IO102-012 CLINICAL TRIAL REPORT ADDENDUM - SYNOPSIS

Name of Sponsor: IO Biotech	**Individual trial table referring to part of the dossier**	***(For national authority use only)***
Name of finished product: IO102		
Name of active ingredient: IO102: an indoleamine 2,3-dioxygenase (IDO) cancer vaccine. IO102 peptide sequence is IDO194-214 (DTLLKALLEIASCLEKALQVF).		

Title of the trial:

An Open-label, Randomized, Phase I/II Trial Investigating the Safety and Efficacy of IO102 in Combination with Pembrolizumab, with or without Chemotherapy, as First-line Treatment for Patients with Metastatic Non-Small Cell Lung Cancer

Protocol Number: IO102-012 (KN-764)

Trial periods:	**Clinical phase:**
First patient on-trial date: 19 September 2018 Interim report database lock date: 12 March 2021 Addendum report database lock date: 30 June 2022	Phase I/II

Objectives:

Primary Objective:

a) Phase I (Safety Run-in): The primary objective of the Phase I Safety Run-in part was to investigate the safety of IO102 in combination with either pembrolizumab alone or pembrolizumab and chemotherapy (carboplatin and pemetrexed) in patients with metastatic non-small cell lung cancer (NSCLC), that were eligible for pembrolizumab treatment as first-line therapy for Stage IV disease.

b) Phase II: The primary objective of the Phase II part of the trial was to assess the efficacy of IO102 in combination with either pembrolizumab alone or pembrolizumab and chemotherapy versus either pembrolizumab alone or pembrolizumab and chemotherapy as measured by objective response rate (ORR) per investigator assessment in patients with metastatic NSCLC, that were eligible for pembrolizumab treatment as first-line therapy.

Secondary Objective:

• To investigate the safety profile and the secondary measures of efficacy including disease control rate (DCR), time to event parameters including duration of response (DOR), progression free survival (PFS), overall survival (OS), and tumor shrinkage.

Exploratory Objectives:

• To evaluate efficacy, including time to event parameters, per immune-related response evaluation criteria in solid tumors (iRECIST).

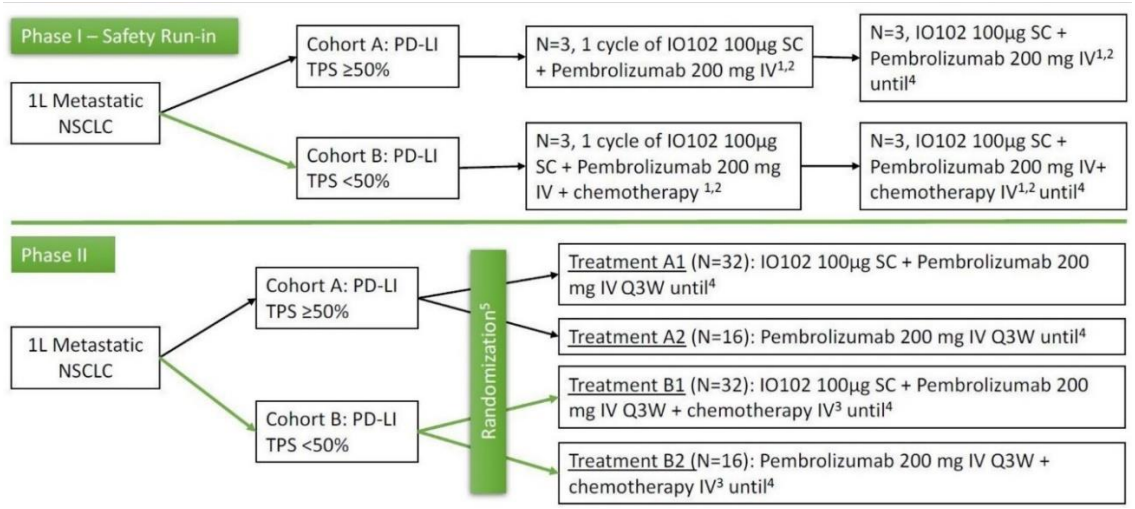
• To evaluate correlation of biomarkers and pharmacodynamic responses with trial treatment in archival and/or fresh tumor biopsy material and/or blood.

Methodology:

This was a Phase I/II, multi-center, international, open-label, randomized trial investigating the safety and efficacy of two parallel cohorts of IO102 (Cohort A and Cohort B) in combination with pembrolizumab alone

or pembrolizumab in combination with chemotherapy as first-line treatment for patients with metastatic NSCLC who had not received prior systemic therapy for their metastatic disease.

The clinical trial consisted of two parts; a Phase I Safety Run-in part and a Phase II part with two parallel randomized cohorts (Cohort A: high programmed death protein ligand 1 [PD-L1] expression; and Cohort B: low PD-L1 expression). By histological subtype, Cohort A included patients with squamous cell carcinoma. Treatments were to be administered for up to 35 cycles of treatment (where one cycle was three weeks).



[1] Safety Monitoring Committee was to review Cohort A, Cycle 1 from initial three patients before proceeding to a further three patients and before enrolling Cohort B data of each combination.

[2] IO102 was to be given additionally on Day 8 of Cycles 1 and 2. IO102 was to be administered every 3 weeks (Q3W).

[3] Chemotherapy (carboplatin + pemetrexed) was to be administered in combination Q3W for 4 cycles, followed by pemetrexed maintenance treatment Q3W if considered applicable by the Investigator.

[4] Until iRECIST confirmed disease progression, unacceptable AEs, intercurrent illness that prevented further administration of trial treatment, Investigator decision, patient withdrew consent, pregnancy of the patient, non-compliance with trial treatment or procedure requirements, or until the patient had received 35 treatment cycles of pembrolizumab.

[5] Phase II patients were to be randomized to the experimental treatment (A1 and B1) or the control treatment (A2 and B2) on a 2:1 ratio, depending on the level of tumor PD-L1 expression.

Patient and Treatment Information

All 6 patients (100%) enrolled into Cohort A and all 6 patients (100%) enrolled into Cohort B of Phase I received trial treatment, all of whom had discontinued from the trial as of the final database lock date.

All 32 patients (100%) enrolled into Experimental Arm A1 and all 16 patients (100%) enrolled into Control Arm A2 of Phase II received trial treatment and had discontinued from the trial as of the final database lock date.

All 33 patients (100%) enrolled into Experimental Arm B1 and 16 of the 17 patients (94.1%) enrolled into Control Arm B2 of Phase II received trial treatment (one patient in Control Arm B2 went off trial prior to

receiving treatment). All enrolled patients in Cohort B had discontinued from the trial as of the final database lock date.

Summary of results and conclusions:

Efficacy Results:

The Phase I intent-to-treat (ITT) population (n=12) was equivalent to the safety population. The Phase II ITT population (n=98) served as the primary analysis population for efficacy endpoints, which included all randomized patients, regardless of whether trial medication was administered or not.

Phase I

Of the 6 patients in Cohort A (IO102 + pembrolizumab), none had complete response (CR), 3 (50%) had partial response (PR), 1 (16.7%) had stable disease (SD), and 2 (33.3%) had progressive disease (PD). The ORR (CR+PR) was 50%. The DCR (CR+PR+SD for ≥24 weeks) was 50%. Five patients (83.3%) died or experienced PD; PFS for these patients ranged from 1.1 to 39.2 months.

Of the 6 patients in Cohort B (IO102 + pembrolizumab + chemotherapy), none had CR, 1 patient (16.7%) had PR, 4 patients (66.7%) had SD, and 1 patient (16.7%) had PD. The ORR was 16.7%. The DCR was 50%. All 6 patients (100%) died or experienced PD; PFS for these patients ranged from 1.9 to 17.1 months.

Phase II Cohort A: PD-L1 TPS ≥50%

Of the 32 patients in Experimental Arm A1 (IO102 + pembrolizumab), 1 patient (3.1%) had CR, 14 patients (43.8%) had PR, 10 patients (31.3%) had SD, and 6 patients (18.8%) had PD. The median DOR was 33 months (95% CI 5.4; -).

Of the 16 patients in Control Arm A2 (pembrolizumab alone), 1 patient (6.3%) had CR, 6 patients (37.5%) had PR, and 7 patients (43.8%) had SD. The median DOR has not been reached at the time of this report.

Endpoint	**Experimental Arm A1** **N=32**	**Control Arm A2** **N=16**
Primary endpoint		
ORR	46.9% (15/32 patients)	43.8% (7/16 patients)
95% Confidence Interval	30.9%; 63.6%	23.1%; 66.8%
Secondary endpoints		
DCR	56.3% (18/32 patients)	50.0% (8/16 patients)
95% Confidence Interval	39.3%; 71.8%	28.0%; 72.0%
Median PFS	6.5 months (95% CI 3.9;14.7)	6.3 months (95% CI 3.9; 32)
Median OS	19 months (95% CI 15.0; -)	32 months (95% CI 16.6; -)

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Median TFST	10.3 months (95% CI 4.6; 23)	7.0 months (95% CI 4.8; 17)

Phase II Cohort B: PD-L1 TPS < 50%

Of the 33 patients in Experimental Arm B1 (IO102 + pembrolizumab + chemotherapy), none had CR, 13 patients (39.4%) had PR, 18 patients (54.5%) had SD, and 1 patient (3.0%) had PD. The median DOR was 15 months (95% CI 6.7; 20).

Of the 17 patients in Control Arm B2 (pembrolizumab + chemotherapy), none had CR, 9 patients (52.9%) had PR, 3 patients (17.6%) had SD, and 2 patients (11.8%) had PD. The median DOR was 8.5 months (95% CI 4.1; 21).

Endpoint	**Experimental Arm B1** **N=33**	**Control Arm B2** **N=17**
Primary endpoint		
ORR	39.4% (13/33 patients)	52.9% (9/17 patients)
95% Confidence Interval	24.7%; 56.3%	31.0%; 73.8%
Secondary endpoints		
DCR	72.7% (24/33 patients)	70.6% (12/17 patients)
95% Confidence Interval	55.8%; 84.9%	46.9%; 86.7%
Median PFS	10.0 months (95% CI 6.2;12.3)	10.1 months (95% CI 6.4; 15)
Median TFST	13.4 months (95% CI 10.4; 15.2)	10.7 months (95% CI 7.2; 19)

Subgroup analyses on pooled Phase I and Phase II Cohorts:

There was an imbalance in histological subtypes at study entry among patients enrolled in Cohort A in both phases of the study.

Among the 39 patients in the Experimental Arm A1, 14 patients (35.9%) had squamous cell carcinoma and 23 patients (59.0%) had adenocarcinoma. Of the 16 patients in the Control Arm A2, 3 patients (18.8%) had squamous cell carcinoma and 13 patients (81.3%) had adenocarcinoma. The proportion of patients with squamous cell carcinoma was much higher in the Experimental Arm A1. The response rate (ORR) in patients with squamous cell carcinoma was comparable between arms A1 and A2 (28.6% and 33.3%, respectively). The response rate in patients with adenocarcinoma was generally higher than in patients with squamous cell carcinoma, with a noticeable higher rate in the Experimental arm A1 compared to Control Arm A2 (56.5% and

46.2%, respectively). However, since the Experimental Arm A1 had more patients with squamous cell carcinoma, ORR in the Experimental Arm A1 did not differ significantly from ORR in the Control Arm A2.

	Adenocarcinoma N=23		**Squamous cell carcinoma N=14**	
	Experimental Arm A1	**Control Arm A2**	**Experimental Arm A1**	**Control Arm A2**
ORR, n (%)	13 (56.5%)	6 (46.2%)	4 (28.6%)	1 (33.3%)
Confidence interval	(34.5%, 76.8%)	(19.2%, 74.9%)	(8.4%, 58.1%)	(0.8%, 90.6%)

A similar imbalance was observed in TPS values among Cohort B patients in both phases. Of the 39 patients in the Experimental Arm B1, 20 patients were TPS <1% (51.3%) and 19 patients were TPS 1-49% (48.7%). Of the 17 patients in the Control Arm B2, 6 patients were TPS <1% (35.3%) and 11 patients were TPS 1-49% (64.7%). The proportion of TPS <1% was much higher in the Experimental arm B1 (51.3%) compared to the Control Arm B2 (35.3%). ORR in TPS <1% patients was generally lower than in patients with TPS 1-49%. This disproportion of TPS score in treatment arms contributed to unfavorable response rate in the Experimental Arm B1.

	TPS <1% N=26		**TPS 1-49% N=30**	
	Experimental Arm B1 N = 20	**Control Arm B2 N = 6**	**Experimental Arm B1 N = 19**	**Control Arm B2 N = 11**
ORR	15.0% (3/20 patients)	33.3% (2/6 patients)	57.9% (11/19 patients)	63.6% (7/11 patients)
Median PFS	7.1 months (95% CI 4.1; 10.9)	13 months (95% CI 5.9; NA)	10.6 months (95% CI 6.0; 17.1)	9.2 months (95% CI 2.0; 12.2)
Median OS	15.5 months (95% CI 12.8; 19.1)	21.3 months (95% CI 9.9; NA)	31 months (95% CI 11.5; NA)	18.6 months (95% CI 7.7; NA)

Regarding the trial's primary efficacy endpoint of ORR by RECIST 1.1 criteria, neither the 15/32 responses observed in the IO102 plus pembrolizumab arm, nor the 13/33 responses observed in the IO102 plus pembrolizumab plus chemotherapy arm are sufficient to recommend those arms according to the trial's decision rules.

Control and Experimental time-to-endpoint plots were generally superimposable. Results of exploratory analysis by iRECIST criteria were qualitatively similar to RECIST findings.

In summary, there is not enough evidence to suggest the addition of IO102 to the two standard regimens can improve efficacy from this study.

Safety Results:

The safety population (n=109) was used to summarize all safety parameters.

Safety of the IO102 combinations were explored for the first time in safety run-in cohorts of six patients where IO102 was combined with either pembrolizumab (Cohort A) or pembrolizumab and chemotherapy (Cohort B).

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Phase I

All 12 patients (100%) who were enrolled and received treatment in Phase I experienced at least one TEAE. TEAEs considered related to any trial treatment were experienced by 9 patients (75.0%), 3 of whom were in Cohort A and 6 of whom were in Cohort B.

Overall in Phase I, TEAEs assessed as serious were experienced by 5 patients (42%), 3 of whom were in Cohort A and 2 of whom were in Cohort B. One patient (8%) in Cohort B experienced a serious TEAE that was also considered related to any trial treatment. Eight patients (67%) experienced severe (Grade 3 or 4) TEAEs. One patient (8%) in Cohort B had a fatal (Grade 5) TEAE. Six patients (50%), 3 patients in each Cohort, had TEAEs leading to dose interruption of pembrolizumab. Five patients (42%) had TEAEs leading to discontinuation of any trial treatment, including discontinuation of IO102 in four patients (33%), discontinuation of pembrolizumab in four patients (33%), and discontinuation of pemetrexed in two patients (17%).

No DLTs were encountered in these cohorts, so the trial proceeded to the randomized portion of the trial.

Phase II

All 97 patients (100%) who were enrolled and received treatment in Phase II experienced at least one TEAE. TEAEs considered related to any trial treatment were experienced by 39 patients (81.3%) in Cohort A and 48 patients (98%) in Cohort B.

Experimental Arm A1

In Experimental Arm A1 of Phase II, 26 patients (81%) experienced a TEAE that was considered related to any trial treatment.. Thirteen patients (41%) experienced a TEAE that was assessed as serious, 2 (6%) of whom had a serious TEAE that was also considered related to any trial treatment. Seventeen patients (53%) experienced a severe (Grade 3 or 4) TEAE, and 1 patient (3%) experienced a Grade 5 (fatal) TEAE. Two patients (6%) experienced a TEAE that led to discontinuation of any trial treatment, including IO102 and pembrolizumab, and 12 patients (38%) experienced TEAEs leading to a pembrolizumab dose interruption. One patient (3%) had a COVID-19 infection.

Control Arm A2

In Control Arm A2 of Phase II, 13 patients (81%) experienced a TEAE that was considered related to any trial treatment. Five patients (31%) experienced a TEAE that was assessed as serious, none of whom had a serious TEAE that was also considered related to any trial treatment. Ten patients (63%) experienced a severe (Grade 3 or 4) TEAE, and 1 patient (6%) experienced a Grade 5 (fatal) TEAE. Two patients (13%) experienced a TEAE that led to discontinuation of pembrolizumab, and 10 patients (63%) experienced TEAEs leading to a pembrolizumab dose interruption. One patient (6%) had a COVID-19 infection.

Experimental Arm B1

In Experimental Arm B1 of Phase II, 32 patients (97.0%) experienced a TEAE that was considered related to any trial treatment. Fourteen patients (42.0%) experienced a TEAE that was assessed as serious, six of whom (18.0%) had a serious TEAE that was also considered related to any trial treatment. Twenty-four patients (73.0%) experienced a severe (Grade 3 or 4) TEAE, and 4 patients (12.0%) experienced a Grade 5 (fatal) TEAE. Twelve patients (36%) experienced a TEAE that led to discontinuation of any study treatment, including discontinuation of IO102 in 7 patients (21.0%), discontinuation of pembrolizumab in 7 patients (21.0%), discontinuation of carboplatin in 1 patient (3.0%), discontinuation of pemetrexed in 11 patients (33.0%).

Twenty-two patients (67.0%) experienced TEAEs leading to a pembrolizumab dose interruption. Two patients (6.0%) had a COVID-19 infection.

Control Arm B2

In Control Arm B2 of Phase II, 16 patients (100.0%) experienced a TEAE that was considered related to any trial treatment. Nine patients (56%) experienced a TEAE that was assessed as serious, six of whom (38.0%) had a serious TEAE that was also considered related to any trial treatment. Fifteen patients (94.0%) experienced a severe (Grade 3 or 4) TEAE. Four patients (25.0%) experienced a TEAE that led to discontinuation of any study treatment, including discontinuation of pembrolizumab in 4 patients (25.0%), discontinuation of carboplatin in 1 patient (6%), discontinuation of pemetrexed in 2 patients (13.0%). Nine patients (56%) experienced TEAEs leading to a pembrolizumab dose interruption. Three patients (19%) had a COVID-19 infection.

In both this safety run-in and the randomized portion of the trial, AEs encountered in arms with IO102 were similar in nature and frequency to those seen in the respective control arms and historically. The only consistently observed toxicities attributable to IO102 were injection-related reactions, all of which were low grade. No new safety signals for IO102 were detected in this study. The addition of IO102 to pembrolizumab did not result in an increase in immune-mediated toxicities and did not lead to increase in treatment discontinuation due to toxicity.

In summary, the addition of IO102 to standard therapies did not appreciably alter the safety profiles of those standard treatments, i.e., the addition of IO102 did not contribute toxicity to the regimen, with the exception of low severity local reactions at IO102 injection sites.

Conclusions:

Administration of IO102 in combination with either pembrolizumab alone or pembrolizumab and chemotherapy was found to:

- Be associated with an ORR of 47.4% in Experimental Arm A1 compared to an ORR of 43.8% in Control Arm A2, and an ORR of 39.4% in Experimental Arm B1 compared to an ORR of 52.9% in Control Arm B2.
- Have a similar safety profile to the respective Control Arms of pembrolizumab alone or pembrolizumab and chemotherapy, with AEs of a similar nature and frequency and no new safety signals detected.
- Be associated with predominantly Grade ≤2 IO102-related TEAEs, particularly injection-related reactions.
- Be associated with a rate of trial discontinuations due to treatment-related TEAEs of 6.3% in Experimental Arm A1 compared to 12.5% in Control Arm A2, and a rate of 21.2% in Experimental Arm B1 compared to 25.0% in Control Arm B2.
- Be associated with a comparable rate of 40.6% of patients with SAEs (regardless of causality) in Experimental Arm A1 compared to 31.3% in Control Arm A2, and 42.4% in Experimental Arm B1 compared to 56.3% in Control Arm B2.

Regarding baseline characteristics: The proportion of TPS <1% was much higher in the Experimental arm B1 (51.3%) compared to the Control Arm B2 (35.3%). ORR in TPS <1% patients was generally lower than in patients with TPS 1-49%. This disproportion of TPS score in treatment arms contributed to unfavorable response rate in the Experimental Arm B1.

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<tr><td colspan="3">It is concluded that IO102 was well tolerated in combination with either pembrolizumab alone or pembrolizumab and chemotherapy, though addition of IO102 to the two standard regimens did not affect their efficacy.</td></tr>
<tr><td colspan="3">Date and version of this report:

Version 1.0, 19 May 2023</td></tr>
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