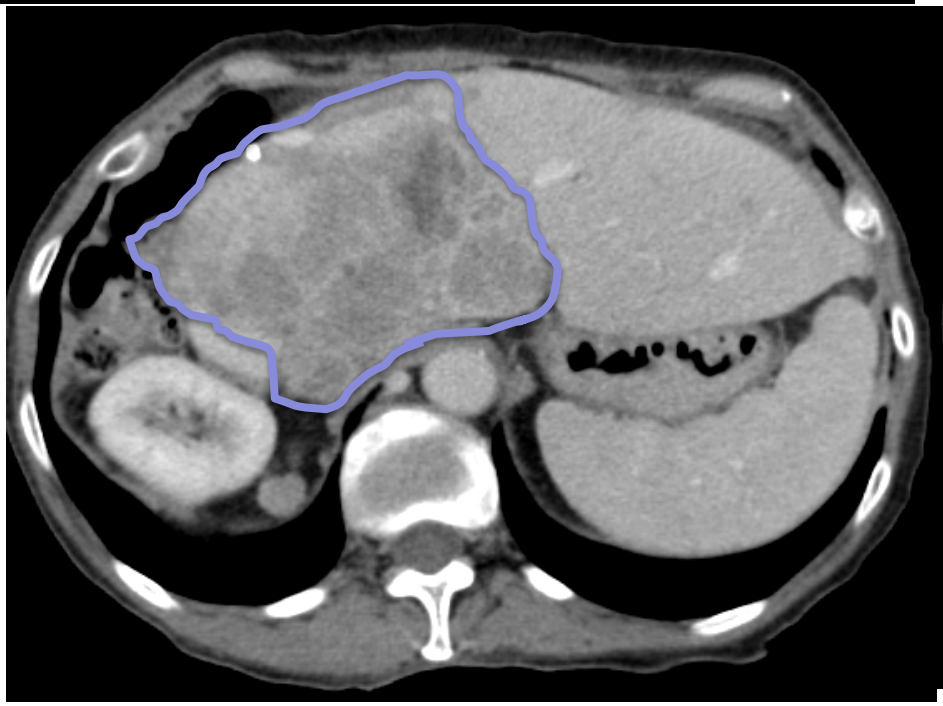
- NCI – trials of combinations
  - Pembrolizumab
  - B-Raf inhibitors
- Lion Biotech
  - Testing NCI approach in multi-centre trials
- Netherlands/Denmark/(UK)
  - Randomized trial Ipilimumab vs TIL

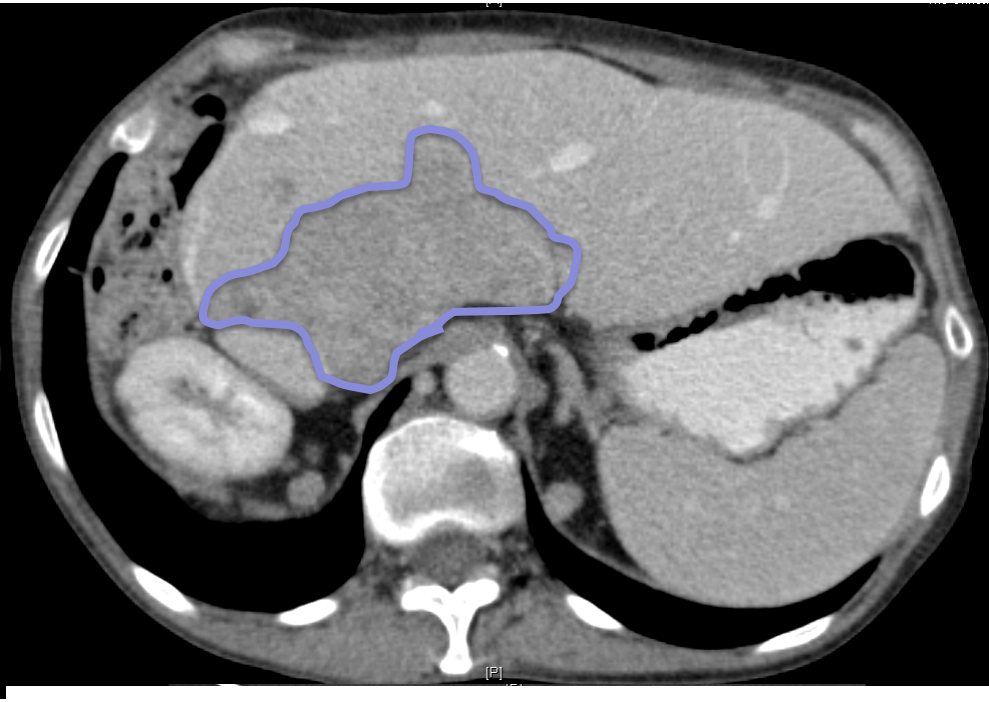
What about other types of Melanoma?



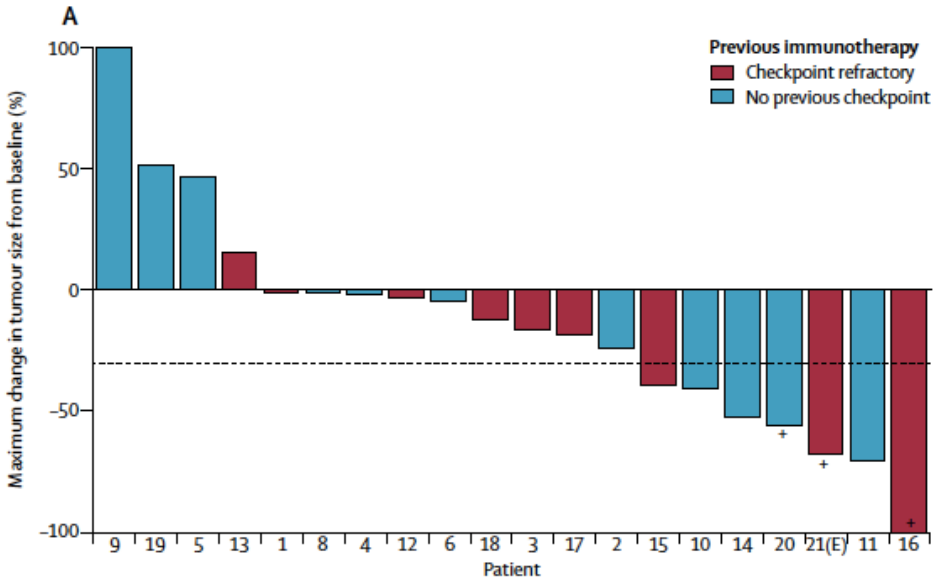
Non-Synonomous Coding Mutations in Exome Sequences

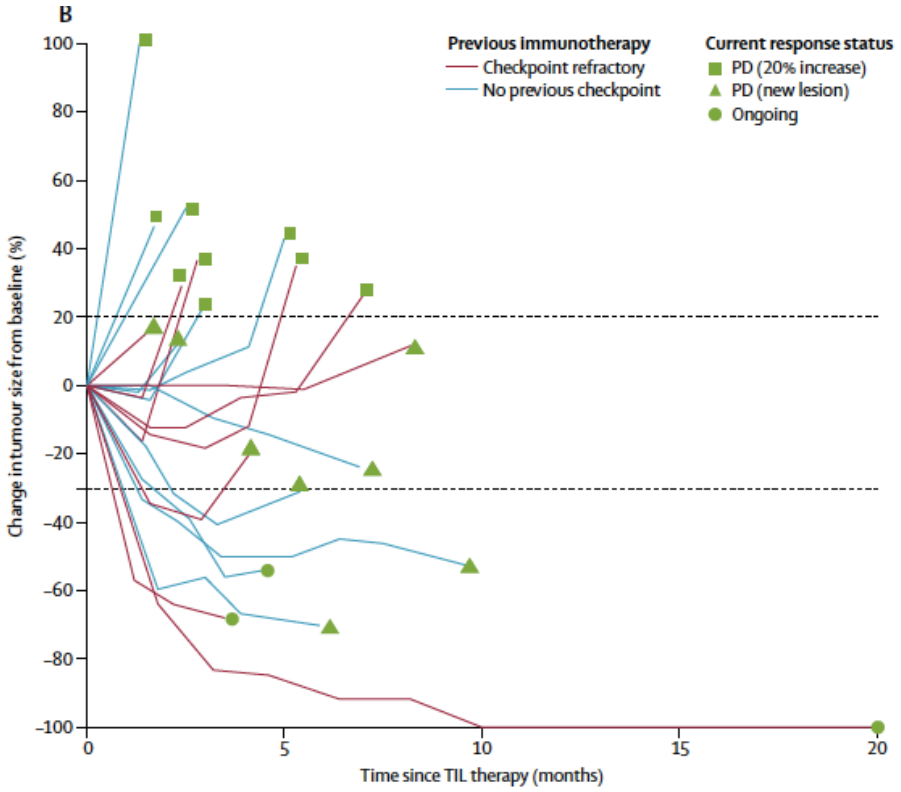






NCI Data in Uveal Melanoma



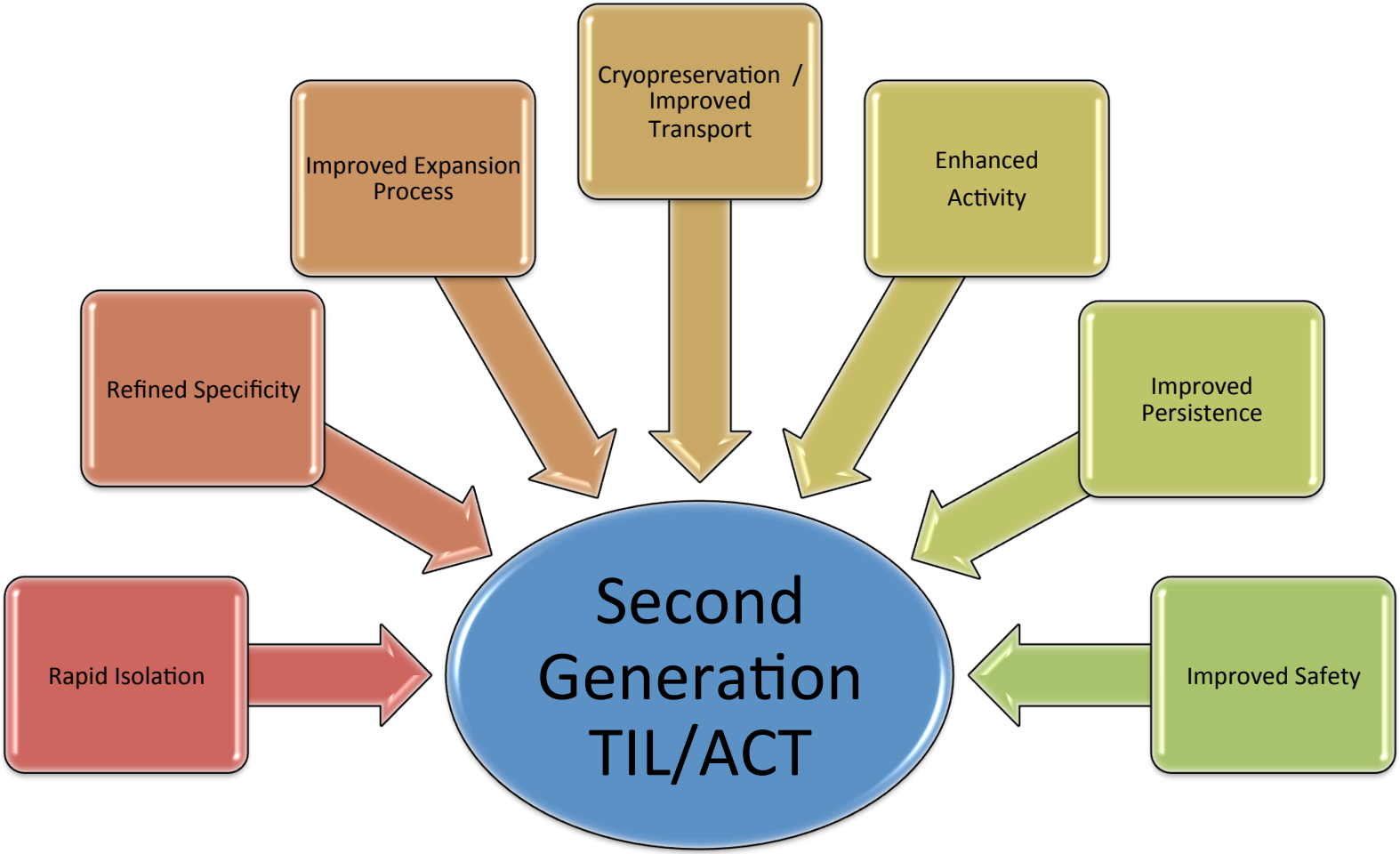


7/21 patients responded

1 complete remission > 21 months
2 other PRs on-going

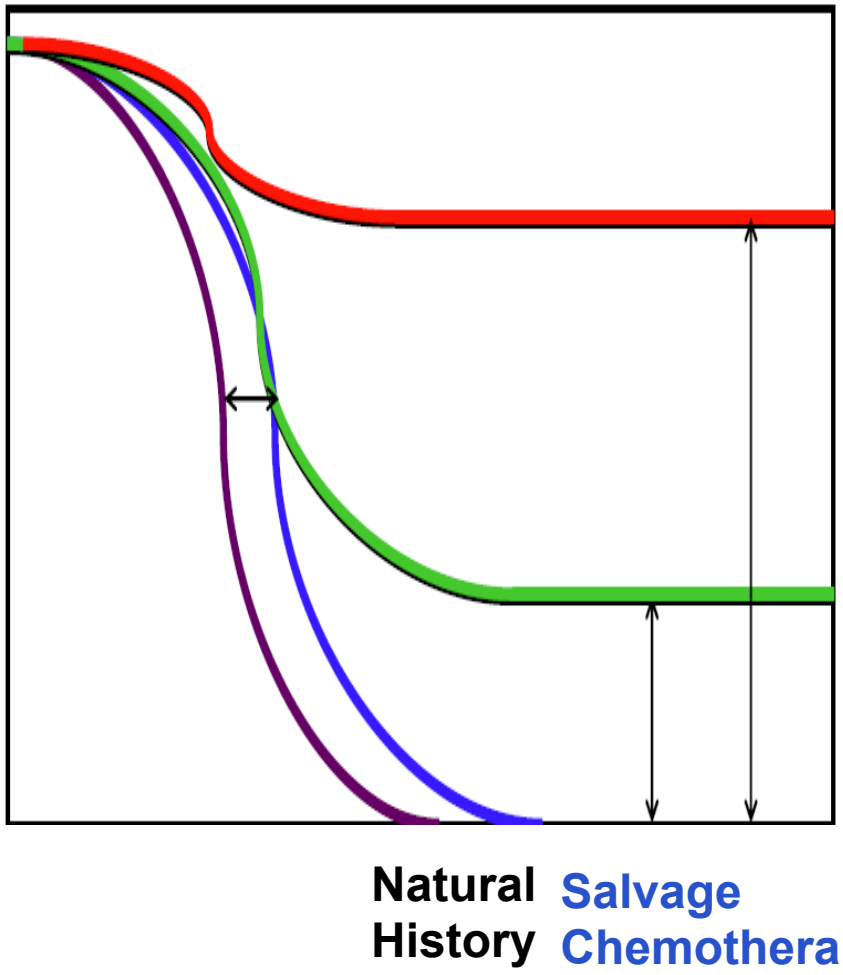
SS Chandran et al., Lancet Oncol 2017;18:792-802.

How do we plan to improve TIL?



Development of Next-Generation Products

- Focus is development of next-generation product
- Greater Efficacy
  - Focus on long-term benefits
- Improved Tolerability
  - Reduced need for toxic conditioning



Conclusions

- TIL therapy can be extremely effective and produce *durable* benefits
  - ***May*** be so effective because they target multiple antigens
    - A Key may be mutated / tumour specific antigens
- In principle active in range of solid tumours but process more complex
  - Processes can be standardised / automated
- Hopefully can become a standard therapy
  - *In principle TIL harvest should be considered when patients are having surgery for metastatic disease*
- *Future potential to engineer in novel activity to enhance activity*

Acknowledgements

Experimental Cellular Therapy Group
(David Gilham)
Vicky Sheard
Hannah Gornall
Vania Baldan

Cellular Therapeutics Ltd
Ryan Guest
Nikki Price
Julie Duckworth
Natalia Kirilova
Holly Askew
Martine Thomas
Roy Cowell

John Bridgeman
Michelle LeBrocq

Clinical Cell Therapy
Fiona Thistlethwaite
Manon Evans
Shien Chow

Melanoma Group
Paul Lorigan
Jackie Hodgetts

GMP TIL Harmonisation Team
Bianca Heemskerk – NKI-AVL
Joost vd Berg - NKI-AVL
Marco Donia – CCIT/Herlev Hospital
Inge-Marie Svane – CCT/Herlev
Ryan Guest – University of Manchester

Surgeons
Aali Sheen
Piotr Krysiak
Deemesh Oudit
Vijay Ramani