IO102-012 INTERIM CLINICAL TRIAL REPORT - SYNOPSIS

Name of Sponsor: IO Biotech	**Individual trial table referring to part of the dossier** **Volume:** **Page:**	***(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 $IDO_{194-214}$ (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)

Principal/Coordinating Investigator name, number of trial centers and countries:

The trial included 17 different trial centers in the United Kingdom, The Netherlands, Germany, and Spain.

Coordinating Investigator:

- James Spicer, MD, Prof. Kings College London, UK.

Principal Investigators:

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Publication (references):

- Poster IASLC 2019 World Conference on Lung Cancer: Conquering Thoracic Cancers Worldwide: *A Phase I/II Trial of IO102 and Pembrolizumab with/without Chemotherapy as First Line Treatment of Metastatic NSCLC*, Provencio, M. *et al*. Journal of Thoracic Oncology, Volume 14, Issue 10, Supplement, October 2019, Page S643.
- Abstract Book of the European Lung Cancer Congress (ELCC) 10-13 April 2019, Geneva, Switzerland: *An open-label, randomized, phase I/II trial of IO102 and pembrolizumab, or IO102, pembrolizumab and chemotherapy, as first-line treatment for patients with metastatic non-small cell lung cancer*. Spicer, J. *et al*. Annals of Oncology, Volume 30, Supplement 2, April 2019, Pages ii65-ii66.

Trial period (years):	**Clinical phase:**
First patient on-trial date: 19 September 2018 Interim report database lock date: 12 March 2021	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).

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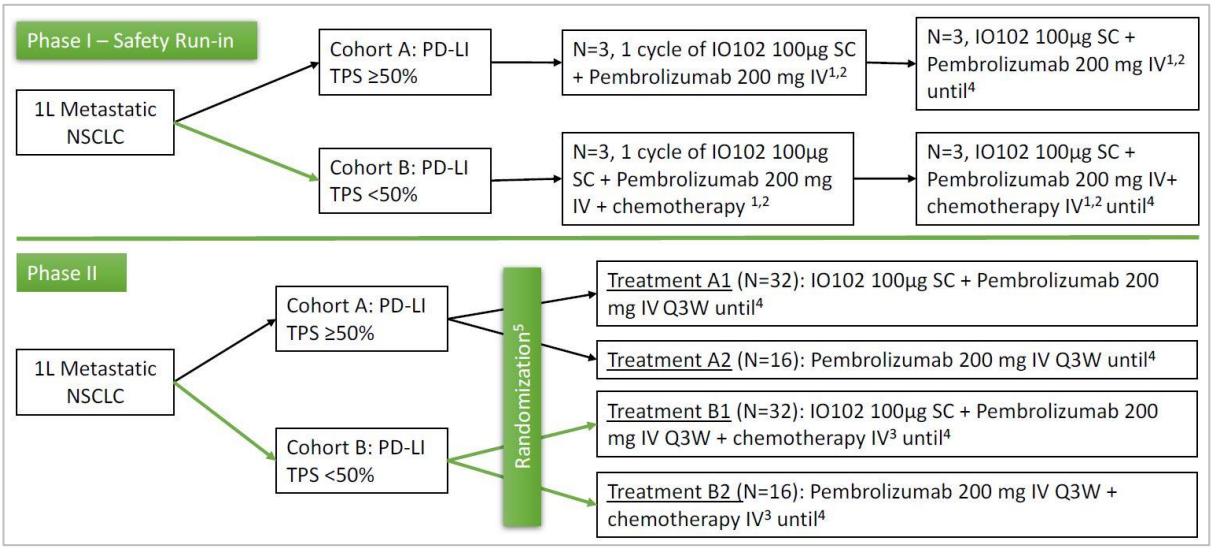
- To evaluate correlation of biomarkers and pharmacodynamic responses with trial treatment in archival and/or fresh tumor biopsy material and/or blood.

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). 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.

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A Safety Monitoring Committee (SMC) monitored the occurrence of any dose limiting toxicities (DLTs) in the Phase I Safety Run-in part of the trial.

The expected duration of the trial was 54 months.

Number of patients (planned and analyzed):

Number of patients planned:

Approximately 108 eligible patients were planned to be enrolled into the trial: 12 patients for Phase I and 96 patients for Phase II. For the Phase II part, 64 patients were required in the experimental arms to perform the efficacy analysis. Recruitment would remain open until the required number of patients were enrolled into the experimental arms of the Phase II part of the trial.

Twelve patients were planned to be enrolled in the Phase I part of the trial: six patients in Cohort A with high PD-L1 expression (defined as tumor proportion score [TPS] of ≥50%) to be treated with IO102 100 µg subcutaneous (SC) Q3W in combination with pembrolizumab 200 mg intravenous (IV) Q3W, and six patients in Cohort B with low PD-L1 expression (defined as TPS of <50%) to be treated with IO102 100 µg SC Q3W in combination with pembrolizumab 200 mg IV Q3W and chemotherapy doublet (carboplatin at a target area under the curve [AUC] of 5 mg/mL + pemetrexed at 500 mg/m^2) administered IV Q3W for 4 cycles, followed by pemetrexed maintenance if justified based on Investigator's judgment.

Ninety-six patients were planned to be enrolled in the Phase II part of the trial. Forty-eight patients with high PD-L1 expression (defined as TPS of ≥50%) were to be enrolled in Cohort A, randomized on a 2:1 basis into Treatment Arm A1 (32 patients) and Treatment Arm A2 (16 patients). Patients in Treatment Arm A1 were to be treated with IO102 100 µg SC Q3W in combination with pembrolizumab 200 mg IV Q3W. Patients in Treatment Arm A2 were to be treated with pembrolizumab 200 mg IV Q3W. Forty-eight patients with low PD-L1 expression (defined as TPS of <50%) were to be enrolled in Cohort B, randomized on a 2:1 basis into Treatment Arm B1 (32 patients) and Treatment Arm B2 (16 patients). Patients in Treatment Arm B1 were to be treated with IO102 100 µg SC Q3W in combination with pembrolizumab 200 mg IV Q3W and chemotherapy doublet (carboplatin at a target AUC of 5 mg/mL + pemetrexed at 500 mg/m^2) administered IV Q3W for 4 cycles, followed by pemetrexed maintenance if justified based on Investigator's judgment. Patients in Treatment Arm B2 were to be treated with pembrolizumab 200 mg IV Q3W and chemotherapy doublet (carboplatin at a target AUC of 5 mg/mL + pemetrexed at 500 mg/m^2) administered IV Q3W for 4 cycles, followed by pemetrexed maintenance if justified based on Investigator's judgment.

Number of patients analyzed:

A total of 12 patients were enrolled into Phase I; 6 patients in Cohort A and 6 patients in Cohort B. Seven of the 12 patients (58.3%) were male and 5 (41.7%) were female, and the median age of Phase I

patients was 61 years (range: 29-78 years). All 12 patients enrolled into Phase I received trial treatment(s) and were therefore included in the safety population.

A total of 98 patients were enrolled into Phase II of the trial; 48 patients within Cohort A and 50 patients within Cohort B. Of the 48 patients in Cohort A of Phase II, 32 patients were randomized the Experimental Arm A1 and 16 patients were randomized to the Control Arm A2. Of the 50 patients in Cohort B of Phase II, 33 patients were randomized to the Experimental Arm B1 and 17 patients were randomized to the Control Arm B2. Within Cohort A, 36 patients (75%) were male and 12 patients (25%) were female, and the median age of patients was 64 years (range: 49-82 years). Within Cohort B, 29 patients (58%) were male and 21 patients (42%) were female, and the median age of patients was 65 years (range: 41-80 years). All 48 patients enrolled into Cohort A of Phase II and 49 of the 50 patients enrolled into Cohort B of Phase II received trial treatment(s) and were therefore included in the safety population. One patient in Control Arm B2 of Phase II went off trial prior to receiving treatment and was therefore not included in the safety population.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Inclusion Criteria

1. Patients with histologically or cytologically confirmed metastatic NSCLC (Cohort A) or non-squamous NSCLC (Cohort B), who had not received prior systemic treatment for their metastatic disease.
   a) No known sensitizing epidermal growth factor receptor or anaplastic lymphoma kinase mutations.
   b) Solitary metastases had to be biopsied to confirm the diagnosis metastasis from NSCLC.
2. PD-L1 tumor expression of ≥50% (Cohort A) or <50% (Cohort B). PD-L1 tumor expression was to be confirmed prior to randomization using the DAKO 22C3 assay, using local/central services.
3. A male participant able to father a child had to agree to use contraception starting with the screening visit and through 120 days after last dose of pembrolizumab or 180 days after last dose of chemotherapy.
4. A female participant was eligible to participate if she was not pregnant not breastfeeding, and at least one of the following conditions applied:
   a) Not a woman of childbearing potential (WOCBP)
   b) A WOCBP who agreed to follow contraceptive guidance starting with the screening visit and through 120 days after last dose of pembrolizumab or 180 days after last dose of chemotherapy.

Note: A WOCBP i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods included hysterectomy, bilateral salpingectomy,

and bilateral oophorectomy. Tubal ligation was NOT a method of permanent sterilisation. A post-menopausal state was defined as no menses for 12 months without an alternative medical cause.

5. The participant (or legally acceptable representative if applicable) provided written informed consent for the trial in accordance with International Council for Harmonization Good Clinical Practice and local legislation prior to admission to the trial.
6. Was ≥18 years of age on day of signing informed consent.
7. Had measurable disease per RECIST 1.1 as assessed by local site Investigator/radiologist. Lesions situated in a previously irradiated area were considered measurable if progression had been demonstrated in such lesions.
8. Had provided a blood sample and archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. Formalin-fixed, paraffin embedded tissue blocks were preferred to slides.

Note: If archival tissue was available, it was preferred this was obtained ≤90 days prior to randomization. If using unstained cut slides, newly cut slides were to be used for the testing, within 14 days from the date slides were cut.

9. Had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.
10. Had adequate organ function as defined in Section 9.3.1. Specimens had to be collected within 10 days prior to the start of trial treatment.

Exclusion Criteria

1. A WOCBP who had a positive urine pregnancy test (e.g., within 72 hours) prior to treatment. If the urine test was positive or could not be confirmed as negative, a serum pregnancy test was required.
2. Had received prior therapy with an anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX40, CD137) and was discontinued from that treatment due to a Grade 3 or higher immune-related adverse event (AE).
3. Had received prior systemic anti-cancer therapy in the first line setting for the participant's metastatic disease (treatment with chemotherapy and/or radiation as part of neoadjuvant/adjuvant therapy was allowed as long as completed at least 6 months prior to diagnosis of metastatic disease).
4. Had received prior radiotherapy to the lung >30 Gy within 6 months of start of trial treatment. Participants had to have recovered from all radiation-related AEs, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout was permitted for palliative radiation (≤2 weeks of radiotherapy) to non-central nervous system (CNS) disease.
5. Had received a live vaccine within 30 days prior to the first dose of trial treatment. Examples of live vaccines included, but were not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin, and typhoid vaccine. Seasonal

influenza vaccines for injection are generally killed virus vaccines and were allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and were not allowed.

6. Was currently participating in or had participated in a trial of an investigational agent (e.g., small molecules, immunotherapy, chemotherapy monoclonal antibodies or any other experimental drug in the neoadjuvant or adjuvant setting) or had used an investigational device within 6 months prior to the first dose of trial treatment.

Note: Participants who had entered the follow-up phase of an investigational trial could participate as long as it had been 6 months after the last dose of the previous investigational agent.

7. Had a diagnosis of immunodeficiency or was receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
8. Had a known additional malignancy that was progressing or had required active treatment within the past 2 years.

Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin or carcinoma in situ (e.g., breast carcinoma, cervical cancer in situ) that had undergone potentially curative therapy were not excluded.

9. Had known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases could participate provided they were radiologically stable, i.e., without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging was to be performed during trial screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of trial treatment.
10. Had severe hypersensitivity (≥Grade 3) to IO102, pembrolizumab, carboplatin, pemetrexed and/or any of its excipients.
11. Had an active autoimmune disease that had required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) was not considered a form of systemic treatment and was allowed.
12. Had a history of (non-infectious) pneumonitis that required steroids or had current pneumonitis.
13. Had an active infection requiring systemic therapy.
14. Had a known history of human immunodeficiency virus (HIV) infection.

Note: No HIV testing was required unless mandated by local health authority.

15. Had a known history of Hepatitis B (defined as Hepatitis B surface antigen reactive) or known active Hepatitis C virus (HCV) (defined as HCV ribonucleic acid [qualitative] detected) infection.

Note: No testing for Hepatitis B and Hepatitis C was required unless mandated by local health authority.

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16. Had a history or current evidence of any condition, therapy, or laboratory abnormality that could confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or was not in the best interest of the patient to participate, in the opinion of the treating Investigator.
17. Had known psychiatric or substance abuse disorders that would interfere with cooperating with the requirements of the trial.
18. Was pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days for Cohort A and 180 days for Cohort B after last dose of trial treatment.
19. Had had an allogenic tissue/solid organ transplant.

Test product, dose and mode of administration, batch number(s):

The dose of IO102 studied in this trial was 100 µg administered as an SC injection Q3W.

IO102 was administered on Day 1 of each 3-week cycle for a maximum of 35 cycles. IO102 was also administered on Day 8 of the first two cycles. IO102 was administered 1 hour prior to pembrolizumab.

0.2 mg IO102 powder for solution was dissolved in 1 mL water for injection and subsequently emulsified with an adjuvant (Montanide ISA 51 VG).

Two batches of IO102 were used in the trial. The batch numbers used were as follows: 18C179-461 and 18C179-485.

Three batches of water for injection + Montanide were used in this trial. The batch numbers used were as follows: 20LHF013/2518449, 19173012/2587854, and 19173012/2587855.

Duration of treatment:

Patients could receive up to a maximum of 35 cycles of treatment in this study.

Within Cohort A of Phase I, patients received a median number of 11.5 cycles of IO102 and pembrolizumab (range: 1-29 cycles). Cohort A patients did not receive chemotherapy treatment.

Within Cohort B of Phase I, patients received a median number of 7 cycles of IO102 and pembrolizumab (range: 3-20 cycles). Cohort B patients also received a median number of 4 cycles of carboplatin (range: 3-4 cycles) and a median number of 6 pemetrexed cycles (range: 3-7 cycles).

In Phase II, Experimental Arm A1 patients received a median number of 10.5 cycles of IO102 and pembrolizumab (range: 1-33 cycles). Experimental Arm A1 patients did not receive chemotherapy treatment.

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Within Control Arm A2 of Phase II, patients received a median number of 7.5 cycles of pembrolizumab (range: 2-26 cycles). Control Arm A2 patients did not receive IO102 or chemotherapy treatment.

In Experimental Arm B1 of Phase II, patients received a median number of 11 cycles of IO102 and pembrolizumab (range: 1-25 cycles). Experimental Arm B1 patients also received a median of 4 cycles of carboplatin (range: 1-4 cycles) and a median of 7 cycles of pemetrexed (range: 1-25 cycles).

Within Control Arm B2 of Phase II, patients received a median number of 11.5 cycles of pembrolizumab (range: 1-23 cycles), a median of 4 cycles of carboplatin (range: 1-4 cycles), and a median of 8 cycles of pemetrexed (range: 1-23 cycles). Control Arm B2 patients did not receive IO102 treatment.

Reference therapy, dose and mode of administration, batch number(s):

Pembrolizumab – The selected dose of pembrolizumab for this trial was 200 mg Q3W administered on Day 1 of each 3-week cycle for a maximum of 35 cycles. Pembrolizumab was administered using a 30-minute IV infusion that had to be completed at least 30 minutes prior to pre-medication for carboplatin and pemetrexed.

Three batches of pembrolizumab were used in the trial. The batch numbers used were as follows: 0000675108, 0000883890, and 0001051054.

Pemetrexed – Pemetrexed was administered at a dose of 500 mg/m^2 as an IV infusion over 10 minutes Q3W until progression or unacceptable AEs. Pemetrexed was administered at least one hour following completion of administration of pembrolizumab.

Five batches of pemetrexed were used in the trial. The batch numbers used were as follows: 1700076C, 1800151A, 1901255B, 1901254A, and 1901254B.

Carboplatin – Carboplatin was administered at a target AUC of 5 mg/mL/min as an IV infusion over 15-60 minutes Q3W for 4 cycles immediately after pemetrexed.

Three batches of carboplatin were used in the trial. The batch numbers used were as follows: W08034, PX03682, and PY02059.

Criteria for evaluation:

Efficacy:

The primary efficacy endpoint of ORR was evaluated according to RECIST version 1.1.

Secondary efficacy endpoints included DCR, time to response (TTR), DOR, PFS, OS, and time from first treatment to commencement of first subsequent treatment or death (TFST). ORR, DOR, PFS and OS were also assessed by baseline PD-L1 expression.

Exploratory efficacy endpoints included assessing time to event parameters according to iRECIST.

Pharmacodynamic:

- Immunoscore (IS) in tumor tissue
- Co-expression of IDO and PD-L1 in tumor tissue
- Tumor mutational burden (TMB)
- Immunomonitoring using blood samples (immunogenic response to IO102 and pembrolizumab e.g., regulatory T-cell analysis, natural killer analysis, macrophage analysis, immunogenic response to combination of IO102 and pembrolizumab)

Safety:

Safety data were summarized for the safety population (all patients who received any trial treatment (IO102 and/or pembrolizumab), regardless of the duration of treatment. This data included occurrence of DLTs, incidence and severity of AEs and serious adverse events (SAEs), including events of clinical interest, ECOG performance status, physical examination, vital signs, electrocardiogram and changes in laboratory values (clinical chemistry and hematology). Common Terminology Criteria for Adverse Events v4.03 was used for grading AEs.

Statistical methods:

All patient data, efficacy, and safety data are summarized. The data have been presented and analyzed separately for the Phase I and Phase II parts of the trial.

For the Phase II part, Cohort A and Cohort B, the null hypothesis that the true ORR <40% was tested against the alternative hypothesis that the true ORR >60%. The null hypothesis would be rejected if 17 or more responses were observed in a cohort. The control arm was an internal control to make sure the population of patients selected in the trial had a similar response rate.

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 19.6 months.

Of the 6 patients in Cohort B (IO102 + pembrolizumab + chemotherapy), none had CR, 1 (16.7%) had PR, 4 (66.7%) had SD, and 1 (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), none had CR, 15 (46.9%) had PR, 10 (31.3%) had SD, and 6 (18.8%) had PD. Of the responding patients, 10 out of 15 were still responding at the time of data cut-off. Therefore, the median DOR was not reached.

Of the 16 patients in Control Arm A2 (pembrolizumab alone), 1 (6.3%) had CR, 6 (37.5%) had PR, and 7 (43.8%) had SD. Of the responding patients, 5 out of 7 were still responding at the time of data cut-off. Therefore, the median DOR was not reached.

Endpoint	**Experimental Arm A1 N=32**	**Control Arm A2 N=16**
Primary Endpoint		
ORR	46.9% (15/32 patients)	43.8% (7/16 patients)
Secondary Endpoints		
DCR	56.3% (18/32 patients)	50% (8/16 patients)
Median PFS	6.5 months (95% CI 3.9;14.3)	6.3 months (95% CI 3.9; -)
Median OS	Not yet reached	Not yet reached
Median TFST	10.3 months	10.1 months

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

Of the 33 patients in Experimental Arm B1 (IO102 + pembrolizumab + chemotherapy), none had CR, 12 (36.4%) had PR, 18 (54.5%) had SD, and 2 (6.1%) had PD. Of the responding patients, 7 out of 12 were still responding at the time of data cut-off. Therefore, the median DOR was not reached.

Of the 17 patients in Control Arm B2 (pembrolizumab + chemotherapy), none had CR, 9 (52.9%) had PR, 3 (17.6%) had SD, and 2 (11.8%) had PD. The median DOR was 8.5 months. Of the 9 responding patients, 3 were still responding at the time of data cut-off.

Endpoint	Experimental Arm B1 N=33	Control Arm B2 N=17
Primary Endpoint		
ORR	36.4% (12/33 patients)	52.9% (9/17 patients)
Secondary Endpoints		
ORR by baseline PD-L1 <1%	17.6% (3/17 patients)	33.3% (2/6 patients)
ORR by baseline PD-L1 between 1-49%	56.3% (9/16 patients)	63.6% (7/11 patients)
DCR	66.7% (22/33 patients)	70.6% (12/17 patients)
Median PFS	9.0 months (95% CI 6.0;12.4)	10.1 months (95% CI 6.4; -)
Median PFS by baseline PD-L1 <1%	8.4 months (95% CI 5.1;12.3)	Could not be calculated
Median PFS by baseline PD-L1 between 1-49%	10.7 months (95% CI 3.5; -)	9.2 months (95% CI 2.0; 12.2)
Median OS	Not yet reached	14.1 months
Median OS by baseline PD-L1 <1%	Not yet reached	14.1 months
Median OS by baseline PD-L1 between 1-49%	Not yet reached	12.8 months
Median TFST	12.8 months	11.9 months

Pharmacodynamic Results:

The only biomarker significantly associated with response was TMB within Experimental Cohort B1. Neither variation in T cell density/IS nor IDO level at baseline were differentiators for clinical response. There was no difference in baseline Kyn/Trp ratio across all the cohorts, nor was there a correlation of baseline Kyn/Trp with clinical response.

Analysis of peripheral blood mononuclear cells for IO102-specific T cells by interferon gamma (IFN-γ) enzyme linked immunosorbent spot (ELISPOT) was limited by paucity of viable specimens due to collection and shipping issues. One patient in each Control Arm (A2 and B2) demonstrated pre-existing responses at baseline. Induction of IO102 response was seen in the Experimental Arms (1 of 1 evaluable patient in A1, 3 of 6 evaluable patients in B1) and Control Arms (1 of 1 evaluable patient in A2, and 1 of 3 evaluable patients in B2) of both cohorts. The small number of observations makes it challenging to determine whether there is an association between experimental treatment and IO102 response.

Safety Results:

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

Phase I

Six patients have been exposed to IO102 + pembrolizumab within Cohort A of Phase I of the IO102-012 trial. All 6 patients (100%) reported at least 1 treatment emergent adverse event (TEAE), 3 of whom

(50%) experienced at least 1 TEAE that was considered related to any trial treatment. Three patients (50%) experienced SAEs, all of which were assessed as unrelated to trial treatment. One patient (16.7%) experienced a treatment-related TEAE which led to discontinuation of any trial treatment.

Six patients have been exposed to IO102 + pembrolizumab + chemotherapy within Cohort B of Phase I of the IO102-012 trial. All 6 patients (100%) reported at least 1 TEAE, as well as at least 1 TEAE that was considered related to any trial treatment. Two patients (33.3%) experienced SAEs, 1 of whom died due to a fatal SAE of diabetic ketoacidosis (assessed as unrelated to any trial treatment). Two patients (33.3%) experienced treatment-related TEAEs which led to discontinuation of any trial treatment.

Phase II Experimental Arm A1

Thirty-two patients have been exposed to IO102 + pembrolizumab within Experimental Arm A1 of Phase II of the IO102-012 trial. All 32 patients (100%) reported at least 1 TEAE, 25 of whom (78.1%) experienced at least 1 TEAE that was considered related to any trial treatment. Thirteen patients (40.6%) experienced SAEs during the trial, which were most commonly reported in the infections and infestations SOC (7 patients; 21.9%). One patient (3.1%) experienced treatment-related TEAEs which led to discontinuation of any trial treatment. One patient (3.1%) died due to a fatal SAE of respiratory deterioration due to COVID-19 (assessed as unrelated to trial treatments).

Phase II Control Arm A2

Sixteen patients have been exposed to pembrolizumab within Control Arm A2 of Phase II of the IO102-012 trial. All 16 patients (100%) reported at least 1 TEAE, 13 of whom (81.3%) experienced at least 1 TEAE that was considered related to trial treatment. Five patients (31.3%) experienced SAEs, which were most commonly reported in the infections and infestations SOC (4 patients; 25%). One patient (6.25%) experienced a treatment-related TEAE which led to discontinuation of trial treatment. One patient died due to a fatal SAE of respiratory infection (assessed as unrelated to trial treatment).

Phase II Experimental Arm B1

Thirty-three patients have been exposed to IO102 + pembrolizumab + chemotherapy within Experimental Arm B1 of Phase II of the IO102-012 trial. All 33 patients (100%) reported at least 1 TEAE, 32 of whom (97%) experienced at least 1 TEAE that was considered related to any trial treatment. Thirteen patients (39.4%) experienced SAEs during the trial, which were most commonly reported in the infections and infestations SOC (7 patients; 21.1%). Six patients (18.2%) experienced treatment-related TEAEs which led to discontinuation of any trial treatment. Two patients (6.06%) died due to fatal SAEs (bacterial endocarditis and ileus), both of which were assessed as unrelated to trial treatments.

Name of Sponsor: IO Biotech	Individual trial table referring to part of the dossier Volume: Page:	*(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 $IDO_{194-214}$ (DTLLKALLEIASCLEKALQVF).		

Phase II Control Arm B2

Sixteen patients have been exposed to pembrolizumab + chemotherapy within Control Arm B2 of Phase II of the IO102-012 trial. All 16 patients (100%) reported at least 1 TEAE, 15 of whom (94%) experienced at least 1 TEAE that was considered related to any trial treatment. Nine patients (56.3%) experienced SAEs, which were most commonly reported in the infections and infestations SOC (5 patients; 31.3%). Three patients (18.8%) experienced treatment-related TEAEs which led to discontinuation of any trial treatment.

In summary, across the trial as a whole, 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 46.9% in Experimental Arm A1 compared to an ORR of 43.8% in Control Arm A2, and an ORR of 36.4% 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 3.1% in Experimental Arm A1 compared to 6.25% in Control Arm A2, and a rate of 18.2% in Experimental Arm B1 compared to 18.8% in Control Arm B2.
- Be associated with a rate of 40.6% of patients with SAEs (regardless of causality) in Experimental Arm A1 compared to 31.3% in Control Arm B2, and 39.4% in Experimental Arm B1 compared to 56.3% in Control Arm B2.

Biomarkers:

- Tissue based: The only biomarker significantly associated with response was TMB within Experimental Arm B1. Neither variation in T cell density/IS nor IDO level at baseline were differentiators for clinical response. There was no difference in baseline Kyn/Trp ratio across all the cohorts, nor was there a correlation of baseline Kyn/Trp with clinical response.
- Blood based: Analysis of peripheral blood mononuclear cells for IO102-specific T cells by IFN-γ ELISPOT was limited by paucity of viable specimens due to collection and shipping issues; no correlation with response was evident.

<table>
<tr><td>Name of Sponsor:

IO Biotech</td><td rowspan="3">Individual trial table referring to part of the dossier

Volume:

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<tr><td>Name of finished product:

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IO102: an indoleamine 2,3-dioxygenase (IDO) cancer vaccine. IO102 peptide sequence is $IDO_{194-214}$ (DTLLKALLEIASCLEKALQVF).</td></tr>
<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, dated 12 October 2022</td></tr>
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