A phase 2 trial of the IO102-IO103 cancer vaccine plus pembrolizumab: results from the first-line cohort of PD-L1 high metastatic non-small cell lung cancer

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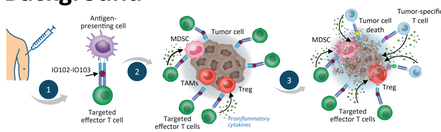
Background



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 tumor microenvironment
3. The inflamed TME becomes immuno-permissive, enabling further tumor cell killing by the recruited tumor-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%; CR rate = 50%; median PFS = ~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 first-line 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, multicenter, basket trial designed to assess the efficacy and safety of treatment with IO102-IO103 in combination with pembrolizumab in patients with mNSCLC, SCCHN or mUBC:

Eligibility criteria
. Metastatic lung adenocarcinoma
. PD-L1 TPS ≥ 50%
. No prior first-line therapy
. Measurable disease
. ECOG performance status 0 or 1

Cohorts
NSCLC, TPS ≥ 50% N = 37
Other cohorts (not presented)
r/m SCCHN, CPS PD-L1 ≥ 20% N = 21 (active, not recruiting)
mUBC, CPS ≥ 10% N = 5 (active, not recruiting)

Treatment and assessments
IO102-IO103 85–85 µg D1/D8 of C1/C2, then D1 only **+ pembrolizumab** 200 mg q3w
Tumor imaging schedule: **First year:** q9w **Second year:** q12w
For up to 2 years

Endpoints
Primary endpoint: • ORR (RECIST 1.1)*
Secondary/exploratory endpoints: • PFS (RECIST 1.1) • Duration of response • Overall survival • Safety

***Statistical methods:**
Primary endpoint defined in the efficacy-evaluable patients who received ≥2 cycles of treatment.
The null hypothesis is 39% ORR to be tested at one-sided type I error of 0.15, per cohort, without multiplicity adjustment.
As an exploratory analysis, ORR will also be analyzed across all cohorts using a Bayesian hierarchical model.

Patient population

Data cut-off 03-Sep-2024
- A total of 37 patients were treated with at least one dose of treatment
- 10 patients are still on treatment
- 27 patients discontinued treatment due to progressive disease (43%), AEs (19%), death before documented progression (8%) or start of new anticancer treatment (3%)

Baseline characteristics NSCLC (N = 37)			
Median age, years	71		
Gender, %		Smoking status, %	
Female	51.4	Current or former	91.9
Male	48.6	Never	8.1
ECOG performance status, %		Stage, %	
0	35.1	IVA	37.8
1	64.9	IVB	59.5

Safety results

All patients received at least one dose of treatment (N = 37)

Summary of AEs, n (%)	NSCLC (N = 37)	All cohorts (N = 63) (NSCLC, SCCHN, UBC)
AE, any grade	35 (94.6)	60 (95.2)
Treatment-related AE, any grade	30 (81.1)	49 (77.8)
Treatment-related, grade 3–4	9 (24.3)	14 (22.2)
Treatment-related, fatal AE (grade 5)	1 (2.7)	1 (1.6)
Treatment-related, serious AEs	4 (10.8)	6 (9.5)
Treatment-related AEs leading to discontinuation	6 (16.2)	10 (15.9)

*The patient discontinued from trial treatment after one cycle due to pneumonitis (grade 3); 5 weeks later, the patient died from a cerebrovascular accident (grade 5), which was attributed to an underlying hyper-coagulable condition possibly exacerbated by the study treatment. The frequency of thromboembolic events was analyzed across the IO102-IO103 program (N = 626). No unexpected safety signals were identified.

Treatment-related AEs, n (%)	NSCLC cohort (N = 37)			
	Total	Grade 1–2	Grade 3–4	Grade 5
Events occurring in ≥10% of NSCLC patients				
Injection-site reactions	14 (37.8)	14 (37.8)	0	0
Asthenia	8 (21.6)	5 (13.5)	3 (8.1)	0
Rash	6 (16.2)	5 (13.5)	1 (2.7)	0
Fatigue	6 (16.2)	5 (13.5)	1 (2.7)	0
Arthralgia	6 (16.2)	6 (16.2)	0	0
Pruritus	4 (10.8)	4 (10.8)	0	0
ALT increased	4 (10.8)	2 (5.4)	2 (5.4)	0
Diarrhea	4 (10.8)	4 (10.8)	0	0
Serious AEs				
Pneumonitis	1 (2.7)	0	1 (2.7)	0
Cerebrovascular accident	1 (2.7)	0	0	1* (2.7)
Pericardial effusion	1 (2.7)	1 (2.7)	0	0
Fatigue	1 (2.7)	0	1 (2.7)	0
Drug hypersensitivity	1 (2.7)	0	1 (2.7)	0
Sepsis	1 (2.7)	0	1 (2.7)	0

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Efficacy results

The NSCLC efficacy data set represents eligible patients with at least two cycles of treatment (N = 31)

Table 1: Primary endpoint and other efficacy endpoints

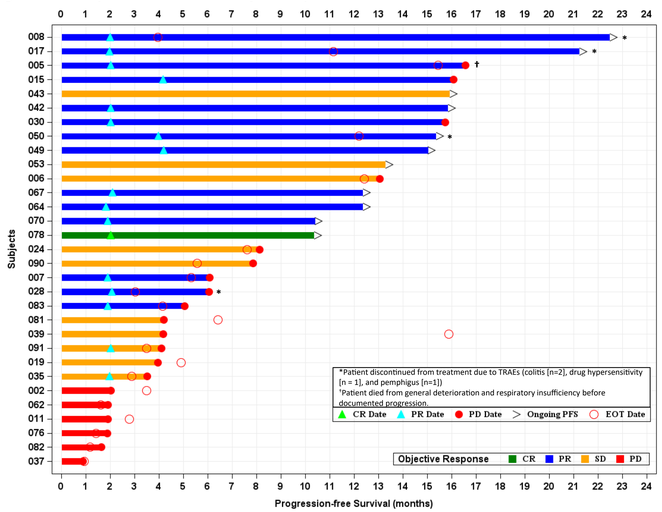
Endpoints Investigator review	N = 31
Median follow-up of 16 months	
Responders	55% (95% CI: 36–73)
Confirmed ORR (RECIST 1.1)	**48% (95% CI: 30–67)**
CR	1 (3.2)
PR	14 (45.2)
SD	10 (32.3)
PD	6 (19.4)
DCR	81% (95% CI: 63–93)
Median duration of response	Not reached
Median PFS, months	**8.1 (95% CI: 4–17)**
12-month PFS rate	48% (95% CI: 30–64)

Table 2: Bayesian hierarchical model[3]

	Cohort A NSCLC	Cohort B SCCHN
Benchmark target rate*	39%	23%
Efficacy evaluable set	**N = 31**	**N = 18**
Posterior probability of confirmed ORR > target rate	> 90%	> 97.5%
Intent-to-treat set	**N = 37**	**N = 21**
Posterior probability of ORR > target rate	> 95%	> 97.5%

The Bayesian hierarchical model by Berry et al. 2013[3] is commonly used in oncology basket trials to explore efficacy across cohorts. SCCHN cohort was reported at ESMO 2024 (Riess et. 2024[4]), where the primary endpoint confirmed ORR 44.4% was statistically significant and it was used here in the Bayesian hierarchical model.
*Study protocol-specified benchmarks are Keynote-042[5] for the NSCLC cohort and Keynote-048[6] for the SCCHN cohort.

Figure 1: Swimmer plot of PFS and confirmed objective response

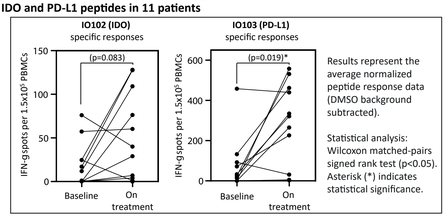


Of 31 patients, 17 (55%) had a PR (n = 16) or CR (n = 1). Two patients (091 and 035) did not have the PR confirmed.
Six patients were not included in the efficacy data set and are therefore not listed on this plot. Of the six patients, one was found ineligible due to squamous histology and five discontinued before completing the second cycle. The reasons for discontinuation were death [n = 2], maculo-papular rash [n = 1], pneumonitis/pulmonary embolism [n = 1], and early progression [n = 1].

Abbreviations: AE, adverse event; ALT, alanine transaminase; CD45, leukocyte common antigen; cfDNA, cell-free DNA; ctDNA, circulating tumor DNA; CI, confidence interval; CPS, combined positive score; CR, complete response; DC, dendritic cell; DCR, disease control rate; DMSO, dimethyl sulfoxide; ECOG, Eastern Cooperative Oncology Group; ELIspot, enzyme-linked immunospot; EOT, end of treatment; GSEA, gene set enrichment analysis; IDO, indoleamine 2,3-dioxygenase; IFN-γ, interferon gamma; IHC, immunohistochemistry; JAK-STAT, Janus kinase - signal transducers and activators of transcription; KRAS, kirsten rat sarcoma virus; LRP1B, Low-density lipoprotein receptor-related protein 1B; MAPK, mitogen-activated protein kinase; MDSC, myeloid-derived suppressor cell; mNSCLC, metastatic non-small cell lung cancer; mPFS, median progression-free survival; mUBC, metastatic urothelial bladder cancer; N, number; NK, natural killer; NSCLC, non-small cell lung cancer; ORR, objective response rate; PBMC, peripheral blood mononuclear cell; PD, progressive disease; PD-L1, programmed cell death (ligand) 1; PD-1, programmed cell-death protein 1; PFS, progression-free survival; PI3K-Akt, phosphoinositide 3-kinase - protein kinase B; PR, partial response; q3w, once every 3 weeks; q9w, once every 9 weeks; q12w, once every 12 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; r/m; recurrent/metastatic; SCCHN, squamous cell carcinoma of the head and neck; SD, stable disease; TAM, tumor-associated macrophage; TGF, transforming growth factor; Th, T helper; TIS, carcinoma in situ; TME, tumor microenvironment; TP53, tumor protein 53; TPS, tumor proportion score; TRAE, treatment-related adverse event; Treg, regulatory T cell

Vaccine-specific T cell response

Figure 2: In vitro ELISpot assay confirming expansion of blood T cell responses to IDO and PD-L1 peptides in 11 patients

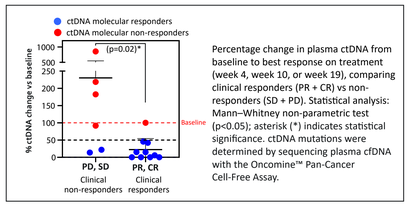


Results represent the average normalized peptide response data (DMSO background subtracted).

Statistical analysis: Wilcoxon matched-pairs signed rank test (p<0.05). Asterisk (*) indicates statistical significance.

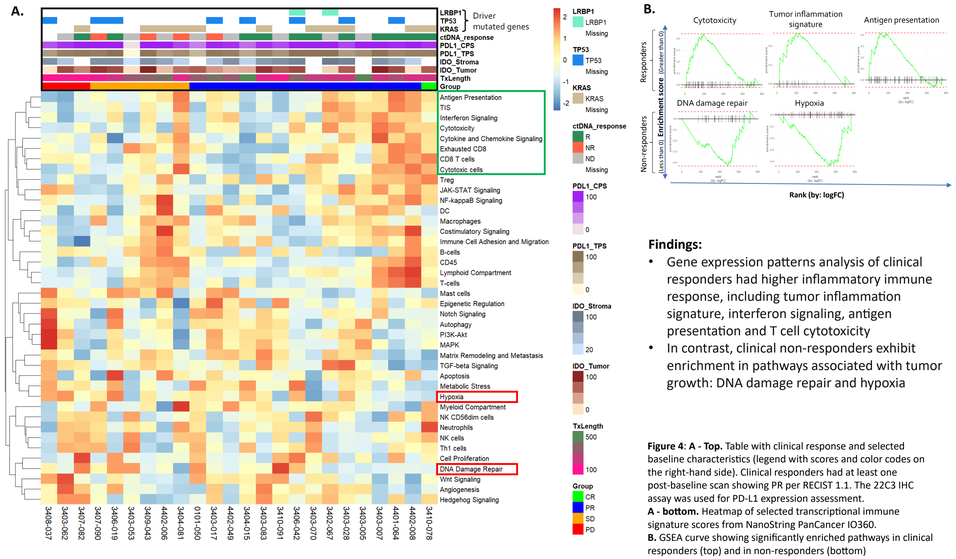
Tracking treatment response

Figure 3. ctDNA response correlates with clinical outcome



Percentage change in plasma ctDNA from baseline to best response on treatment (week 4, week 10, or week 19), comparing clinical responders (PR + CR) vs non-responders (SD + PD). Statistical analysis: Mann–Whitney non-parametric test (p<0.05); asterisk (*) indicates statistical significance. ctDNA mutations were determined by sequencing plasma cfDNA with the Oncomine™ Pan-Cancer Cell-Free Assay.

Correlation between baseline markers and clinical response



Findings:
- Gene expression patterns analysis of clinical responders had higher inflammatory immune response, including tumor inflammation signature, interferon signaling, antigen presentation and T cell cytotoxicity
- In contrast, clinical non-responders exhibit enrichment in pathways associated with tumor growth: DNA damage repair and hypoxia

Figure 4: A - Top. Table with clinical response and selected baseline characteristics (legend with scores and color codes on the right-hand side). Clinical responders had at least one post-baseline scan showing PR per RECIST 1.1. The 22C3 IHC assay was used for PD-L1 expression assessment.
A - bottom. Heatmap of selected transcriptional immune signature scores from NanoString PanCancer IO360.
B. GSEA curve showing significantly enriched pathways in clinical responders (top) and in non-responders (bottom)

Conclusions

- IO102-IO103 + pembrolizumab as first-line treatment of PD-L1 high metastatic NSCLC demonstrated promising activity with an ORR of 48%, a DCR of 81%, and ~50% of patients without disease progression at 12 months in the efficacy evaluable population
- Median duration of response, currently not reached, will build on the totality of encouraging data
- Using Bayesian hierarchical model to explore efficacy across cohorts, provides additional confidence in strength of data with posterior probability of confirmed response rate exceeding the benchmark
- Safety data is consistent with previously reported data for IO102-IO103 in combination with anti-PD-1, with no unexpected safety signals
- Vaccine-specific T cell responses to both IO102 (IDO) and IO103 (PD-L1) were detected in patients on treatment
- Following promising data for the SCCHN cohort (ORR of 44%; mPFS 6.5 months) and previous data in melanoma (ORR of 80%; mPFS 26 months), these data in NSCLC add to the body of evidence supporting further study of IO102-IO103 in combination with anti-PD-1 therapy

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