SCOPE, A phase 2 clinical trial with off-the-shelf DNA plasmid vaccine in first line advanced melanoma combined with checkpoint blockade shows good T cell responses which correlate with long progression free survival

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Poster CT237

1. Background: what are iSCIB1+ and SCIB1?

- iSCIB1+ and SCIB1 are off-the-shelf DNA vaccines that induce tumour-specific T cell responses against melanoma antigens TRP-2 and gp100.
- CD8 and CD4 T cell epitopes from TRP-2 and gp100 are incorporated into an antibody framework which allows Fc targeting of activated dendritic cells to elicit a dual mechanism of action:
  - **Direct presentation:** uptake of plasmid and expression of engineered antibody by antigen-presenting cells (APCs).
  - **Cross presentation:** secretion of the engineered antibody which is targeted to CD64 FcγR present on dendritic cells via its Fc domain.
- Compared to the HLA-A2 restricted SCIB1, **iSCIB1+** has a modified Fc region and contains additional epitopes covering a broad range of HLA haplotypes (A2, A3, A31, Bw4, B35 and B44) representing **80% of the population**.
- iSCIB1+ and SCIB1 are currently being evaluated in the phase 2 **SCOPE trial** in combination with checkpoint inhibitors (CPIs) for patients with advanced unresectable melanoma.

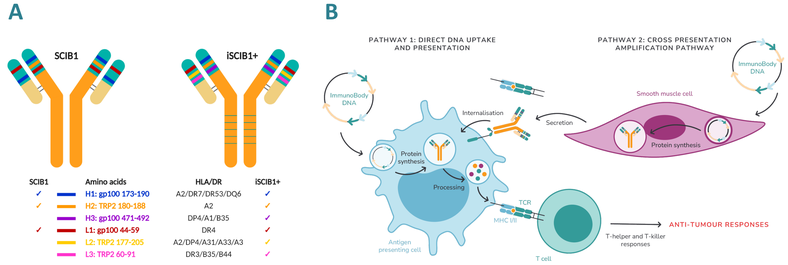

Figure 1. (A) SCIB1 and iSCIB1+ are off-the-shelf DNA vaccines which incorporate CD8 and CD4 T cell epitopes from melanoma antigens TRP-2 and gp100 into an APC targeting antibody framework. iSCIB1+ has a modified Fc region and contains additional epitopes covering a broad range of HLA haplotypes. (B) iSCIB1+ and SCIB1 elicit anti-tumour immune responses via dual mechanisms of direct presentation and cross presentation.

2. SCOPE trial study design

- A Phase 2, multicenter, open-label study of iSCIB1+ or SCIB1 in combination with ipilimumab plus nivolumab in advanced melanoma.
- Eligible patients with stage IIIB/IV unresectable melanoma were treated with ipilimumab and nivolumab plus either iSCIB1+ or SCIB1 (8mg i.m.) via the needle-free injection device Stratis® (Pharmajet).
- Analysis of patient responses were stratified into HLA matched (positive for at least one of HLA-A2, A3, Bw4, B35 or B44) and HLA non matched.
- iSCIB1+ and SCIB1-specific T cell responses were assessed via a combination of IFNγ ELISpot and single-cell RNA- & TCR-sequencing.

3. iSCIB1+ shows good PFS and T cell responses

- **iSCIB1+** treated HLA-matched patients had an improved **PFS of 74% at 16 months.**
- This compares favourably to CPI alone (median PFS of 11.5 months)[1].
- Among 200 grade 3 or greater adverse events, only 4 (uveitis) were solely related to vaccine and were rapidly resolved upon treatment.

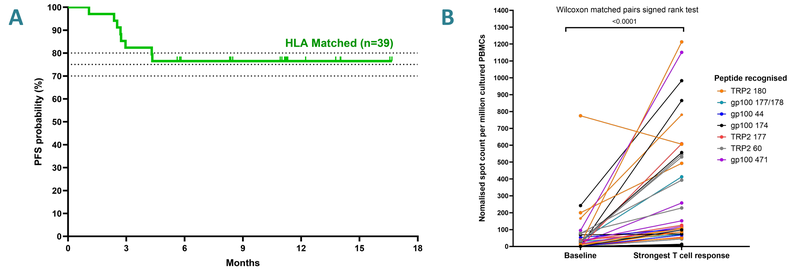

Figure 2. (A) Progression Free Survival for HLA matched (n=39) patients treated with iSCIB1+. (B) T cell responses to iSCIB1+ peptides assessed by cultured IFNγ ELISpot for 34 patients who had an evaluable imaging scan. Data from interim data cut on 27th October 2025.

Clinical response	Number of patients	High magnitude T cell response (30 patients)	Response to both gp100 and TRP2 (39 patients)
CR/PR	41	22/30 (73%)	28/39 (72%)
SD	17	5/30 (17%)	7/39 (18%)
PD	8	3/30 (10%)	4/39 (10%)
Overall:	66	30	39

Table 1. Summary of clinical and immunology responses in HLA matched patients treated with iSCIB1+ or SCIB1 + CPIs. High magnitude T cell response ≥150 spots per million cultured cells. Percentiles defined responses as low, medium and high.

4. iSCIB1+ encodes nested CD8 epitopes presented by a broad range of HLA types

- CD4 and CD8 T cell responses have been observed for each iSCIB1+ encoded peptide (data not shown).
- Multiple nested epitopes and HLA restrictions have been confirmed and iSCIB1+ specific TCRs have been isolated from vaccinated patients.

iSCIB1+ encoded peptide	Nested epitopes confirmed	HLA restriction confirmed	TCR(s) isolated
TRP2 180	1 CD8	HLA-A2	2 CD8
gp100 44	1 CD8	HLA-A2?	Pending
gp100 174	3 CD8	HLA-A2, HLA-A3, HLA-Cw12	7 CD8
TRP2 177	1 CD8	HLA-A2	2 CD8
TRP2 60	3 CD8	HLA-B35, Cw07:02	1 CD8
gp100 471	4 CD8 & 4 CD4	HLA-A1, HLA-B35, HLA-DR, HLA-DP	2 CD8 & 2 CD4

Table 2. Summary of confirmed nested epitopes, confirmed HLA restrictions, and specific TCRs isolated and validated for each iSCIB1+ encoded peptide.

5. iSCIB1+ specific TCRs kill melanoma target cells

- 14 iSCIB1+ specific TCRs (12 CD8 and 2 CD4) were isolated from patients
- iSCIB1+ specificity and cytotoxic capability of TCRs were confirmed using TCR transduced human T cells and melanoma cell lines.
- Cultured cells expressing iSCIB1+ specific CD8 TCRs had a polyfunctional transcriptional profile similar to precursor exhausted (Tpex) cells, which have been shown to maintain the anti-tumour T cell pool[2].

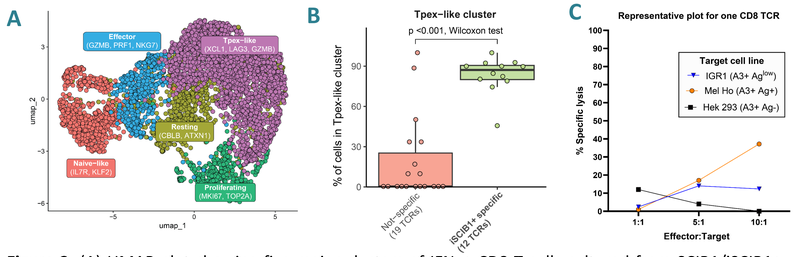

Figure 3. (A) UMAP plot showing five major clusters of IFNγ+ CD8 T cells cultured from SCIB1/iSCIB1+ treated patients. (B) Percentage of cells in Tpex-like cluster expressing either non-specific or iSCIB1+ specific CD8 TCRs. (C) Representative data for an HLA-A3 restricted iSCIB1+ specific CD8 TCR showing killing of melanoma cell lines by TCR transduced T cells. Specific lysis calculated relative to Triton X-100.

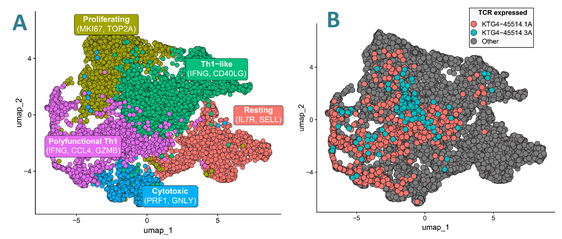

Figure 4. UMAP plots showing IFNγ+ CD4 T cells cultured from SCIB1/iSCIB1+ treated patients with cells highlighted by either (A) five major clusters of cells or (B) expression of one of the two iSCIB1+ specific CD4 TCRs.

- Cultured cells expressing iSCIB1+ specific CD4 TCRs had a polyfunctional Th1 transcriptional profile (IFNγ, CCL4, granzyme B).

6. Conclusions

- iSCIB1+ in combination with CPIs showed an improved PFS of 74% at 16 months without an increase in clinically meaningful adverse events.
- iSCIB1+ generates polyfunctional memory CD4 and CD8 T cell responses via a broad range of HLA alleles.
- These data support a registrational, randomized, controlled trial of iSCIB1+ with potential to redefine frontline therapy for unresectable advanced melanoma.

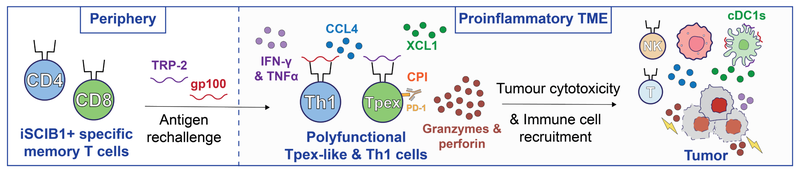

Figure 5. Proposed mechanism of action for iSCIB1+ in combination with CPIs.

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