Clinical Study Report Synopsis	
Drug Substance	IPH5201
Study Code	D6770C00001
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NCT Number	04261075

A Phase 1, First-in-Human, Multicenter, Open-label, Dose escalation Study of IPH5201 as Monotherapy or in Combination with Durvalumab ± Oleclumab in Advanced Solid Tumors

Study dates:

Date of early study termination: 16 June 2022. The Phase I program was halted due to business strategy decisions, not due to any safety concerns.

First participant enrolled: 03 March 2020

Last participant last visit: 16 June 2022

The analyses presented in this report are based on a clinical data lock date of 21 October 2022

Phase of development:

Clinical pharmacology (I)

International Co-ordinating Investigator:

PPD
CCI
CCI
CCI CCI
CCI

Sponsor's Responsible Medical Officer:

PPD
PPD, Global Clinical Lead Early Global Development
Kloosterstraat
5349 AB Oss
The Netherlands

This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents.

Study center(s)

Participants received study treatment at 8 centers in 4 countries worldwide.

Publications

At the time of writing this report, the following publications have been published:

Imbimbo M, Hollebecque A, Italiano A, McKean M, Macarulla T, Castanon E, et al. IPH5201 as monotherapy or in combination with durvalumab (D) in advanced solid tumours. Annals of Oncology 2022;16 (suppl_1):100104.

Powderly J, Bendell JC, Carneiro BA, Italiano A, Macarulla Mercade T, Castanon Alvarez E, et al. A phase I, first-in-human, multicenter, open-label, dose-escalation study of IPH5201 as monotherapy or in combination with durvalumab ± oleclumab in advanced solid tumours. Annals of Oncology 2020;31 (suppl_4):S728-29.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate safety and tolerability, to determine MTD, RP2D, or HPDD of IPH5201 when administered as monotherapy or in combination with durvalumab ± oleclumab in subjects with advanced solid tumors	Incidence of AEs, SAEs, DLTs, abnormal laboratory parameters, abnormal vital signs, and abnormal ECG results
Secondary	
To evaluate the preliminary antitumor activity of IPH5201 in subjects with advanced solid tumors when administered as monotherapy or in combination with durvalumab ± oleclumab	OR (RECIST v1.1) DC (RECIST v1.1)
To characterize the PK of IPH5201 as monotherapy and in combination with durvalumab ± oleclumab	Systemic PK of IPH5201 Serum IPH5201 concentrations
To determine the PK of durvalumab and oleclumab when administered in combination with IPH5201	Serum trough concentrations (durvalumab) Serum trough concentrations (oleclumab)
To determine the immunogenicity of IPH5201 as monotherapy and in combination with durvalumab ± oleclumab	Incidence of antidrug antibodies (IPH5201)
To determine the immunogenicity of durvalumab in combination with IPH5201 ± oleclumab	Incidence of antidrug antibodies (durvalumab)
To determine the immunogenicity of oleclumab in combination with IPH5201 + durvalumab	Incidence of antidrug antibodies (oleclumab)

See Section 8 of the CSP for exploratory endpoints.

AE = adverse event; CSP = Clinical Study Protocol; DC = disease control; DLT = dose-limiting toxicity; ECG = electrocardiogram; HPDD = highest protocol-defined dose (in the absence of establishing the MTD); MTD = maximum tolerated dose; OR = objective response; PK = pharmacokinetics; CCI [redacted] CCI [redacted]; RP2D = recommended Phase 2 dose; SAE = serious adverse event.

Study design

This was a Phase I first-in-human, multicenter, open-label, dose-escalation study to evaluate the safety, tolerability, antitumor activity, pharmacokinetics, and immunogenicity of IPH5201 in adult participants with advanced solid tumors when administered as a monotherapy or in combination with durvalumab ± oleclumab. Treatment with IPH5201 in combination with oleclumab was not initiated due to an overall company strategy decision to halt the Phase I program. This decision was not due to safety concerns and a separate Phase II study, sponsored by Innate Pharma, is ongoing (NCT05742607).

Target population and sample size

The study population included adult participants, ≥ 18 years of age, with histologically or cytologically confirmed advanced solid tumors (including CCI and CCI) that were refractory to standard therapy or for which no standard therapy exists.

The study was planned to consist of 3 separate dose-escalation parts:

- Part 1: In the IPH5201 monotherapy dose-escalation part, participants with advanced solid tumors were to receive 1 of 4 planned dose levels of IPH5201 (CCI CCI) via CCI on Day 1 then every 3 weeks (Q3W).
- Part 2: In the IPH5201 plus durvalumab combination therapy dose-escalation part, participants with advanced solid tumors were to receive 1 of 3 dose levels of IPH5201 (CCI) and CCI durvalumab via CCI on Day 1 then Q3W.
- Part 3: In the IPH5201 plus durvalumab and oleclumab combination therapy dose-escalation part, participants with CCI were to receive 1 of 3 dose levels of IPH5201 (CCI), CCI durvalumab, and CCI oleclumab via CCI Q3W, all drugs administered on Day 1.

The study was designed to enroll a maximum of CCI in the dose-escalation phase and additional participants may have been enrolled if additional dose levels or treatment schedules were to be explored. CCI

Investigational product and comparator(s): dosage, mode of administration and batch numbers

CCI

Refer to Appendix 16.1.6 for batch numbers used in this study.

Duration of treatment

CCI [redacted]

Statistical methods

Refer to Appendix 16.1.1 for the Clinical Study Protocol and refer to Appendix 16.1.9 for the Statistical Analysis Plan.

Study population

A total of 75 participants were enrolled (signed informed consent) at 8 study centers across 4 countries. Of these 75 participants, 18 were screen failures and did not receive treatment. Among the remaining 57 participants, 38 were assigned to IPH5201 monotherapy, and 19 were assigned to IPH5201 in combination with durvalumab and received treatment. The most common reason for discontinuation of both IPH5201 and durvalumab was confirmed PD (93.0% of participants treated with IPH5201 monotherapy and 89.5% of participants treated with IPH5201 in combination with durvalumab). The most common end of study status was death, in 40 (70.2%) participants; 38 of these deaths were due to disease under investigation.

Summary of efficacy results

Overall, no response was seen in participants treated with either IPH5201 monotherapy or IPH5201 in combination with durvalumab, however 23/57 participants (40.4%) had a best overall response of stable disease. A total of 18/38 participants treated with IPH5201 monotherapy had a best overall response (BoR) of stable disease (SD) and 5/19 participants treated with IPH5201 in combination with durvalumab had a BoR of SD.

Summary of pharmacokinetic results

Pharmacokinetic data will be presented in a Clinical Study Report (CSR) Addendum.

Summary of safety results

During the study, no maximum tolerated dose (MTD) was declared; one patient in the combination cohort experienced a dose-limiting toxicity at a dose of CCI [redacted] IPH5201 (IPH5201 CCI [redacted] in combination with durvalumab CCI [redacted] Q3W). The highest protocol-defined dose (HPDD) of CCI [redacted] IV Q3W was reached for both IPH5201 monotherapy and in combination with durvalumab (CCI [redacted] Q3W). This HPDD has been carried forward into the ongoing Phase II study with IPH5201.

Overall, the median duration of exposure to IPH5201 was 9.29 weeks (range: 3.0 to 66.1 weeks) and overall, the median duration of exposure to durvalumab was 8.71 weeks

(range: 3.0 to 66.1 weeks). There was a low incidence of dose interruptions or omissions in all treatment cohorts.

Overall, adverse events (AEs) were reported for CCI. A total of CCI had AEs of Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher. No AEs with fatal outcome were reported in this study and a total of CCI had a serious adverse event. The number of participants who had an AE that led to discontinuation was low. Overall, CCI (35.1%) experienced at least one adverse event of special interest (AESI) for IPH5201 and CCI) experienced at least one AESI/adverse event of possible interest (AEPI) for durvalumab.

Overall, the most frequently reported (occurring in ≥ 15% of participants) AEs were fatigue (CCI), CCI (CCI), CCI CCI), CCI CCI

In total, 38 (66.7%) participants had at least one AE causally-related to any treatment, in the opinion of the Investigator. CCI

CCI; 38 (66.7%) participants due to the disease under investigation.

Conclusion(s)

- IPH5201 was well tolerated when used alone or in combination with durvalumab (CCI Q3W) up to a dose of CCI Q3W.
- The safety profile was manageable, with the most common (occurring in ≥ 15% of participants) treatment-related AEs being infusion related reactions and fatigue; no new safety signals were identified beyond those observed with durvalumab monotherapy.
- No MTD was identified, one patient in the combination cohort experienced a dose-limiting toxicity at dose of CCI (IPH5201 CCI in combination with durvalumab CCI Q3W). The HPDD of CCI IV Q3W was reached for both IPH5201 monotherapy and combination with durvalumab (CCI Q3W), both administered on Day 1. This HPDD has been carried forward into the Phase II study with IPH5201
- Overall, no response was seen in CCI CCI