An open-label, randomized, Phase 3 clinical trial of IO102-IO103 in combination with pembrolizumab versus pembrolizumab alone in patients with previously untreated, unresectable, or metastatic (advanced) melanoma

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This study has been transitioned to CTIS with ID 2024-511996-13-00 check the CTIS register for the current data. The primary objective is to investigate the efficacy of IO102-IO103 in combination with pembrolizumab (compared with pembrolizumab alone…

Ethical review	Approved WMO
Status	Pending
Health condition type	Skin neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON53663

Source
ToetsingOnline

Brief title
IO102-IO103 and/or Pembrolizumab in Advanced Melanoma

Condition

- Skin neoplasms malignant and unspecified

Synonym
melanoma, Skin cancer

Research involving
Human

Sponsors and support

Primary sponsor: IO Biotech ApS
Source(s) of monetary or material Support: Industry

Intervention

Keyword: IO102-IO103, Melanoma, Pembrolizumab, Skin cancer

Outcome measures

Primary outcome

PFS, defined as the time from randomization to the first documented disease progression (based on Independent Review Committee (IRC) in accordance with RECIST v1.1) or death from any cause. Patients who have not progressed or died at the time of analysis will be censored at the date of assessment from their last disease assessment.

Secondary outcome

• Overall Response Rate (ORR) defined as the percentage of patients achieving a confirmed partial response (PR) or confirmed complete response (CR). ORR will be determined by the IRC in accordance with RECIST v1.1.

• OS, defined as the time from randomization until death from any cause. Patients not known to have died will be censored at the date they were last known to be alive

• Duration of Response (DoR) based on IRC

• Time to Response (TTR) based on IRC

• Time to Complete Response (TTCR) based on IRC

• Disease Control Rate (DCR) based on IRC

• PFS and ORR, which will be assessed by the investigator according to RECIST

v1.1

Study description

Background summary

Cancer cells are naturally attacked by cells of the immune system, including cytotoxic T- cells. Cancer cells can induce a state of tolerance whereby they can escape this immune system response. This effect is brought about by many different mechanisms; some of the most important are through overexpression of the programmed death protein-1 (PD-1) and programmed death-ligand 1 (PD-L1) molecules and the metabolic enzyme indoleamine 2,3-dioxygenase (IDO). The PD-1 receptor is expressed on various cells, including T- cells. The blocking of PD-1 on Tcells
by PD-1 blocking antibodies protects the T cells from the inactivation signal from PD-L1 expressed by cancer cells or immune regulatory cells. In treatment-naive patients with advanced melanoma, pembrolizumab (a PD-1 blocking antibody) has previously been shown to provide a clinical response rate of 45%. Spontaneous T*cell reactivity against PD-L1 and IDO has been identified in the tumor microenvironment and in the peripheral blood of various cancer patients and healthy donors. The IDO reactive CD8+ T-cells were cytotoxic and could kill both cancer cells and immune regulatory dendritic cells in vitro. The PD-L1 reactive CD8+ T-cells were also cytotoxic and able to kill cancer cells and myeloid derived suppressor cells (MDSCs). Therefore, boosting specific T-cells that recognize immune regulatory proteins, such as IDO and PD-L1, may directly modulate immune regulation. Due to the distinctive mechanisms of action, the combination of treatment with a monoclonal antibody (mAb) targeting PD-1 and IDO + PD-L1 peptides is hypothesized to have synergistic effects. There is nothing to suggest that combining pembrolizumab with the experimental IDO and PD-L1 peptides should be more toxic than treatment with pembrolizumab alone. The PD-L1 peptide (PD-L19-27; IO103) and IDO peptide (IDO194*214; IO102) both contain CD8+ T-cell epitopes as well as CD4+ T-cell epitopes. The PD*L1 and IDO peptides boosts the natural immunity mediated by PD-L1 and IDO specific T-cells. These can attack and kill regulatory immune cells and cancer cells, as well as support additional anticancer immunity by the release of helper cytokines.
In vivo proof-of-concept (PoC) studies in syngeneic mouse tumor models reveal that IDO-targeting immunotherapeutic induces expansion of IDO-specific T-cells in mice, leading to demonstrable antitumor therapeutic responses accompanied by reduction of IDO+ immune suppressive cells in the tumor. In addition, efficacy of IDO in a syngeneic mouse colon carcinoma model, CT26, is further improved by coadministration of anti-PD-1 antibody. Currently, one ongoing trial

investigates IO102-IO103 in combination with nivolumab (PD-1 blocking antibody) standard of care in patients with melanoma. The clinical trial is a Phase 1/2 trial and includes 30 patients with metastatic melanoma in a first line setting (NCT03047928, MM1636). This ongoing, open-label, single-center trial started in October 2017 and is investigating safety and efficacy of combination therapy with nivolumab and the IDO/PD-L1 (IO102-IO103) dual-antigen immunotherapeutic. Data from this trial has been reported and shows encouraging efficacy and a manageable safety profile.
A summary of efficacy outcomes (5 October 2020) with a median duration of follow-up of 23 months showed a confirmed response (PR or CR) was observed in 24 of 30 (80%) patients, of whom 13 of 30 (43.3%) patients experienced a CR. An updated summary of outcomes was presented during AACR 2022 with a cutoff of 1 December 2021, the median progression free survival (mPFS) was 25.3 months and median overall survival (mOS) was not reached. The three-year survival probability is 73%.

Study objective

This study has been transitioned to CTIS with ID 2024-511996-13-00 check the CTIS register for the current data.

The primary objective is to investigate the efficacy of IO102-IO103 in combination with pembrolizumab (compared with pembrolizumab alone) in terms of progression-free survival (PFS). The secondary objectives are to further explore the efficacy of IO102-IO103 in combination with pembrolizumab compared with pembrolizumab alone in terms of ORR, OS, and CRR to investigate the safety and tolerability of the treatment.

Study design

This clinical trial includes an initial safety evaluation of IO102-IO103 + pembrolizumab and will be conducted approximately after the first 20 patients have been randomized and received >=1 cycle to allow >=10 patients receiving IO102-IO103+pembrolizumab to be evaluated.

Patients will be stratified based on the following factors:
• Disease stage: Stage III (unresectable) and IV M1a-b vs stage IV M1c-d
• Proto-oncogene B-Raf (BRAFV600) mutation status: mutated vs wild type

All patients will receive pembrolizumab 200 mg intravenous (IV) every three weeks (Q3W) for a maximum of 35 cycles (up to 2 years treatment).
Patients randomized to IO102-IO103 will also be given IO102-IO103 subcutaneous (SC) Q3W. The dose of each of IO102 and IO103 will be 85 *g. Each patient can be treated for a maximum of 37 administrations in total (up to 2 years of treatment).
An independent data monitoring committee (IDMC) will monitor the occurrence of

emerging adverse events (AEs). The IDMC charter will specify further details.

The trial will screen a total of approximately 500 patients and randomize 380 patients in approximately 100-125 sites in around 20 countries. Recruitment will remain open until the required number of patients are randomized into the trial. The total duration of the trial is approximately 70 months.

The overall trial begins when the first patient signs the informed consent form. The overall trial ends after the final overall survival (OS) follow-up analysis. Any patient remaining on treatment at this time will continue to receive treatment for up to 35 (Q3W) cycles.
Following completion of trial treatment, patients are to be followed up after trial treatment every 24 weeks for disease progression (if applicable) and until the final survival update or death (whichever is earlier).

Intervention

Group 1: IO102-IO103: SC administration (IO102 85 µg and IO103 85 µg Q3W in combination with pembrolizumab (IV administration 200 mg Q3W).
Group 2: Pembrolizumab: IV administration (200 mg Q3W).

Study burden and risks

A subject will undergo extra examinations and tests which make the visits last longer than the subject is used to. Additionally, participation in this study may affect the subject's eligibility for enrolling in a subsequent clinical trial.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Histologically or cytologically confirmed stage III (unresectable) or stage IV melanoma, as per American Joint Committee on Cancer 8th edition guidelines not amenable to local therapy
- Patients are treatment naive, that is, no previous systemic anticancer therapy for unresectable or metastatic melanoma. For clarification, the following patients are eligible:
- Patients with proto-oncogene B-Raf (BRAFV600) mutation-positive melanoma are eligible if treatment naive and without rapidly progressive disease as per investigator assessment. Documented BRAFV600 mutation status must be available from all patients prior to trial entry.
- Patients who have received previous adjuvant and/or neoadjuvant therapy with targeted therapy or immune therapy are eligible if administered the last dose at least 6 months before inclusion in this trial (randomization), and if relapse did not occur during active treatment or within 6 months of treatment discontinuation.
- ECOG performance status score 0 or 1 assessed within 10 days before randomization
- At least 1 measurable lesion (not a cutaneous lesion) according to response evaluation criteria for solid tumors (RECIST v1.1) and confirmed by IRC.
- Provision of archival (obtained within 3 months), or newly acquired biopsy tissue not previously irradiated, and blood at screening for biomarker assessments. Formalin-fixed, paraffin embedded (FFPE) tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue.
- Patients are able and willing to provide written informed consent for the trial in accordance with ICH-GCP and local legislation before admission to the trial.
- Other protocol defined inclusion criteria may apply.

Exclusion criteria

- Uveal/ocular, acral or mucosal melanoma
- Patients with known or suspected central nervous system (CNS) metastases or with the CNS as the only site of active disease are excluded with the following exception:
* Patients with controlled (stable) brain metastases will be allowed to enroll (subject to baseline confirmation). Controlled (stable) brain metastases are defined as those with no radiographic progression for at least 4 weeks after radiation and/or surgical treatment at the time of signed informed consent. Patients must have been off steroids for at least 2 weeks before signed informed consent and have no new or progressive neurological signs and symptoms.
- Patient has received previous radiotherapy within 2 weeks of start of trial treatment (visit 2). Patients must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (<=2 weeks of radiotherapy) to non-CNS disease.
- Patients with BRAFV600-positive disease who are experiencing rapidly progressing disease and/or have received standard first-line therapy with BRAF and/or MEK inhibitor for unresectable or metastatic disease
- Received a live or live-attenuated vaccine within 30 days before the first dose of trial treatment. Patients are also prohibited from receiving live or attenuated vaccine(s) throughout the duration of protocol therapy and/or within 90 days of the last dose of protocol therapy. Administration of killed vaccines, mRNA based (e.g., covid-19) and vector-based vaccines are allowed.
- Other protocol defined exclusion criteria may apply.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-07-2022
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	IO102-IO103 + Montanide ISA 51 VG Sterile
Generic name:	IO102-IO103 + Montanide ISA 51 VG Sterile
Product type:	Medicine
Brand name:	Keytruda
Generic name:	Pembrolizumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	07-03-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	22-04-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	11-05-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-05-2022
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	02-08-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-08-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-10-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-10-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-12-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-01-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-03-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-03-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-06-2023
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	26-06-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-12-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-02-2024
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2024-511996-13-00
EudraCT	EUCTR2021-004594-32-NL
ClinicalTrials.gov	NCT05155254
CCMO	NL79874.041.22