A phase 2 trial of the IO102-IO103 vaccine plus pembrolizumab: completed cohort for first line treatment of advanced Squamous Cell Carcinoma of the Head and Neck (SCCHN)

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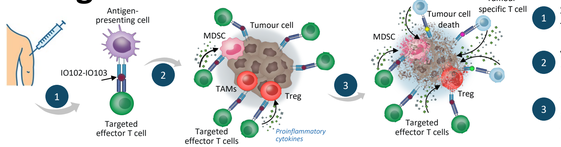
Background



1. Subcutaneous injection with IO102-IO103 cancer vaccine to activate T cells against IDO+ and PD-L1+ cells
2. Vaccine-activated T cells attack and kill target-expressing immunosuppressive cells in the tumour microenvironment
3. The inflamed TME becomes immuno-permissive, enabling further tumour cell killing by the recruited tumour-specific T cells

Proof of concept in 30 patients with anti-PD-1 naïve metastatic melanoma treated with IO102-IO103 and nivolumab:[1,2]
ORR = 80% (73% per RECIST 1.1); CR rate = 50%; mPFS = ~26 months

Other trials designed to assess the efficacy and safety of treatment with IO102-IO103 are ongoing:
- Fully recruited phase 3 registration trial of IO102-IO103 + pembrolizumab in 1L advanced melanoma (NCT05155254)
- Ongoing neoadjuvant/adjuvant phase 2 trial of IO102-IO103 + pembrolizumab in resectable melanoma and SCCHN (NCT05280314)

Study design

IOB-022/KN-D38 is a phase 2, non-comparative, open-label, multicentre, basket trial designed to assess the efficacy and safety of treatment with IO102-IO103 + pembrolizumab in patients with SCCHN, mNSCLC, and mUBC:

Eligibility criteria	Cohorts	Treatment and assessments	Endpoints
Recurrent or metastatic SCCHN PD-L1 CPS ≥ 20% No prior first line therapy Measurable disease ECOG performance status 0 or 1	**SCCHN (HPV ±)** **N = 21** **Other cohorts (data not shown)** mNSCLC, TPS ≥ 50% N = 37 (active, not recruiting) mUBC, CPS ≥ 10% N = 5 (active, not recruiting)	**IO102-IO103** **85–85 µg D1/D8 of C1/C2, then D1 only + pembrolizumab 200 mg q3w** **Tumour imaging schedule: First year q9w Second year q12w** **For up to 2 years**	**Primary endpoint:** • ORR (RECIST 1.1)* **Secondary/exploratory endpoints:** • PFS (RECIST 1.1) • DoR • OS • Safety

- KEYNOTE-048[3] showed ORR of 23%, DCR of 53%, and mPFS of 3.4 months for pembrolizumab monotherapy
- The null hypothesis is 23% ORR to be tested at one-sided type I error of 0.15

*Primary endpoint defined in the efficacy-evaluable patients who received ≥2 cycles of treatment.

Efficacy results

The SCCHN efficacy data set represents eligible patients with at least two cycles of treatment (N = 18)

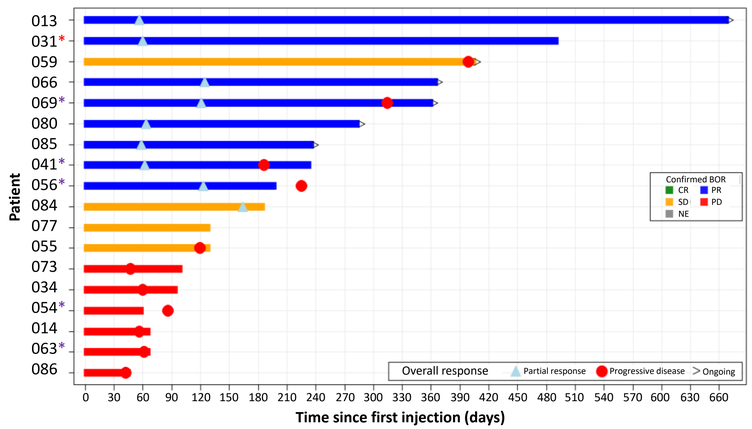
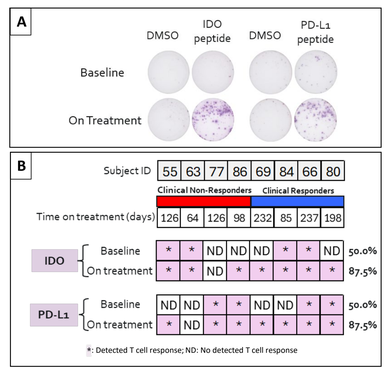


Figure 1: Duration of treatment, time to response, and best overall response per RECIST 1.1.
Out of 18 patients, nine (50%) obtained a partial response (PR; light blue triangle). One patient (084) did not have the response confirmed due to death from intercurrent illness. Median duration of response was not yet reached at the time of data cut-off (02-Aug-2024).

Vaccine-specific T cell response

ELISpot comparing baseline and on-treatment (best response) blood T cell responses to IDO and PD-L1 peptides

Findings (from eight of the 18 patients with SCCHN reported with evaluable blood samples, includes four responders and four non-responders):
- All the analysed patients in the clinical responder group showed both IO102 & IO103 T cell responses on treatment
- 75% of the analysed patients showed a T cell response to both IO102 & IO103 on treatment and the other 25% showed a T cell response to either IO102 or IO103 on treatment



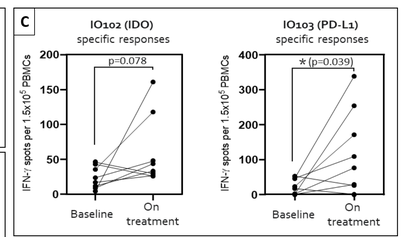


Figure 4: A. Representative images of 24-hour IFN-γ ELISpot responses following a 7-day in vitro restimulation with peptides + IL-2. **B.** Results showing presence/absence of response to specific peptides at baseline/on treatment. Statistical analysis: Distribution-free resampling (DFR) method (p<0.05). If <3 replicates, response was defined when number of spots in peptide wells was >2X than in control (DMSO). **C.** Specific T cell responses comparing baseline vs best response on treatment. Results represent the average normalised peptide response data (DMSO background subtracted). Statistical analysis: Wilcoxon matched-pairs signed rank test (p<0.05).

Baseline characteristics

All patients received at least one dose of treatment (N = 21)

Characteristics	SCCHN (N = 21)
Median age, years	69.0
Sex, %	
Female	33.3
Male	66.7
ECOG performance status, %	
0	23.8
1	76.2
Smoking status, %	
Current or former	66.7
Never	33.3
Disease status, %	
Metastatic (stage IVC)	57.1
Recurrent, non-metastatic (stage IVA/B)	33.3
Newly diagnosed, non-metastatic (stage IVA)	9.5
Primary tumour location, %	
Hypopharynx	5
Larynx	10
Oral cavity	44
Oropharynx	**38**
Paranasal cavity	5

Characteristics oropharynx	N = 8*
Median age, years	71.5
Stage at screening, n (%)	
IVA/B	2 (25.0)
IVC	6 (75.0)
HPV/p16 status, n (%)	
Positive	7 (87.5)
Negative	1 (12.5)
Smoking status, n (%)	
Current or former	7 (87.5)
Never	1 (12.5)

*Two patients are not included in the efficacy data set. One patient was judged to be ineligible following screening, and one patient received <2 cycles of treatment.

Safety results

Data cut-off 02-Aug-2024

Summary of adverse events, n (%)	SCCHN (N = 21)	All cohorts (N = 63) (NSCLC, SCCHN, UBC)
AEs, any grade	20 (95.2%)	60 (95.2%)
Treatment-related AEs, any grade	16 (76.2%)	49 (77.8%)

Treatment-related adverse events, n (%)*	SCCHN cohort (N = 21)	
	Grade 1–2	Grade 3–4
Events occurring in ≥10% of SCCHN patients		
Hypothyroidism	4 (19.0)	
Fatigue	4 (19.0)	
Rash	3 (14.3)	
AST increased	3 (14.3)	1 (4.8)
ALT increased	3 (14.3)	
Injection site reaction	3 (14.3)	
Grade 3–4 events occurring in SCCHN patients**		
GGT increased		1 (4.8)
Platelet count decreased		1 (4.8)
Conjunctivitis		1 (4.8)***
Colitis		1 (4.8)***
Immune thrombocytopenia (SAE)		1 (4.8)****

*Events were attributed (possibly or probably related) to IO102-IO103, pembrolizumab, or both by the investigator in the case-report form; **No treatment-related grade 5 AEs were reported; ***This AE led to treatment discontinuation; ****This was the only treatment-related SAE. Platelet count: $19*10^9$/L (grade 4) led to treatment discontinuation. The SAE resolved to grade 2 after 6 days of corticosteroid treatment.

*HPV-positive/oropharyngeal tumours; *HPV-negative/oropharyngeal tumour.

Best overall response, n (%) RECIST 1.1	N = 18
Partial response (PR)	8 (44.4)
Stable disease (SD)	4 (22.2)
Progressive disease (PD)	6 (33.3)
ORR, % (95% CI)	44.4 [21.5; 69.2]

Other endpoints	N = 18
6-month PFS rate, %	60.6
Disease control rate (PR + SD), n (%)	12 (66.7)
mPFS, months (95% CI)	6.6 [2.04; 13.14]

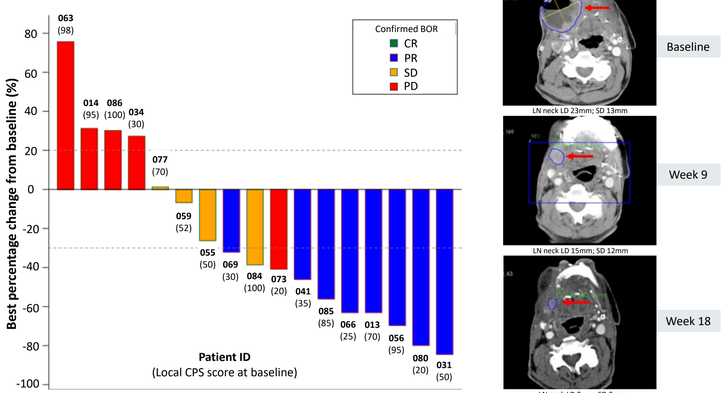


Figure 2: Best percentage change in the sum of diameters of target lesions compared to baseline. Out of 17 patients with post-baseline scans, 12 had a reduction in the sum of diameters. Patient 054 died from progressive disease before the first scan and is therefore not depicted in the plot. Patient 084 did not have the response confirmed due to death from intercurrent illness. Patient 073 had a mixed response with shrinkage of pulmonary metastasis (target lesion) but progression of bone lesions.

Figure 3: Patient 013 imaging from baseline and weeks 9, 18, and 81, including longest (LD) and shortest (SD) diameters of neck lesion. The patient also had 2 other target lesions (a lymph node in the neck and a metastasis in the chest wall) driving the partial response

Baseline biomarker analysis

Comparing baseline immune expression profiles and biomarker status for patients with and without clinical response

Findings:
- Overall, no difference was observed in levels of T cell infiltration scores between clinical responders and non-responders
- A higher macrophage signature (potentially M2 based on the observed trend in Arg1 signature scores) and a higher stroma signature were found to be associated with clinical non-responders
- There was no clear association between HPV status, smoking status, TMB score, and clinical response, though this analysis was limited by sample size

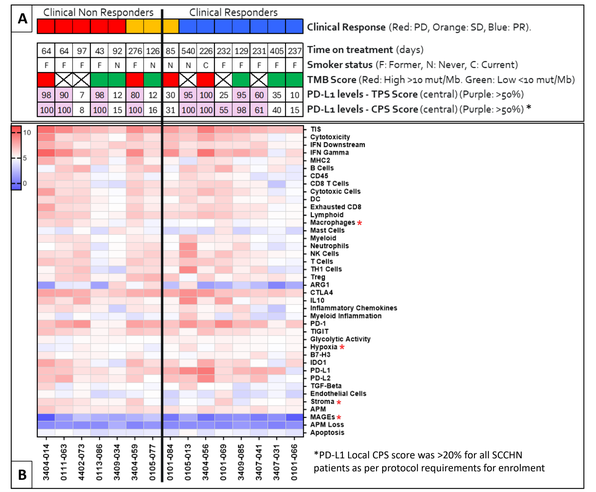


Figure 5: **A.** Table with clinical response and selected baseline characteristics. Clinical responders had at least one post-baseline scan showing PR per RECIST 1.1 **B.** Heatmap of selected transcriptional immune signature scores from Nanostring PanCancer 360. Statistical analysis: Unpaired t test comparing score in clinical responders vs non responders (*: Statistically different, p<0.05).

*PD-L1 Local CPS score was >20% for all SCCHN patients as per protocol requirements for enrolment

Conclusion

- Primary endpoint was met with a confirmed ORR of 44.4% in efficacy evaluable patients with PD-L1 high SCCHN
- Encouraging mPFS of 6.6 months and DCR of 66.7% supports the improved activity of adding IO102-IO103 to pembrolizumab as 1L treatment for recurrent or metastatic SCCHN (inclusive of HPV-positive and -negative patients)
- Safety data in the current trial is consistent with previously reported data for anti-PD1 monotherapy and combination therapy with IO102-IO103, with no unexpected safety signals
- Vaccine-specific T cell responses to both IO102 (IDO) and IO103 (PD-L1) were detected after treatment
- Further investigation in a randomised clinical trial should be conducted to build on these findings

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References: 1. Kjeldsen *et al. Nat Med* 2021;27:pages2212–23; 2. Lorentzen *et al. J Immunother Cancer* 2023;11(5):e006755; 3. Burtness *et al. Lancet* 2019;394(10212):1915–28

Abbreviations: 1L, first line; AE, adverse event; ALT, alanine transaminase; Arg1, arginase 1; AST, aspartate aminotransferase; C, cycle; CI, confidence interval; CPS, combined positive score; CR, complete response; D, day; DMSO, dimethyl sulfoxide; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; GGT, gamma-glutamyl transferase; HPV, human papillomavirus; IDO, indoleamine 2,3-dioxygenase; IFN-γ, interferon gamma; IL-2, interleukin-2; MDSC, myeloid-derived suppressor cell; mNSCLC, metastatic non-small cell lung cancer; mPFS, median progression-free survival; mUBC, metastatic urothelial bladder cancer; N, number; NE, not evaluable; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; PD-(L)1, programmed cell death (ligand) 1; PD, progressive disease; PR, partial response; q3w, once every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumours; SAE, serious adverse event; SCCHN, squamous cell carcinoma of the head and neck; SD, stable disease; TAM, tumour-associated macrophage; TMB, tumour mutational burden; TME, tumour microenvironment; TPS, tumour proportion score; Treg, regulatory T cell

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