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A DNA plasmid melanoma cancer vaccine, SCIB1 and iSCIB1+ combined with nivolumab and ipilimumab in advanced unresectable melanoma induces potent clinically meaningful CD8 T cell responses in 80% of the patient population

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Background

- SCIB1 and iSCIB1+ are off the shelf DNA vaccines incorporating CD8 and CD4 epitopes from TRP2/gp100 into an antibody framework to allow Fc targeting of activated dendritic cells to elicit a dual mechanism of action **(Figure 1).**
  - **Direct presentation:** uptake of plasmid and expression of engineered antibody by antigen-presenting cells.
  - **Cross presentation:** secretion of the engineered antibody which is targeted to CD64 FcγR present on dendritic cells via its Fc domain.
- SCIB1 and iSCIB1+ have a synergistic effect in melanoma when combined with checkpoint inhibitors (CPI). SCIB1 induced T cell responses in HLA-A2 patients; iSCIB1+ has additional epitopes covering more HLA haplotypes, HLA-A2, A3, A31, Bw4, B35 and B44 representing 80% of the population.
- In a Phase 2 trial patients with advanced unresectable melanoma were treated with SCIB1 or iSCIB1+ in combination with CPI. Objective response rate (ORR), Disease Control Rate (DCR) and Progression Free Survival (PFS) determined by RECIST 1.1 were assessed along with the immunogenicity of SCIB1 and iSCIB1+ using a cultured IFNγ ELISpot assay, single cell RNA- and TCR-seq analysis

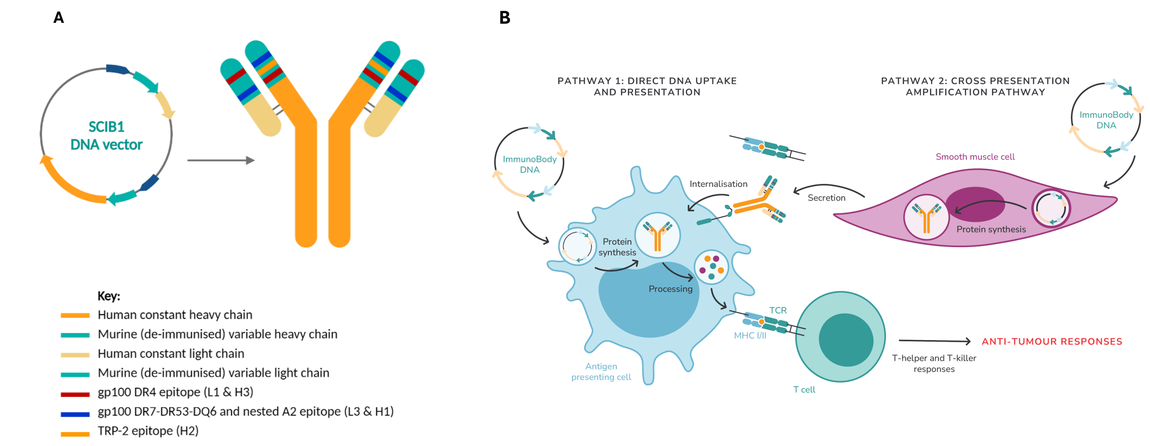

Figure 1. (A) SCIB1 is an off-the-shelf DNA vaccine which incorporates CD8 and CD4 T cell epitopes from melanoma antigens TRP-2 and gp100 into an APC targeting antibody framework. (B) SCIB1 elicits anti-tumour immune responses via dual mechanisms of direct presentation and cross presentation.

SCOPE Trial study design

- SCOPE is an ongoing phase 2, open-label, single-arm study evaluating immune response, safety, and efficacy of SCIB1/iSCIB1+ in first-line advanced melanoma across 16 UK sites.
- Eligible patients with stage IIIB/IV unresectable melanoma were treated with ipilimumab, nivolumab and SCIB1 (cohort 1) or iSCIB1+ (cohort 3) via the needle-free injection device Stratis® Pharmajet.
- Presented here are data on functional T cell responses for 34 patients enrolled in cohort 3 that express at least one of the following HLA alleles: A2, A3, A31, Bw4, B35 and B44. Also, a summary of T cell response data for 40 patients enrolled in cohort 1 (SCIB1 plus ipilimumab and nivolumab).

iSCIB1+ induces significant T cell responses post vaccination

- The IFNγ ELISpot assay was used to detect the expansion of peptide specific T-cells. At the time of the data cut-off, 34 HLA matched patients in cohort 3 had evaluable post vaccination immunology blood samples and an imaging scan had been performed.
- For each patient, a T-cell response was assessed at screening (baseline) and at least one time point post vaccination. The T-cell response to the peptides included in the iSCIB1+ immunotherapeutic was assessed following an 8–12-day culture period. The reactivity to TRP2 180, gp100 177 or gp100 178, gp100 44, gp100 174, TRP2 177, TRP2 60 and gp100 471 was assessed at screening and compared to the post vaccination response. A representative plot for two patients is shown in **Figure 2 (B and C).**
- For each patient, the strongest T-cell response to any peptide post-vaccination was compared to the corresponding response at screening **(Figure 2A)**. A highly significant ($p<0.001$) increase in T-cell response was seen post-vaccination in 32/34 patients (94%). The strongest T cell response was detected at week 25 (range 10-50 weeks). The majority of patients had pre-existing T cell responses to iSCIB1+ peptides, these expanded upon vaccination.

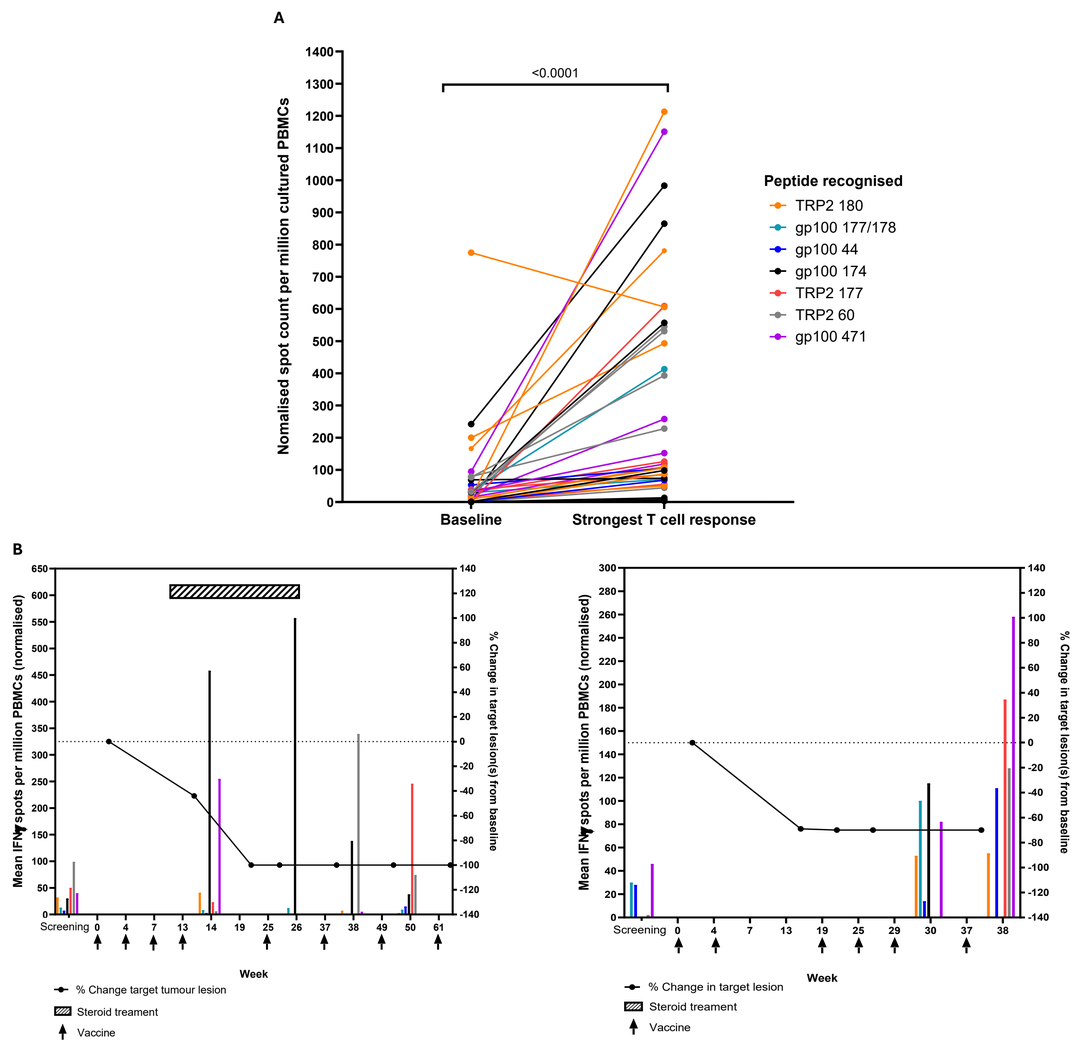

Figure 2. (A) Strong T-cell responses were observed at the time of data cut-off for 34 patients in cohort 3 enrolled in the ongoing SCIB1-002 clinical trial, for those who had both an evaluable imaging scan and T-cell data. All T-cell data sets passed the assay acceptance criteria. Significance was determined using Wilcoxon matched pairs signed rank test. **(B)** Representative plot for two patients recruited into cohort 3 (iSCIB1+)

Reactive T cells express markers associated with cytotoxicity

- Single cell RNA- and TCR-sequencing was performed on IFNγ+ CD8 T cells sorted from 5 patients (9 TCRs) with strong responses to SCIB or iSCIB1+ peptides.
- SCIB1 and iSCIB1+ reactive CD8 T cells expressed cytotoxic markers and markers of memory T cells.

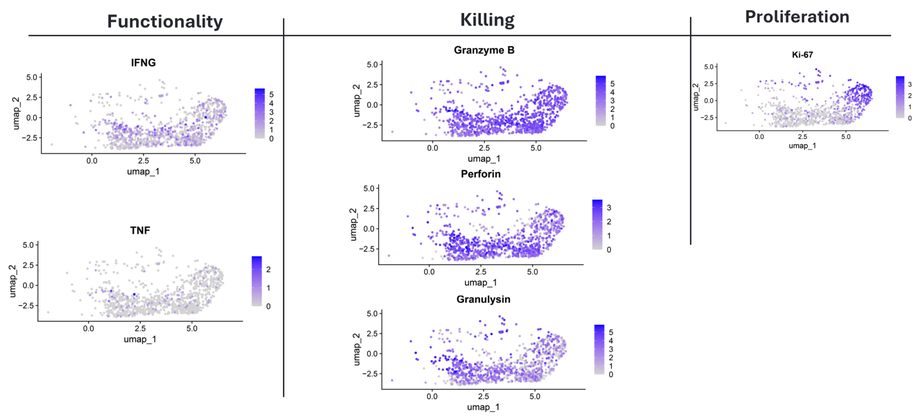

Figure 3. Cells cultured from patients immunised with SCIB1 or iSCIB1+ were stimulated overnight with gp100 or TRP2 peptides, reactive CD8 T cells were sorted on IFNγ and CD8 expression by flow cytometry. TCR and RNA sequencing was performed. TCRs were tested in the lentivirus system, once a positive TCR was identified the corresponding gene expression clusters were generated. This plot represents 1065 CD8 T cells with functionally validated gp100 or TRP2 specific TCRs. One dot per cell. Grey = no expression.

Nested CD8+ epitopes recognised post vaccination

- CD8 T cells specific for nested epitopes contained within the longer iSCIB1+ peptides are detected in patients post vaccination, demonstrating that *in vivo* these peptides are processed from the iSCIB1+ construct.
- A range of specific TCRs have been isolated and characterised from HLA-A2 and non-HLA-A2 patients

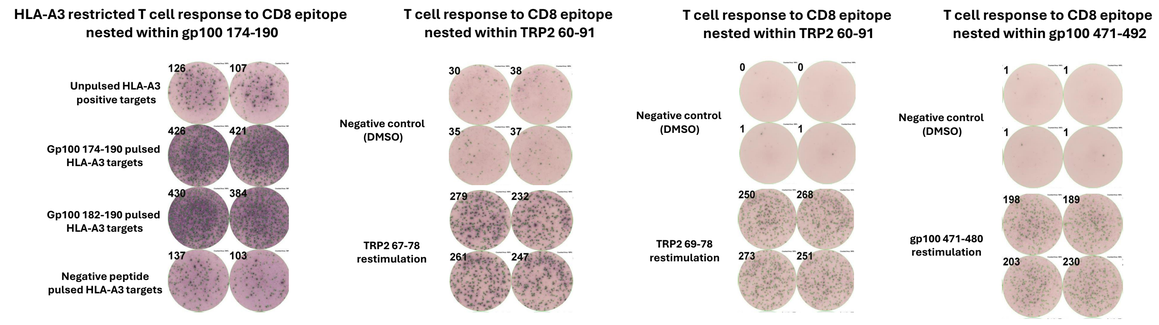

Figure 4. PBMCs from iSCIB1+ vaccinated patients were cultured for 8-12 days in the presence of full length iSCIB1+ peptides or small predicted nested peptides, and cytokine support. Cultured cells were restimulated in an IFNγ ELISpot assay with peptide alone or peptide pulsed HLA-matched target cells.

- TCR-sequencing was performed on IFNγ+ CD8 T cells sorted from patients with strong responses to iSCIB1+ peptides.
- To date 9 TCRs have been isolated and characterised from 5 patients, the HLA restriction has been identified for four of these, they are HLA-A2, A3, Cw12.

HLA selection

- The iSCIB1+ immunotherapeutic incorporates peptides from the TRP2 and gp100 melanoma antigens. These peptides are predicted to bind HLA-A1, A2, A3, A33, B35, B44, DR3 and DP4, which means the majority of the population could benefit from the iSCIB1+ immunotherapeutic.
- To confirm that these epitopes work in all patients, HLA eligibility in cohort 3 was unrestricted, but all patients were HLA typed at screening. **Figure 5** shows HLA alleles represented in cohort 3.
- Clinical responses were examined for each HLA allele where peptides are predicted to bind.
- The HLA subgroup analysis showed that clinical responses were higher in participants that were HLA-A2, A3, A31, B35, B44. In addition, the analysis also showed that clinical responses were higher in participants that were HLA-Bw4 positive (74%). HLA-Bw4 is a public serological epitope that is present on approximately one third of HLA-B alleles including B44 and certain HLA-A alleles. Given its association with increased clinical response, HLA-Bw4 has been included in the HLA biomarker criteria for future iSCIB1+ studies.
- Notable exceptions were observed in participants with HLA-A1 and HLA-A33. These participants exhibited lower ORRs of 39% or 0%, respectively. This suggests that either the predictive algorithm for HLA-A1 binding was incorrect, the peptide had a low binding affinity, or it is incorrectly cleaved from iSCIB1+. Therefore, HLA-A1 will not be selected as a biomarker for future studies. HLA-A33 was also excluded from further biomarker analysis due to its extremely low frequency in the general population (0.9%) and due to only one enrolled participant possessing the allele, who experienced progressive disease.
- Patients with permissive alleles (HLA-A2, A3, A31, B35, B44 and Bw4) demonstrated a higher response of 70% (range 64-75%), compared to 45% (range 33-50) in the non-permissive group **(Figure 6)** which is consistent with the response rate reported for CPIs.
- Based on this data the HLA target population for the Phase 3 trial are participants that express at least one of the following HLA alleles: A2, A3, A31, Bw4, B35 and B44.

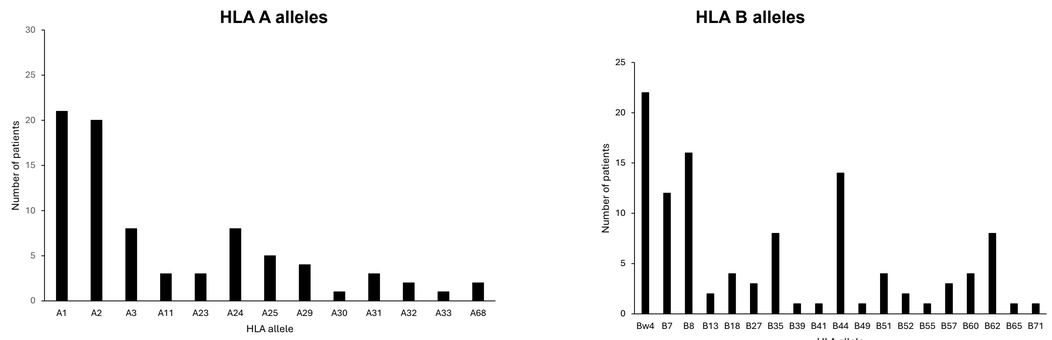

Figure 5. HLA alleles represented in Cohort 3. HLA-A and B alleles represented in cohort 3 (48 patients). HLA frequency in cohort 3: HLA-A2 42%, A1 44%, A3 17%, A31 6%, A33 2%, B35 17%, B44 28%, Bw4 48%. Only one HLA allele is represented in patients who are homozygous for an HLA allele.

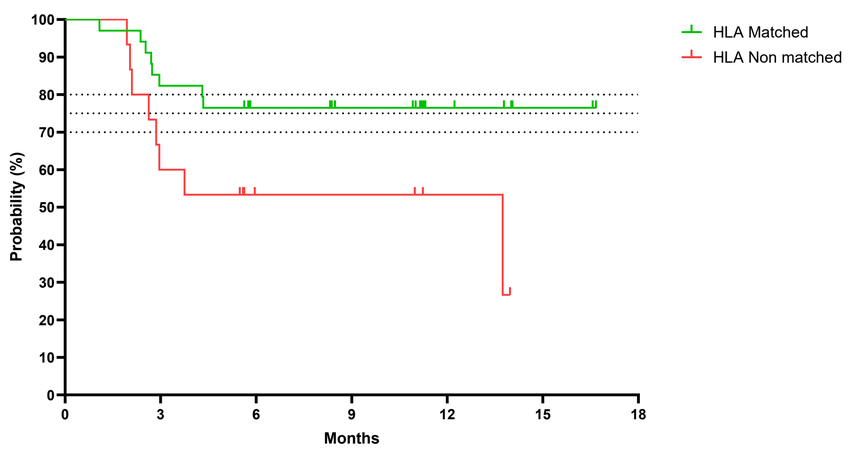

Figure 6 Progression Free Survival HLA matched vs non-HLA matched patients in cohort 3 (49 patients). Red = non-HLA matched patients (n =10) Green = HLA matched patients (n=39). (interim data cut 27th October 2026).

Summary of clinical and immunology responses

- Patients who generated a T-cell response to both gp100 and TRP2 peptides post-vaccination with iSCIB1+ exhibited better tumor control with tumours reducing in size or disappearing (PR/CR, 70%), suggesting that antigen loss was less likely amongst responders to both peptides (**Table 1B**).
- Nine patients (9/32) generated a T cell response to just one antigen, six patients responded to TRP2 only and three responded to gp100 only, 6/9 (67%) of these patients had a poorer outcome with stable disease or progression.
- Patients that generated a high magnitude iSCIB1+ specific T cell response exhibited better tumour control: 73% vs 13% in those with Progressive Disease.
- A similar trend is observed with patients vaccinated with SCIB1 (**Table 1A**). Patients who generated a T-cell response to both gp100 and TRP2 peptides post-vaccination with SCIB1 exhibited better tumor control with tumours reducing in size or disappearing (PR/CR, 75%).
- Patients that generated a high magnitude SCIB1 specific T cell response exhibited better tumour control: 73% of those with CR/PR had a high magnitude T cell response versus only 7% of those with PD.

A Cohort 1 SCIB1

Clinical response	Number of patients	High magnitude T cell response (15 patients)	Response to both gp100 and TRP2 (16 patients)
CR/PR	22	11/15 (73%)	12/16 (75%)
SD	9	3/15 (20%)	3/16 (19%)
PD	1	1/15 (7%)	1/16 (6%)
No T cell response	8 (6 PR/CR, 2 SD)	N/A	N/A
Overall:	32	15	16

B Cohort 3 iSCIB1+

Clinical response	Number of patients	High magnitude T cell response (15 patients)	Response to both gp100 and TRP2 (23 Patients)
CR/PR	19	11/15 (73%)	16/23 (70%)
SD	8	2/15 (13%)	4/23 (17%)
PD	7	2/15 (13%)	3/23 (13%)
No T cell response	2 (SD)	N/A	N/A
Overall:	34	15	23

Table 1. Summary of clinical and immunology responses in HLA matched patients in Cohort 1 (A) and Cohort 3 (B). High magnitude T cell response = >150 spots per million cultured cells. Percentiles defined responses as low, medium and high.

Conclusions

- These data support that SCIB1 and iSCIB1+ induces significant potent T cell responses, resulting in positive clinical responses.
- Strong vaccine induced T cell responses are associated with better tumour control.
- Patients who generate a T-cell response to both gp100 and TRP2 peptides post-vaccination exhibited better tumor control, and making antigen loss less likely.
- Vaccine induced T cell responses correlate with decrease in tumour size, as noted at the first scans, as well as with a durable response, reflected in improved Progression Free Survival.

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Disclosures:
BMS, Eisai and Ipsen, Invited Speaker
Merck Serono, Other, Personal, Consultancy
Aveo Pharmaceuticals, Local PI, Institutional
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