Advanced Therapy Treatment Centres

LONDON ADVANCED THERAPIES

Treating solid tumours with ATMPs

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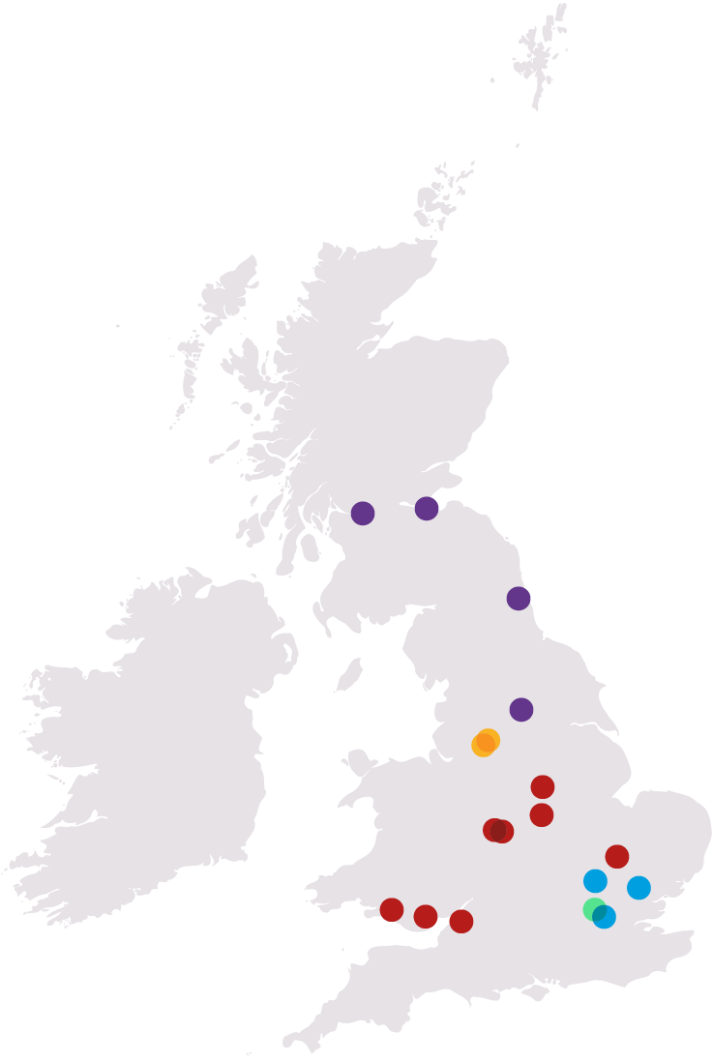


Funded by

INDUSTRIAL STRATEGY

UK Research and Innovation

Coordinated by

CATAPULT Cell and Gene Therapy

Who are LAT and the ATTCs?

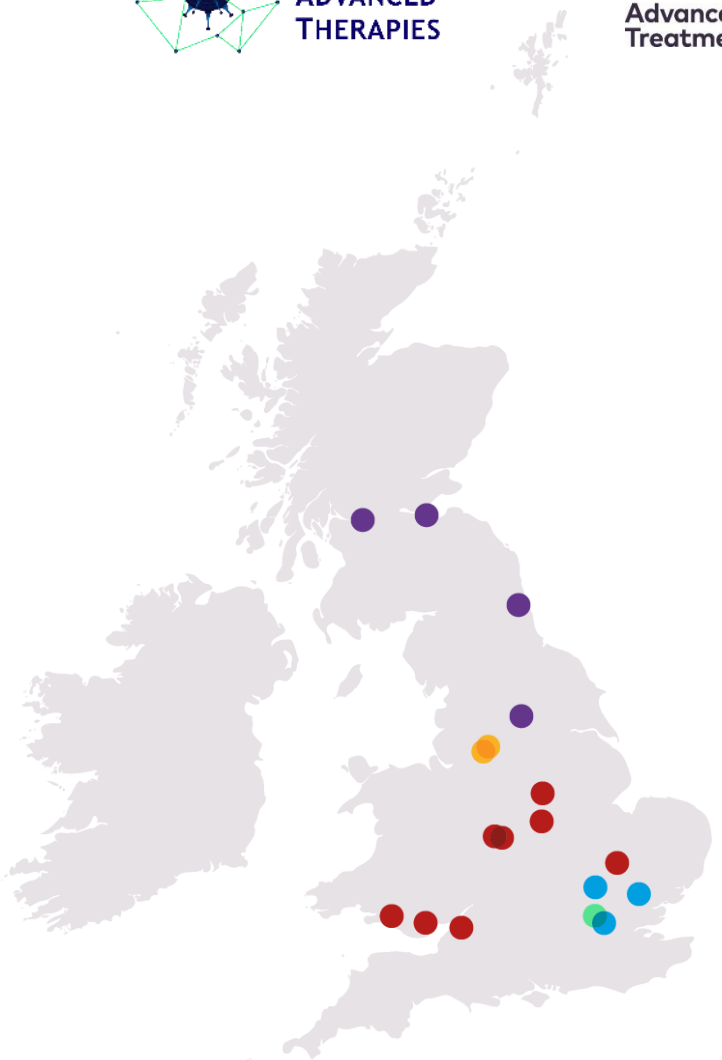
The ATTC (Advanced Therapy Treatment Centre) network is funded by Innovate UK and the Industrial Strategy Challenge Fund

London Advanced Therapies (LAT) is funded by Research England

The centres are working together, along with the Cell and Gene Therapy Catapult to specifically look at the training requirements for the current workforce and what needs to be put in place for them to be ready to deliver the treatments that are currently being developed.

This series of webinars is designed to help increase the awareness of advanced therapies and their impact in the clinic

Find out more at https://www.theattcnetwork.co.uk/



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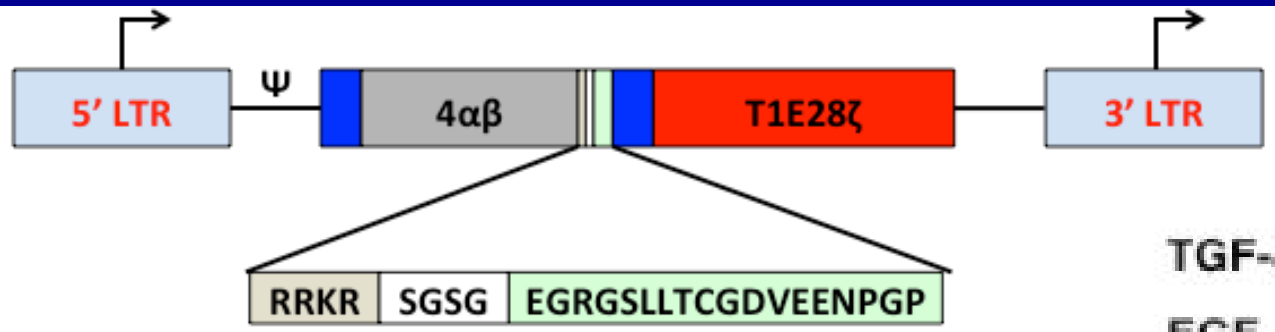
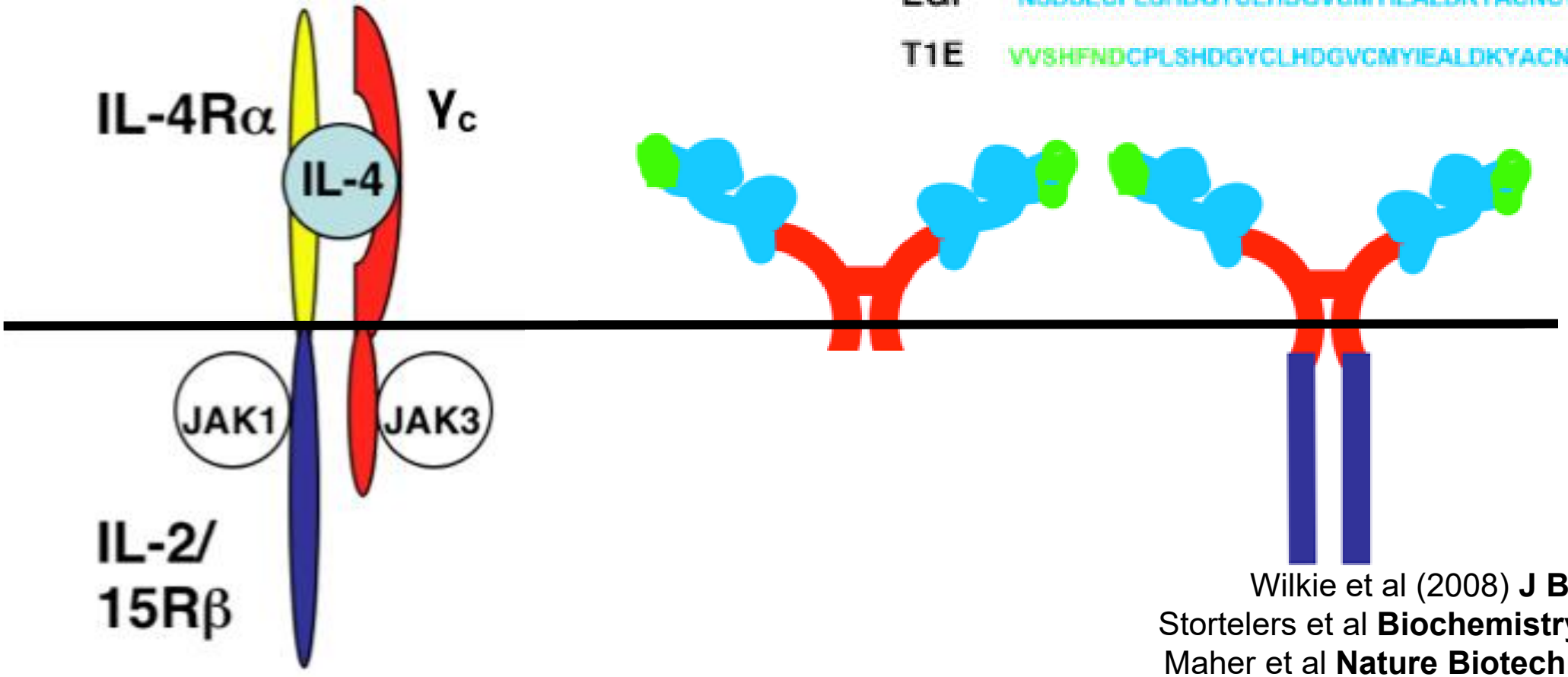
T4 Immunotherapy: 4αβ and T1E28ζ



TGF-α VVSHFNDCPDSHTQFCFHGTCRFLVQEDKPACVCHSGYVGARCEHADLLA

EGF NSDSECPLSHDGYCLHDGVCMYIEALDKYACNCVVGYIGERCQYRDLKWWELR

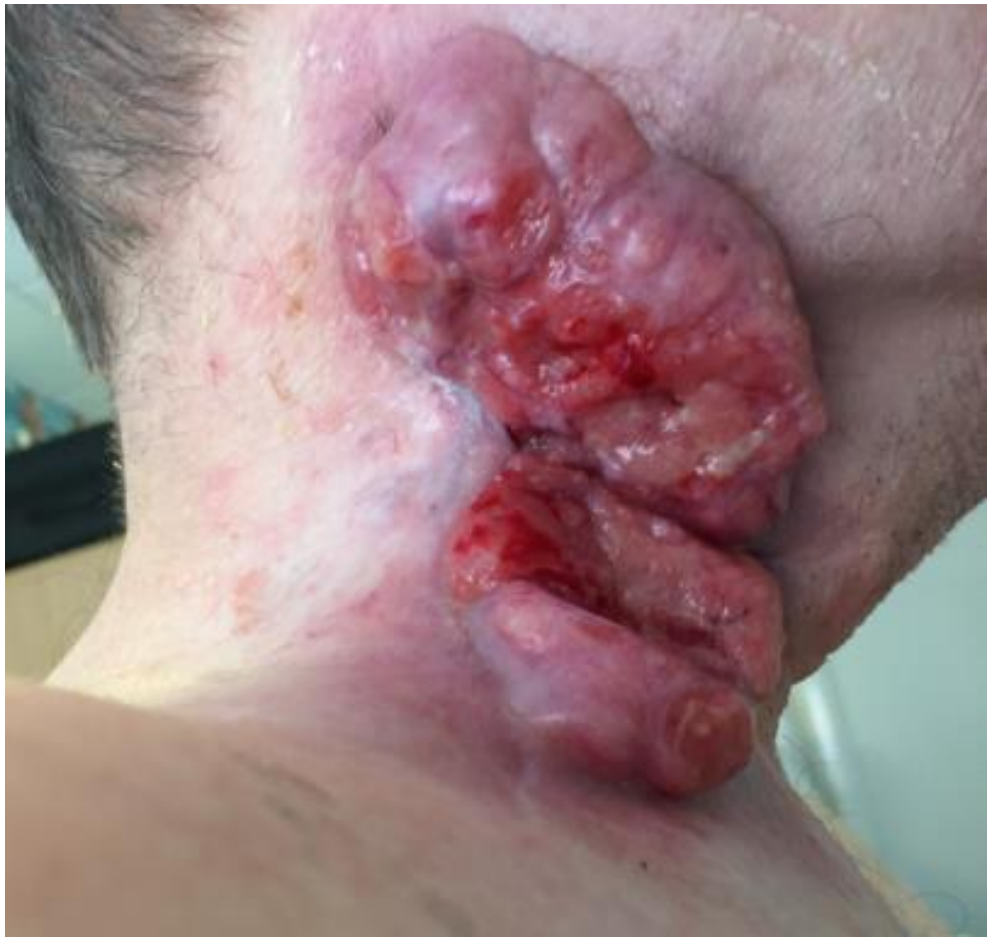
T1E VVSHFNDCPLSHDGYCLHDGVCMYIEALDKYACNCVVGYIGERCQYRDLKWWELR



Wilkie et al (2008) **J Biol Chem.** 285: 25538-44
Stortelers et al **Biochemistry** (2002) 41(13):4292-301
Maher et al **Nature Biotechnology** (2002) 20(1):70-5

HNSCC: The unmet need

- Sixth commonest cause of cancer death worldwide
- 12,061 cases and 4,047 deaths in the UK in 2015
  5-year survival 50%
- Highly driven by ErbB family:
  - >90% $EGFR^{+}$
  - ErbB2: up to 31%
  - ErbB3: 21%
  - ErbB4: 55%.
- Most tumors express two or more family members, facilitating resistance to traditional targeted agents
- Most patients succumb to loco-regional disease
- Burden of co-morbidity is high



National Head & Neck Cancer Audit, 2011
Profile of Head and Neck Cancers in England (National Cancer Intelligence Network)
Rogers et al (2005) **Cancer Metastasis Rev** 24(1) 47-69
Vermorken and Specenier (2010) **Ann Oncol** 21 (suppl 7): vii252-vii261
Silva et al (2010) **Oral Dis.** 16(8):774-80

Primary unmet need: improved control of loco-regional disease

- Death/morbidity primarily due to loco-regional disease

The Guy's and St Thomas' MDT (catchment 1.5M)

- Approximately 350 new cases per year (increasing)
- Large proportion with locally advanced/ recurrent disease
- Disease course changing with anti-PD-1 containing regimens, but outcomes remain poor for most.

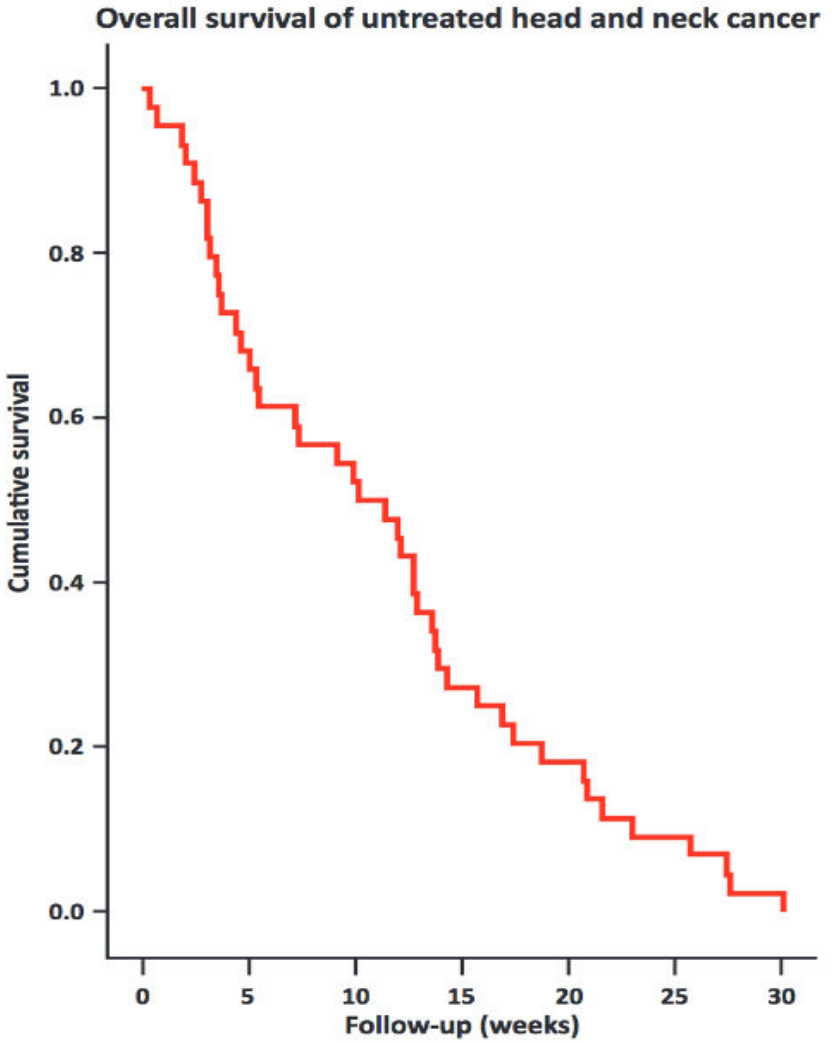


Fig. 1. Overall Kaplan–Meir Survival for untreated patients with HNSCC.

Jeannon et al. (2011) **Clin Otolaryngol**. 36(4):384-8.

Trial Design

Design

- First in man.
- Single centre.
- 3+3 dose escalation design.
- Single dose of fresh cell product administered by intra-tumoural injection at multiple points within target lesion, akin to T-VEC.

Cohort	Target Dose ($T4^+$ cells)	Dose range (cells)	Volume (mL)
-1*	$3x10^6$	$3x10^6$	1+/- 0.2
1	$1x10^7$	$3\text{-}10x10^6$	1+/- 0.2
2	$3x10^7$	$1.1\text{-}3x10^7$	1+/- 0.2
3	$1x10^8$	$3.1\text{-}10x10^7$	2+/- 0.2
4	$3x10^8$	$1.1\text{-}3x10^8$	3+/- 0.2
5	$1x10^9$	$3.1\text{-}10x10^8$	4+/- 0.2
6 (Flu/Cy)	$1x10^8$	$3.1\text{-}10x10^7$	4+/- 0.2

Inclusion/ Exclusion Criteria

- SCCHN: Locally recurrent or metastatic (brain metastases excluded).
- ECOG-PS 0-2.
- No imminent airway obstruction, unless tracheostomy in place.
- No imminent tumour-mediated infiltration of major blood vessels.
- No clinically active autoimmune disease.
- No prior splenectomy.
- No anti-coagulant use.

Primary Endpoint

- Dose limiting toxicity of T4 immunotherapy graded according to NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0.

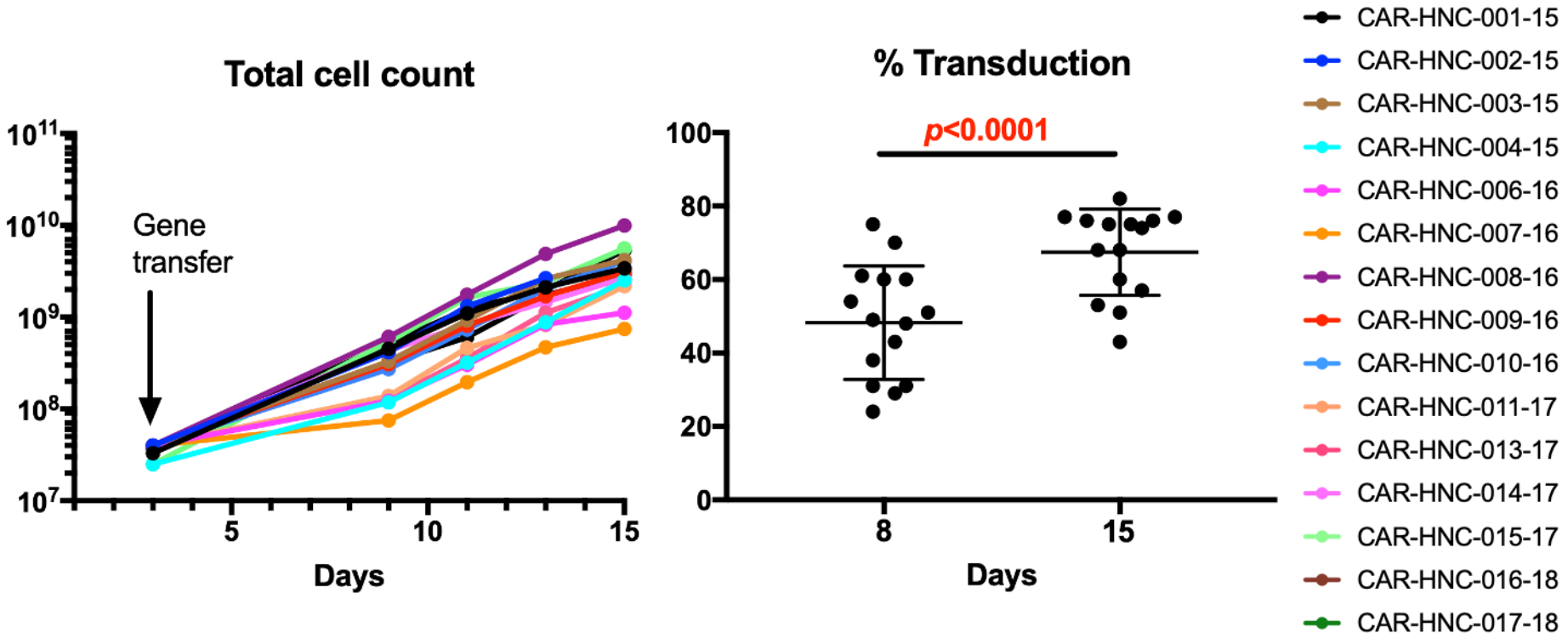
Secondary Endpoints

- Translational endpoints.
- Response by RECIST 1.1.

van Schalkwyk et al (2013) **Hum Gene Ther Clin Dev** 24(3):134-142.

No	Cohort	Age	PS	Gender	T4 dose	Primary site	Prior treatment
1	1	56	1	Male	1×10^7	Nasal cavity	Surgery x 3; Radical RT; CTX -Cisplatin, 5-FU, Cetuximab
2		59	1	Female	1×10^7	Oral (Tongue)	Surgery x 1; Radical RT; CTX - Cisplatin, 5-FU
3		59	1	Male	1×10^7	Oral (Tongue)	Surgery x 1; Radical RT; CTX - Cisplatin, 5-FU
4	2	57	1	Female	3×10^7	Oral (Tongue)	Surgery x 4; Adjuvant RT; CTX – Cisplatin, Carboplatin; Palliative RT
5		50	2	Male	Died before treatment	Oral (Tongue)	Surgery x 0; Radical RT; CTX - Cisplatin
6		55	1	Male	3×10^7	Oral (Tongue)	Surgery x 1; Palliative RT; CTX - Cisplatin, 5FU, Cetuximab
7		78	2	Male	3×10^7	Oral (Tonsil)	Surgery x 0; Radical RT; CTX courses x 0
8	3	62	1	Male	1×10^8	Neck	Surgery x 3; Radical RT; CTX – Cisplatin, 5FU, Cetuximab, Docetaxel, Carboplatin
9		81	0	Male	1×10^8	Oral (Buccal mucosa/ mandible)	Surgery x 4; Radical RT; CTX courses x 0
10		64	1	Male	1×10^8	Oral (Palate and oropharynx)	Surgery x 1; Radical RT; CTX – cisplatin, 5FU
11	4	61	0	Female	3×10^8	Oral (Mandibular alveolus)	Surgery x 0; Radical RT; CTX courses x 0
12		36	N/A	Male	Failed screening	Oral (Tongue)	Surgery x 1; Radical RT; CTX courses x 0
13		66	N/K	Male	3×10^8	Oral (Oropharyngeal)	Surgery x 1; RT x 1 (nature unknown); CTX courses x 1 (nature unknown)
14		82	1	Male	3×10^8	Oral (Tongue)	Surgery x 1; RT x 1 (dose unknown); CTX courses x 0
15	5	39	1	Male	1×10^9	Nasopharyngeal	Surgery x 1; RT x 1; CTX courses x 1
16		57	1	Female	1×10^9	Mandible	Surgery x 2; RT x 2; CTX courses x 1
17		61	1	Male	1×10^9	Oral (Tonsil)	RT x 1; CTX x 3; Pembrolizumab
18	6	46	1	Male	1×10^8	Oral	RT x 1; CTX x 2

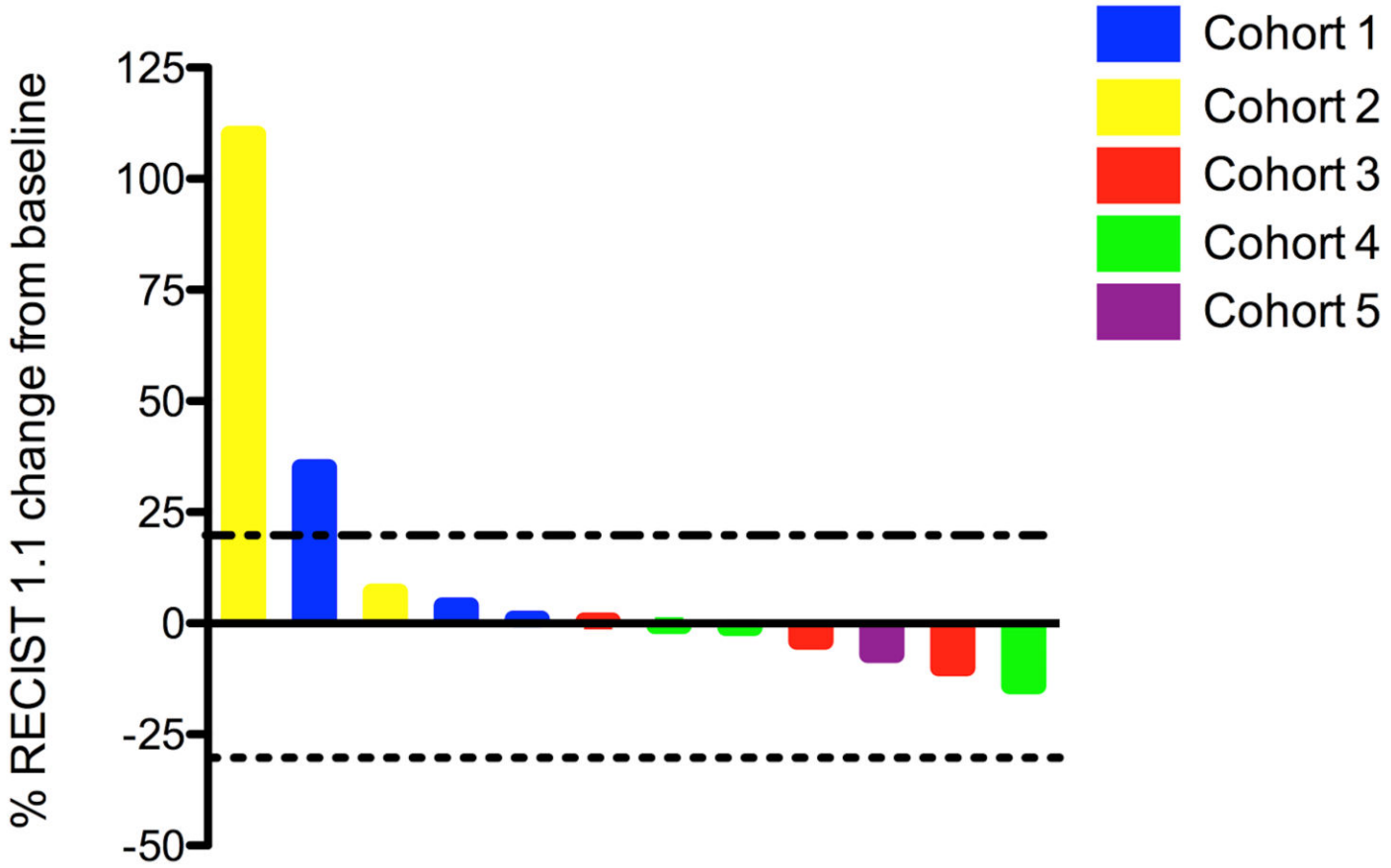
Manufacturing



Safety and tumour response to T4 immunotherapy

Cohort	Target Dose ($T4^+$ cells)	Dose range (cells)	Volume (mL)
-1*	$3x10^6$	$3x10^6$	1+/- 0.2
1	$1x10^7$	$3\text{-}10x10^6$	1+/- 0.2
2	$3x10^7$	$1.1\text{-}3x10^7$	1+/- 0.2
3	$1x10^8$	$3.1\text{-}10x10^7$	2+/- 0.2
4	$3x10^8$	$1.1\text{-}3x10^8$	3+/- 0.2
5	$1x10^9$	$3.1\text{-}10x10^8$	4+/- 0.2

- No DLTs, CRS or neurotoxicity
- Local inflammatory reactions + fever
- Stable disease in 9/13 patients by RECIST (6 weeks).
- MABEL appears to be 10^8 $T4^+$ T-cells.
- 1 patient (baseline tumour shown in slide 7) achieved a very good response to subsequent T-VEC and pembrolizumab (close to CR).
- Patient 15 had further shrinkage of primary tumour when assessed after 10 weeks, with progression noted at distant sites of disease.



van Schalkwyk et al (2013) **Hum Gene Ther Clin Dev** 24(3):134-142.

Current CD19 CAR-T products

	Axicabtagene ciloleucel brexucabtagene autoleucel **(Kite)**	**Tisagenlecleucel (Novartis)**	**Lisocabtagene maraleucel (Celgene)**
Anti-CD19 scFv			
Hinge			
Transmembrane			
Costimulatory domain	CD28	4-1BB	4-1BB
Essential activation domain	CD3ζ	CD3ζ	CD3ζ
Gene transfer	Gammaretrovirus	Lentivirus	Lentivirus
NHL indication	**Adult patients with R/R DLBCL and PMBCL, after ≥2 lines of systemic therapy[1] Mantle Cell Lymphoma**	**Adult patients with R/R DLBCL after ≥2 lines of systemic therapy[2]**	**Lisocabtagene maraleucel FDA Feb 2021 R/R DLBCL**

Potential for 2-5 year growth

Current Landscape Oncology Haematology

Potential Market Haematology Oncology

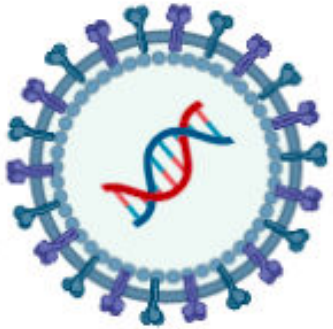
Non-malignant indications. Transplant rejection, Inflammatory bowel Disease, Virally driven hepatitis.. And onwards

The Immune Effector Cell Cycle

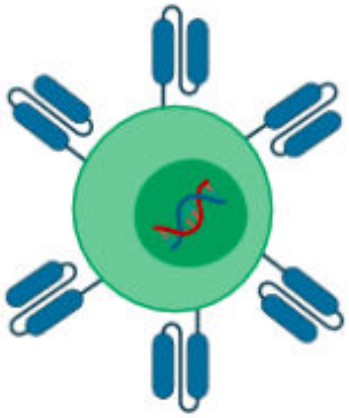
Clinical care:
Patient selection
Risk
Consent
Preconditioning
Infusion
Aftercare

'Starts' and finishes with the patient

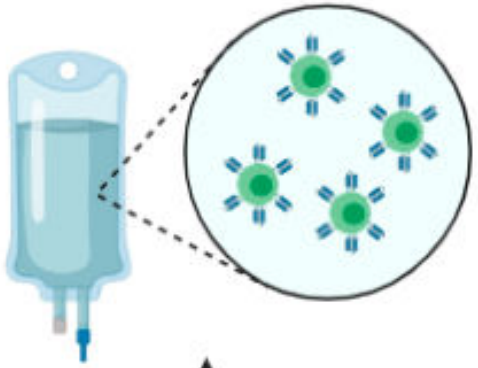
Procurement: Blood or tumour



Gene modification step: CART, TCR, co-stimulation



Manufacturing



Release
Shipment
Storage

Challenges in Solid Tumours

Efficacy

- Homing
- TAAs
- T-cell persistence/survival
- Immunosuppressive tumour micro-environments
- Target loss/relapse

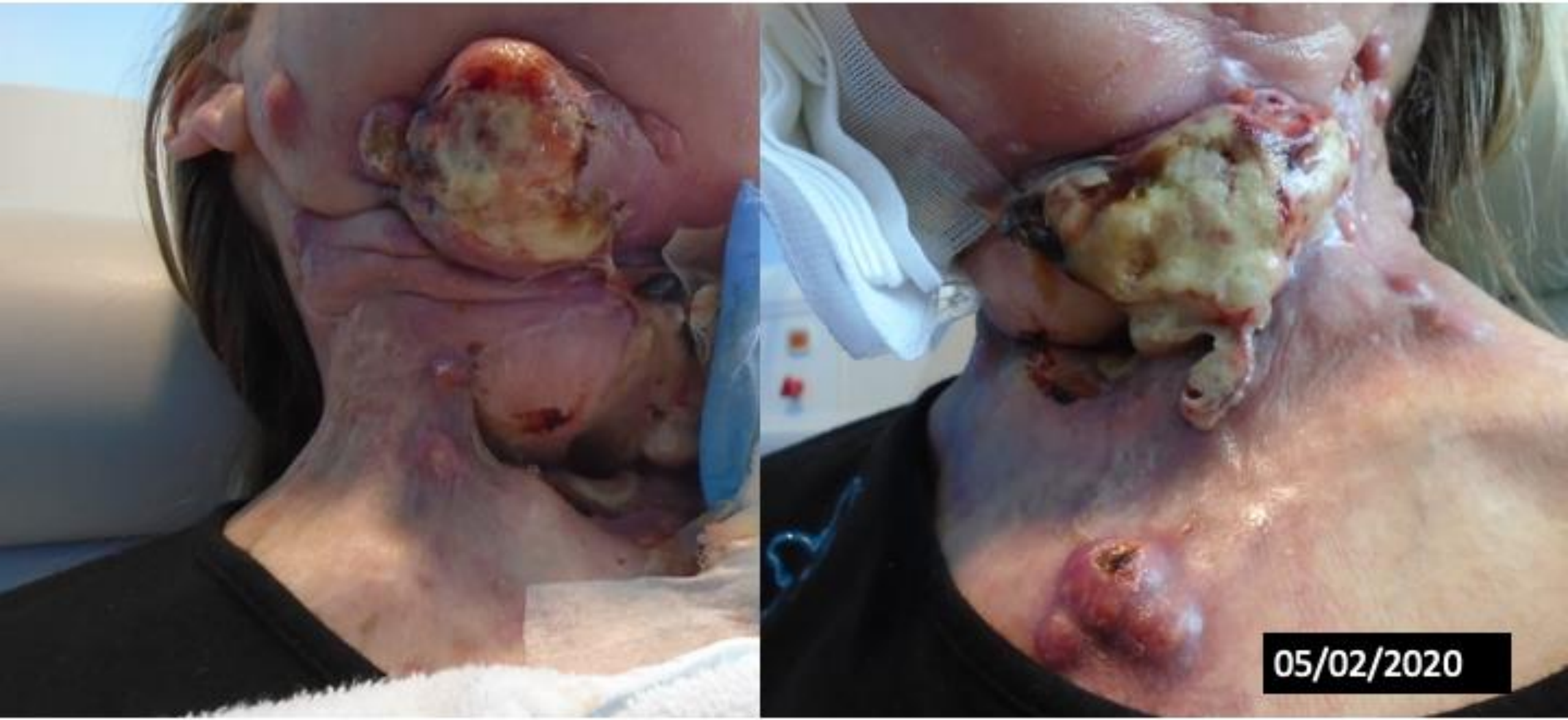
Practicality

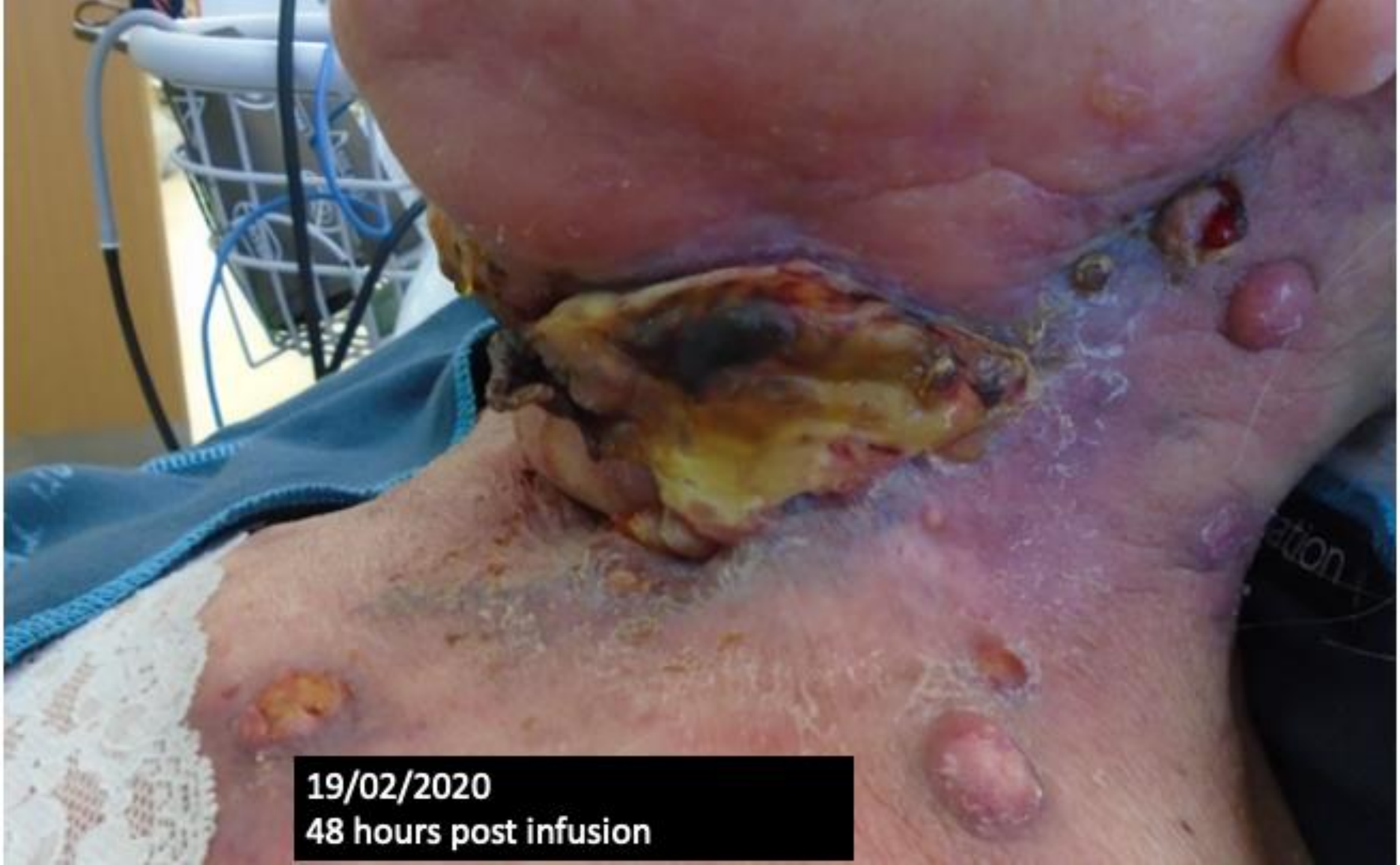
- Cost
- Complexity
- Workforce

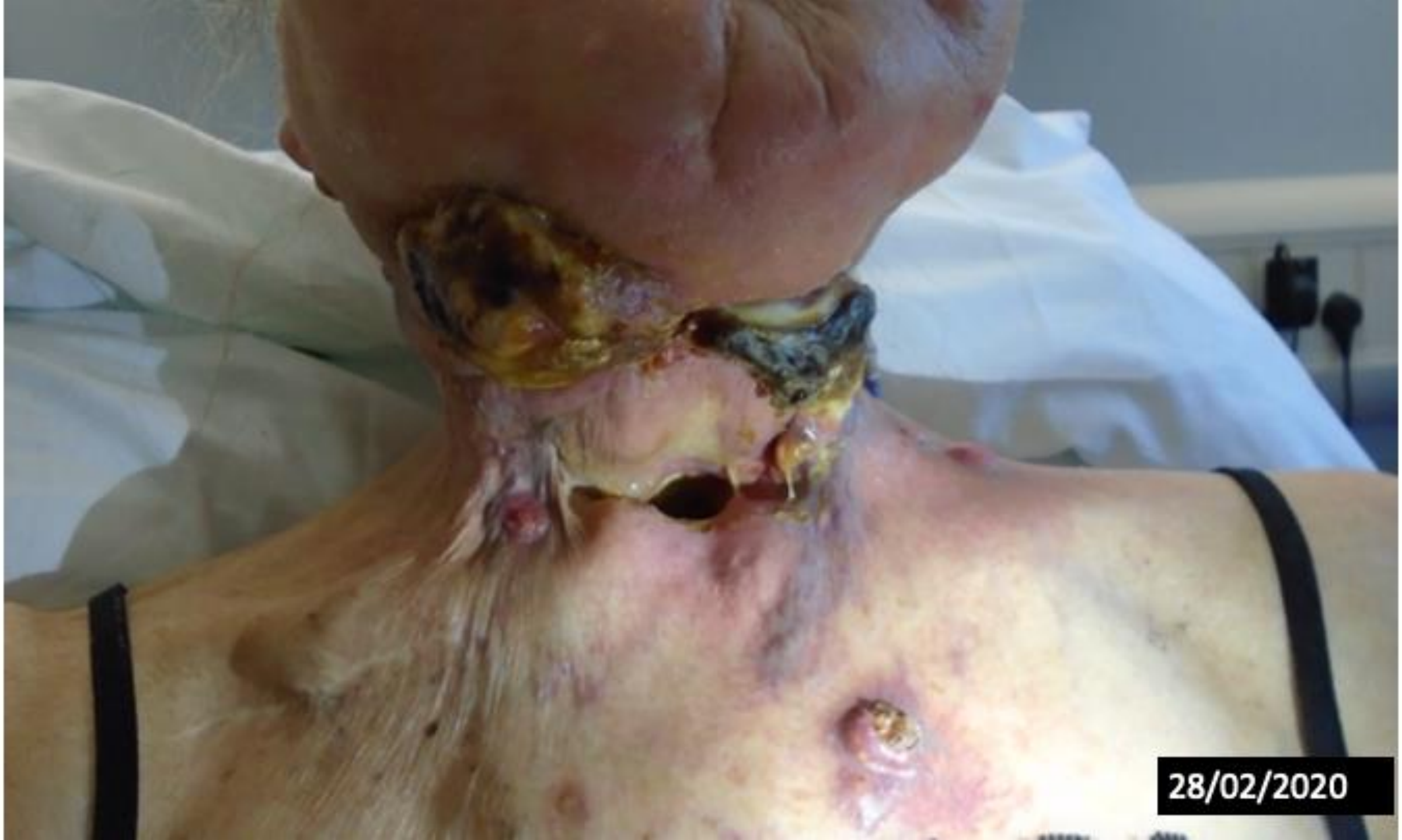
Toxicity

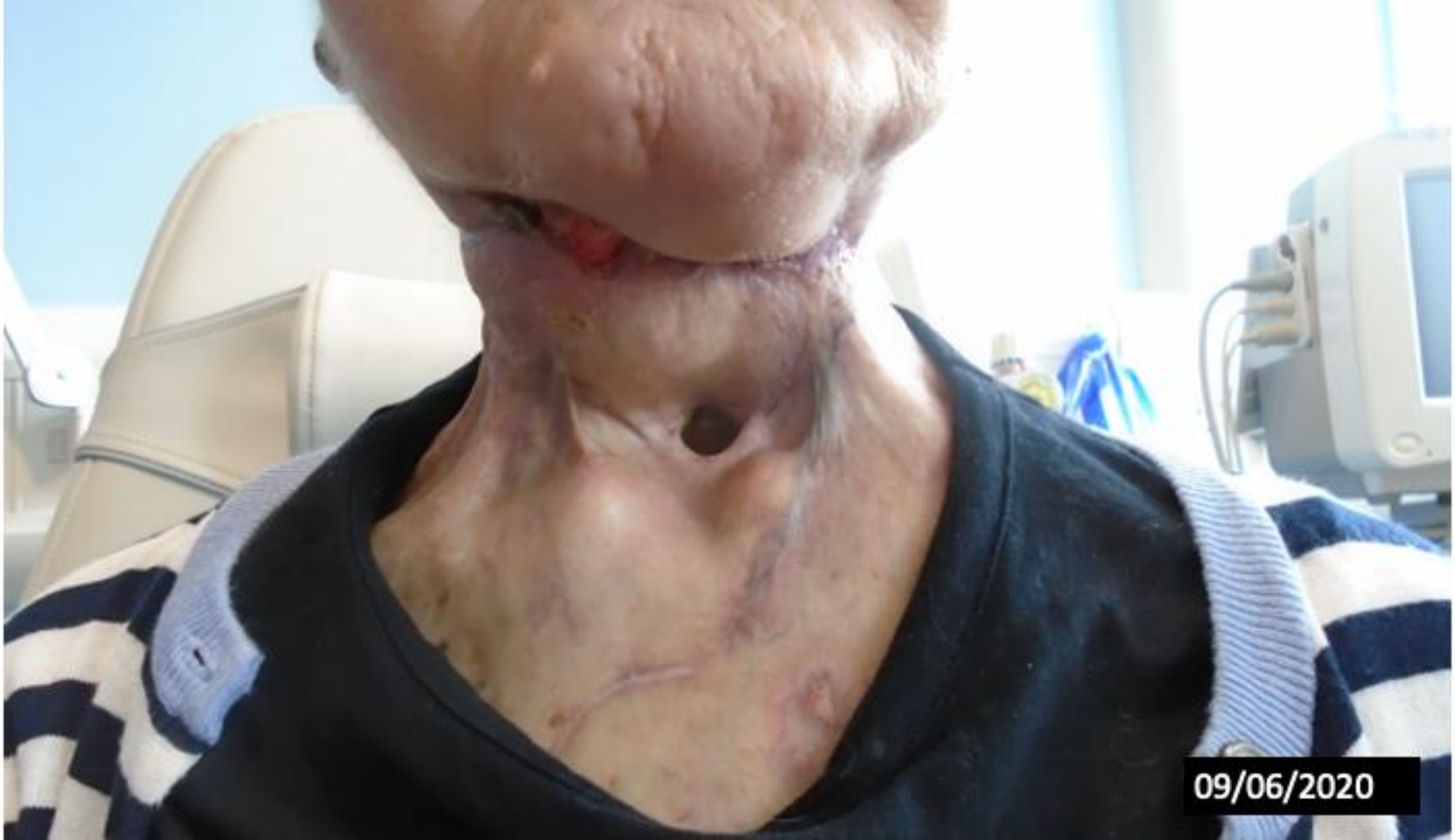
- Cytokine release syndrome (CRS)
- Immune effector cell associated neurotoxicity syndrome (ICANS)
- Hemophagocytic lymphohistiocytosis (HLH)
- Living drug
- Lymphodepletion related toxicity
- Therapeutic window

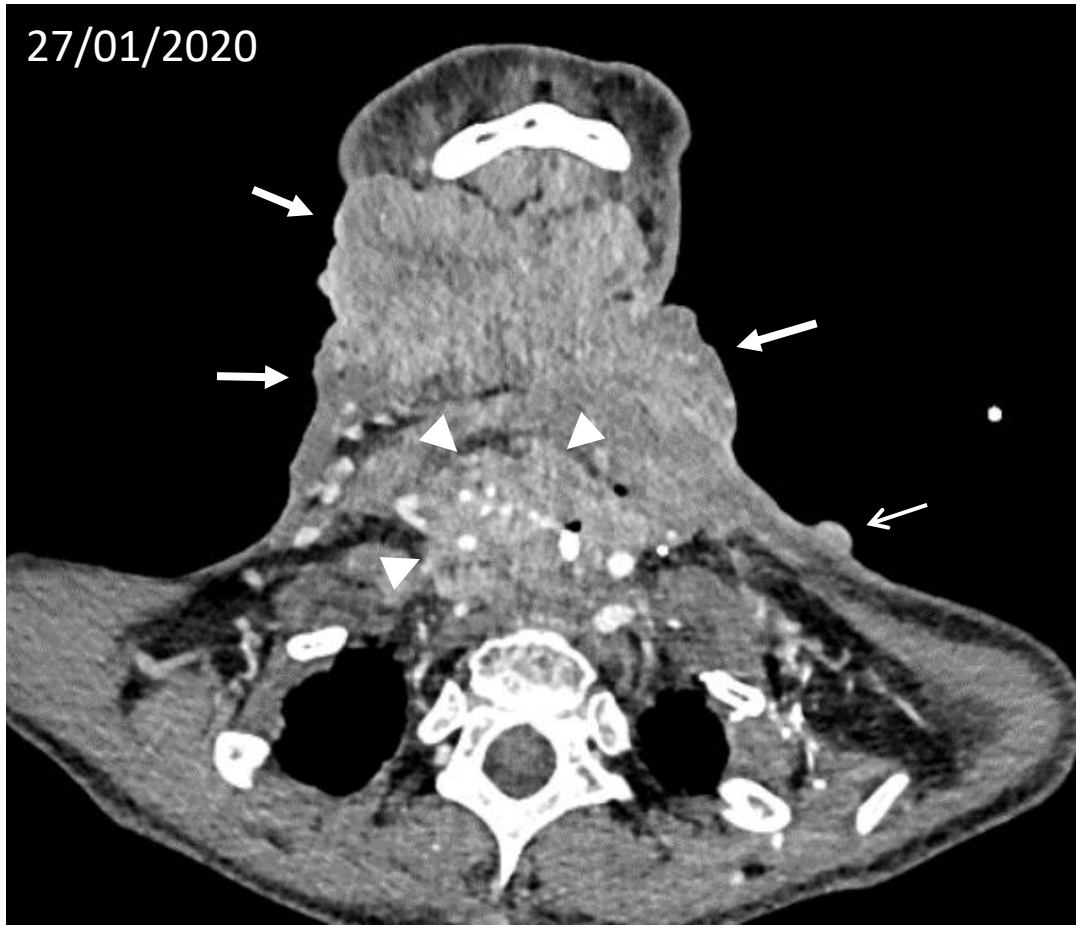
60y. Supraglottic SCC 2017: chemo+rad. Recurrence 2019: Salvage surgery. December 2019:local Recurrence. TIL harvest 06/01/2020. Pembrolizumab 07/01/2020. PD in disease and hypercalcaemia. NMLD 10/02/2020. TIL 17/02/2020

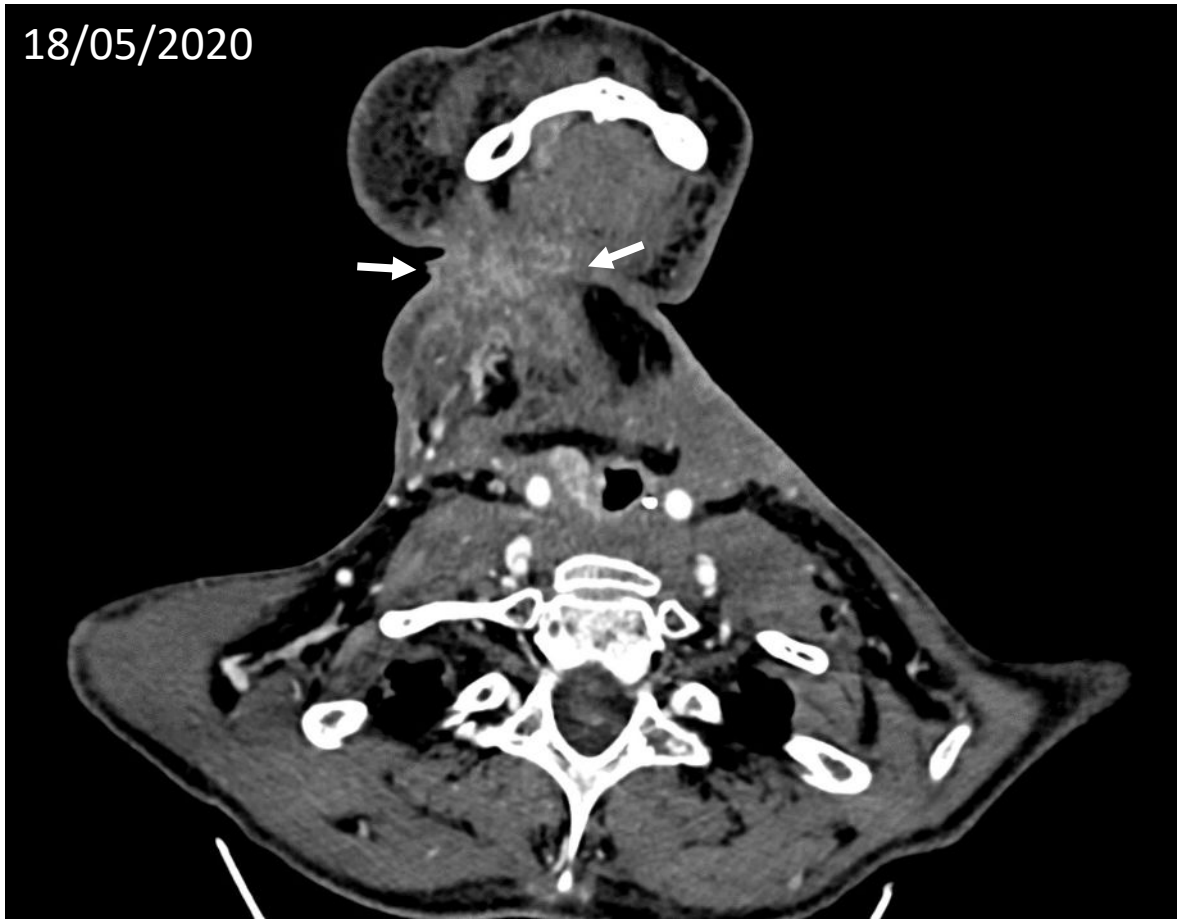



19/02/2020
48 hours post infusion


28/02/2020


09/06/2020





Left: Axial post-contrast CT neck at baseline demonstrating extensive tumour infiltration of the submental and submandibular soft tissues (arrows) along with left cervical cutaneous nodularity (open arrow) and deep soft tissue infiltration of the laryngopharyngeal reconstruction (arrowheads).
Right: Axial post-contrast CT in the same patient demonstrating an excellent partial response to treatment with a significant reduction in the volume of submental and submandibular disease (arrows); there has been interval resolution of the cutaneous nodularity and deep infiltration of the laryngopharyngeal reconstruction.

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wellcome

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Guy's & St Thomas' NHS Foundation Trust
& King's College London


Guy's
Cancer

IEC therapy in solid tumours: managing challenges and expectations

Linda Gomm

NHS
Guy's and St Thomas'
NHS Foundation Trust

Patient Pathway

- Patient referral
- Screening and Eligibility
- Surgery or Apheresis
- Lymphodepletion
- Cell Infusion
- Ward inpatient stay
- Follow up

Challenges

- Large referral area
- Multiple hospital visits
- Multiple tumour sites/MDT’s
- Manufacturing dates v’s surgeon availability
- Trial protocol- complicated schedules
- Pharmacy
- Extended hospital stays/GCCU
- Training
- Managing expectations
- Regulatory

Top tips….

- Effective communication
- Weekly MDT
- PI oversight
- IEC operational group
- Robust training package
- Governance structure