PROTOCOL TITLE: A PHASE I OPEN LABEL, DOSE ESCALATION AND DOSE EXPANSION STUDY TO INVESTIGATE THE SAFETY, PHARMACOKINETICS, PHARMACODYNAMICS AND ANTI-TUMOUR ACTIVITY OF IPN60090 AS SINGLE AGENT AND IN COMBINATION IN PATIENTS WITH ADVANCED SOLID TUMOURS

STUDY PROTOCOL

STUDY NUMBER: D-US-60090-001

IPN60090

EudraCT number: 2018-003681-13

ClinicalTrials.gov number: NCT03894540

IND number: 141766

Version 3.0: 10 December 2019 (incorporating amendment 2)

(Version 2.0: 24 May 2019; incorporating amendment 1)

(Version 1.2: 21 December 2018)
(Version 1.1: 20 December 2018)
(Version 1.0: 29 October 2018)

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All serious adverse events (SAEs) and pregnancies must be reported immediately using the electronic data capture (EDC) system. If the EDC system is not available, the SAE form must be emailed to PPD (if not possible to email).

purpose other than that contemplated herein without the sponsor's prior written authorisation.

INVESTIGATOR'S AGREEMENT

Investigator Agreement and Signature:

I have read and agree to Protocol D-US-60090-001 entitled A Phase I, Open Label, Dose Escalation and Dose Expansion Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics and Anti-tumour Activity of IPN60090 as Single Agent and in Combination in Patients with Advanced Solid Tumours. I am aware of my responsibilities as an investigator under the guidelines of Good Clinical Practice (GCP), local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

NAME: PPD

TITLE: PRINCIPAL INVESTIGATOR SIGNATURE:

DATE:

OFFICE: PPD

Sponsor's Representative Signature:

NAME: PPD

SIGNATURE:

DATE:

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SUMMARY OF CHANGES

The initial version of the protocol (Version 1.0) was released on 29 October 2018, Version 1.1 was released on 20 December 2018, Version 1.2 was released on 21 December 2018, and Version 2.0 (including Amendment 1.0) was released on 24 May 2019. The current version of the protocol (Version 3.0) was released on 10 December 2019 and includes Amendment 2.0. The respective protocol amendment forms were prepared and are provided in Appendix 10 (Table 1).

Table 1 List of Protocol Amendments

Amendment	Release date	Amendment form
Version 1.2	21 December 2018	Appendix 10
Version 2.0 (Amendment 1.0)	24 May 2019	Appendix 10
Version 3.0 (Amendment 2.0)	10 December 2019	Appendix 10

SYNOPSIS

Name of Sponsor/Company: IPSEN Bioscience
Name of Finished Product: IPN60090 **Name of Active Ingredient(s):** IPN60090
Title of Study: A Phase I, Open Label, Dose Escalation and Dose Expansion Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics and Anti-tumour Activity of IPN60090 as Single Agent and in Combination in Patients with Advanced Solid Tumours **Study Number:** D-US-60090-001
Number of Planned Centres: From one centre in the United States of America to approximately 50 sites worldwide over the dose escalation and expansion parts of the study
Planned Study Period: Dose Escalation: Q1 2019 to Q3 2020 Dose Expansion: Q3 2020 to Q4 2022 **Phase of Development:** Phase I
Study Type: Interventional, safety, efficacy, pharmacokinetics (PK), pharmacodynamics (PD)
Objectives: This study will evaluate the safety, the PK, PD and anti-tumour activity of IPN60090 as a single agent (Part A) and in combination with pembrolizumab (Part B) or paclitaxel (Part C) in patients with advanced solid tumours. Part D will evaluate the safety of IPN60090 as a single agent and explore the effect of food on the IPN60090 PK profile. Specific objectives and corresponding endpoints for the study are outlined below. ***Primary:*** • To assess the safety and tolerability of oral IPN60090 as a single agent (Part A and Part D) and in combination therapy with pembrolizumab (Part B) or paclitaxel (Part C). **For Dose Escalation Only:** • To determine the maximum tolerated dose (MTD) if reached, and the recommended dose (RD) of IPN60090 as a single agent (Part A) and in combination therapy with pembrolizumab (Part B) or paclitaxel (Part C). ***Secondary*:** • To assess the preliminary anti-tumour activity of IPN60090 as a single agent (Part A and Part D) and in combination with pembrolizumab (Part B) or paclitaxel (Part C) in patients with or without biomarker selected specific tumour types. • To characterise the PK and PD profile of IPN60090 as a single agent (Part A and Part D) and in combination with pembrolizumab (Part B) or paclitaxel (Part C). • To assess the effect of food on the PK profile of a single administration of IPN60090 (Part D). • To document the concentrations of pembrolizumab and paclitaxel (Parts B and C). • To document the potential development of antibodies against pembrolizumab (Part B). • To evaluate biomarkers of patient stratification and correlate them with clinical outcome.

Exploratory:

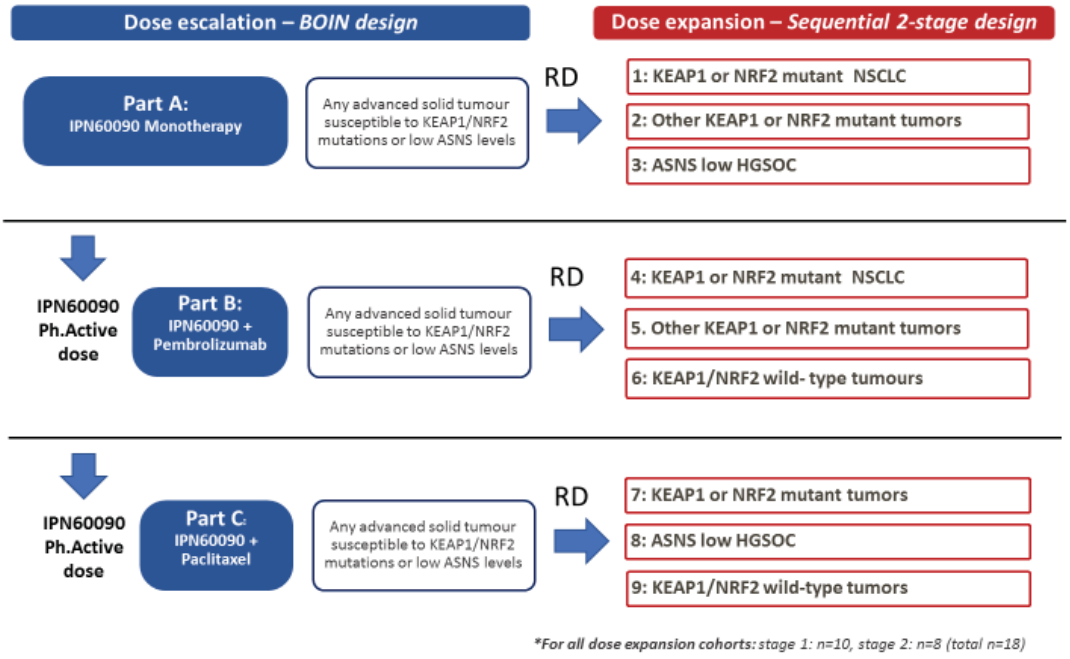
- To analyse exploratory biomarkers in archival and fresh biopsy samples, including biomarkers of response or resistance to the treatment, and associate them with clinical outcome.
- To collect biobank samples for potential future analysis of biomarkers (optional, informed consent required).

Study Hypothesis: IPN60090 will have a manageable safety profile to permit further clinical development as a single agent and in combination with pembrolizumab or paclitaxel in patients with advanced solid tumours and will demonstrate preliminary efficacy and anti-tumour effects as a monotherapy and/or in combination with pembrolizumab or paclitaxel across Kelch-like ECH-associated protein 1 (KEAP1)/ nuclear factor erythroid 2-related factor 2 (NRF2) mutant solid tumours and in low protein expression level of asparagine synthetase ($ASNS^{low}$) solid tumours.

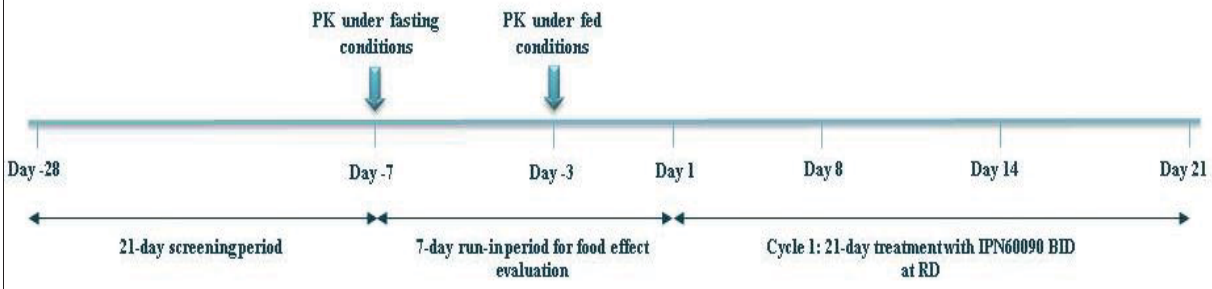
Methodology:

This is a phase I, first in human, open-label, dose escalation and dose expansion study of IPN60090 as a single agent or in combination in patients with advanced solid tumours. As summarised in Figure 1, the study will be divided into four parts.

Figure 1 IPN60090: Summary of Early Clinical Development



PART D



ASNS=asparagine synthetase; BID=bis in die (twice daily); BOIN=Bayesian Optimal Interval; HGSOC= high-grade serous ovarian cancer; KEAP1=Kelch-like ECH-associated protein 1; NRF2=nuclear factor erythroid 2–related factor 2; NSCLC=non-small cell lung cancer; Ph.=pharmacologically; RD=recommended dose

Part A: The dose escalation will explore the safety profile and establish the MTD (if reached), the target engagement or PD levels (glutamate:glutamine (Glu:Gln) ratio in peripheral blood mononuclear cells (PBMC)) and the RD of single agent IPN60090 in biomarker unselected patient populations. During the dose expansion portion, safety and tolerability at the RD will be assessed further, and the preliminary anti-tumour activity of IPN60090 will be explored in three different cohorts (non-small cell lung cancer (NSCLC) KEAP1 or NRF2 mutant, other KEAP1 or NRF2 mutant tumours and high-grade serous ovarian cancer (HGSOC) $ASNS^{low}$).
Part B: The dose escalation will explore the safety profile and establish the MTD (if reached) and the RD of IPN60090 in combination with pembrolizumab. During the dose expansion portion, safety and tolerability at the RD will be assessed further, and preliminary anti-tumour activity of this combination will be explored.
Part C: The dose escalation will explore the safety profile and establish the MTD (if reached) and the RD of IPN60090 in combination with paclitaxel. During the dose expansion portion, safety and tolerability at the RD will be assessed further, and preliminary anti-tumour activity of this combination will be explored.
Parts B and C: These dose escalations in combination with pembrolizumab or paclitaxel will be initiated at the first dose with pharmacological activity (at least 50% inhibition of Glu:Gln ratio in PBMCs at trough plasma concentration (C_{trough}; 12 hours postdose) on Day 14 in 66% of patients treated at this dose level) and with good tolerability as identified in Part A.
Part D: This cohort will evaluate the safety of IPN60090 administered as a single agent and explore the effect of a moderate fat meal on the PK profile of IPN60090 administered as a single dose under fasting and fed conditions at the RD as defined by the Safety Review Committee (SRC).

Part A – Dose Escalation with IPN60090 as a Single Agent

Dose escalation of IPN60090 will be conducted in patients with biomarker-positive and biomarker-negative advanced solid tumours.
These patients will not be selected for KEAP1/NRF2 mutation status and may be wild-type or mutated. Patients may have tumours with any level of asparagine synthetase (ASNS) expression.
Seven dose levels are planned to be tested and the study will follow a Bayesian Optimal Interval (BOIN) design for dose escalation, with accelerated titration, using N=1, up to dose level (DL) 3 (included). At all dose levels, IPN60090 will be administered as a twice daily (BID) oral dose (every 12 hours) during or after a meal, starting from Day 1 of each 21-day cycle. The predefined dose escalation plan is described in Table 2.

Table 2 Dose Escalation Phase I-Part A

DL1	DL2	DL3	DL4	DL5	DL6	DL7
20 mg BID	40 mg BID	80 mg BID	180 mg BID	320 mg BID	480 mg BID	720 mg BID

BID=bis in die (twice daily); DL=dose level

Part A monotherapy dose escalation will enrol single-patient cohorts for the first three dose levels (if no Grade 2 adverse event (AE) that is at least possibly related to the study drug(s) or dose limiting toxicity (DLT) is observed) and then cohorts of three patients each at the predefined dose levels. If a Grade 2 AE that is at least possibly related to the study drug(s) or DLT is observed in a single-patient cohort (first three dose levels), two additional patients will be added at this dose level with the same rules for escalation and de-escalation as the cohorts of three patients. At any point, additional patients may be enrolled as required for safety assessment and/or biomarker analysis. Following each cohort DLT assessment period, the observed DLT data will be used to determine the dose level for the next cohort in accordance with the escalation and de-escalation rules for a local BOIN design using a target

toxicity rate of 30% with escalation and de-escalation thresholds of 23.6% and 35.9%, respectively. Following the completion of enrolment, the MTD will be estimated at the dose level at which the isotonic estimate of the DLT rate is closest to 30%.
At the end of each part, up to two dose levels may be repeated in order to reach a total of 18 patients at each dose level to collect more PK/PD information to better define the RD. The decision to repeat a dose level will be made by the SRC. Safety data from these additional patients will not be included in the BOIN design to determine the MTD but will be evaluated by the SRC and ultimately be taken into consideration for RD selection.

MTD Definition

The MTD is defined as the maximum dose of IPN60090 that may be administered BID for 21 days, so that no more than 30% of patients experience a DLT. The MTD will be determined by the dose for which the isotonic estimate of DLT rate is closest to 30% of patients experiencing a DLT.

DLT Assessment Period

The DLT assessment period will consist of the first 21 days of treatment (one cycle). The SRC will evaluate safety and available PK and PD data after patients have completed at least one cycle of treatment in order to make a decision on dose escalation, and to determine the MTD and the RD. The SRC may decide to evaluate an intermediate, not predefined, previously evaluated or not previously-evaluated dose or a less frequent dosing schedule that will not exceed the MTD level, if evaluation of toxicity at such a dose or schedule is desired. More details about the SRC are included in Section 4.3.1 and will be described in the SRC charter.

DLT Criteria

The DLTs for Part A are defined for the investigational medicinal product (IMP)-related, probably related or possibly related AEs according to National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 that occur during the defined DLT assessment period (over the 21 days following the first dose of IPN60090). Other clinically significant or persistent toxicities may be considered a DLT following review by the SRC. Detailed DLT definitions are included in Section 3.1.2.1 of the protocol.

Patient Eligibility for Dose Escalation Decision

Any patient who does not complete the DLT assessment period for any reason other than a DLT will be considered nonevaluable for dose escalation decisions and MTD assessment and will be replaced by an additional patient at that same dose level. Patients will be considered eligible for the DLT assessment only if they are able to receive ≥75% of the total planned IPN60090 dose over the DLT assessment period. Noncompliant patients will also be replaced. The SRC may decide to enrol additional patients based on the safety, PK or PD data.

Treatment Duration - Additional Cycles

Patients will be offered IPN60090 treatment beyond Cycle 1 as long as they continue to experience clinical benefit, in the opinion of the investigator, until the earlier of disease progression, symptomatic deterioration, poor tolerability despite appropriate medical management or any of the other reasons for treatment discontinuation. Patients who experience a DLT (or other toxicities considered related, probably related or possibly related to the study treatment) will be permitted to continue to receive study treatment at a lower dose level than the dose at which the DLT was observed, at the discretion of the investigator, and will be followed for safety. Biomarker-positive patients who are enrolled and receive study treatment at initial dose levels below the pharmacologically active range for at least two cycles with good tolerability, and achieve and maintain at least stable disease (SD), may be escalated to a higher dose level that has been tested and proven to be well tolerated, at the recommendation of the SRC. These patients will be treated outside of the BOIN design.
Patients who discontinue study treatment for reasons other than disease progression (for

example toxicity) should continue to undergo scheduled tumour assessments approximately every 12 weeks until disease progression, initiation of further systemic cancer therapy, death, or until the study closes, whichever occurs first.

Part B – Pembrolizumab Combination Dose Escalation

The dose escalation portion of Part B is a phase I, open-label, dose escalation study to evaluate the safety, tolerability, PK and PD of IPN60090 given as a BID oral dose (every 12 hours) during or after a meal, in combination with pembrolizumab, over a 21-day cycle. Dose escalation of IPN60090 in combination with pembrolizumab will be conducted in patients with biomarker-positive and biomarker-negative advanced solid tumours.

These patients will be unselected for KEAP1/NRF2 mutation status and may be KEAP1/NRF2 wild-type or mutated; patients may have tumours with any level of ASNS expression. Previous treatment with checkpoint inhibitor therapy is allowed.

This dose escalation in combination with pembrolizumab will be initiated at a dose level showing pharmacological activity (at least 50% inhibition of Glu:Gln ratio in PBMCs at C_{trough} (12 hours postdose and predose for the following dose) on Day 14 of Cycle 1 in 66% of patients treated at this dose level) and with good tolerability as identified in Part A. The IPN60090 dose being tested in the dose escalation of Part B will always remain lower than that being tested in the dose escalation of Part A (at least one dose level lower than the highest dose tested in Part A).

Three dose levels of IPN60090 are planned to be tested with an additional lower dose level (DL-1) if DL1 is not tolerated. The study will follow a BOIN design for dose escalation.

At all dose levels, IPN60090 will be administered orally BID starting from Day 1 of each 21-day cycle and pembrolizumab will be administered as one intravenous (i.v.) infusion every 21 days (±1 day in Cycle 1 and ±3 days in all other cycles) starting from Day 1 of each cycle. The predefined dose escalation plan is described in Table 3.

Table 3 Dose Escalation Phase I-Part B in Combination with Pembrolizumab

Dose level	Dose level -1	Dose level 1	Dose level 2	Dose level 3
Planned dose of IPN60090 [a]	80 mg BID	180 mg BID	320 mg BID	480 mg BID
Planned dose of pembrolizumab	200 mg Q3W[b]	200 mg Q3W[b]	200 mg Q3W[b]	200 mg Q3W[b]

BID=bis in die (twice daily); Q3W=every three weeks (21 days)
a dose levels are examples; the actual starting dose will be determined by PD from the Part A dose escalation
b or according to the local approved label for particular tumour types

Dose finding will begin at DL1. The study will enrol in cohorts of three patients at the predefined dose levels until up to six cohorts have been enrolled. Following each cohort, the observed DLT data will be used to determine the dose level for the next cohort in accordance with the escalation and de-escalation rules for a local BOIN design using a target toxicity rate of 30% with escalation and de-escalation thresholds of 23.6% and 35.9%, respectively.

Following the completion of enrolment, the MTD will be estimated as the dose level at which the isotonic estimate of the DLT rate is closest to 30%.

If the first dose level of IPN60090 in combination with 200 mg pembrolizumab is not well tolerated, upon the decision of the SRC, the dose of IPN60090 may be de-escalated and thus a new cohort may start with DL-1.

At the end of each part, up to two dose levels may be repeated in order to reach a total of 18 patients at each dose level to collect more PK/PD information to better define the RD. The decision to repeat a dose level will be made by the SRC. Safety data from these additional patients will not be included in the BOIN design to determine the MTD but will be evaluated by the SRC and ultimately be taken into consideration for RD selection.

MTD Definition
The MTD is defined as the maximum dose of IPN60090 that may be administered BID for 21 days, in combination with an i.v. infusion of 200 mg of pembrolizumab (or according to the local approved label for particular tumour types), so that no more than 30% of patients experience a DLT. The MTD will be determined by the dose for which the isotonic estimate of DLT rate is closest to 30% of patients experiencing a DLT.

DLT Assessment Period
The DLT assessment period will consist of the first 21 days of treatment (one cycle). The SRC will evaluate safety and available PK and PD data in order to make a decision on dose escalation, and to determine the MTD and the RD. The safety data reviewed by the SRC will include the safety findings and DLTs observed during the DLT assessment period from the previous cohort. The SRC may decide to evaluate an intermediate, not predefined, previously evaluated or not previously-evaluated dose or a less frequent dosing schedule that will not exceed the MTD level if evaluation of toxicity at such a dose or schedule is desired.

DLT Criteria
The DLTs are defined for the IMP-related, probably related or possibly related AEs according to the NCI-CTCAE version 5.0 that occur during the defined DLT assessment period (over the 21 days following the first dose of IPN60090 combined with pembrolizumab).
Other clinically significant or persistent toxicities may be considered a DLT following review by the SRC.
Detailed DLT definitions are included in Section 3.1.2.2 of the protocol.

Patient Eligibility for Dose Escalation Decision
Any patient who does not complete the DLT assessment period for any reason other than a DLT will be considered nonevaluable for dose escalation decisions and MTD assessment and will be replaced by an additional patient at that same dose level. Moreover, patients will be considered eligible for the DLT assessment only if they received ≥75% of the total planned IPN60090 dose and one infusion of pembrolizumab over the DLT assessment period. Noncompliant patients will also be replaced. The SRC may decide to enrol additional patients based on the safety, PK or PD data.

Treatment Duration - Additional Cycles
Patients will be offered IPN60090 + pembrolizumab treatment beyond Cycle 1 as long as they continue to experience clinical benefit, in the opinion of the investigator, until the earlier of confirmed disease progression, symptomatic deterioration, poor tolerability despite appropriate medical management or any of the other reasons for treatment discontinuation. Patients who experience a DLT (or other toxicities considered related, probably related or possibly related to the study treatment) will be permitted to continue to receive study treatment at a lower dose level than the dose at which the DLT was observed, at the discretion of the investigator and will be followed for safety. Patients who discontinue study treatment for reasons other than disease progression (for example toxicity) should continue to undergo scheduled tumour assessments approximately every 12 weeks until confirmed disease progression, or initiation of further systemic cancer therapy, death, or until the study closes, whichever occurs first.

Part C – Paclitaxel Combination Dose Escalation
The dose escalation portion of Part C is a phase I, open-label, dose escalation study to evaluate the safety, tolerability, PK and PD of IPN60090 given as a BID oral dose (every 12 hours) during or after a meal, in combination with paclitaxel (IPN60090 to be taken at least 2.5 hours before the start of the paclitaxel infusion), over a 21-day cycle.
Dose escalation of IPN60090 in combination with paclitaxel will be conducted in patients with biomarker-positive and biomarker-negative advanced solid tumours.

These patients will be unselected for KEAP1/NRF2 mutation and may be KEAP1/NRF2 wild-type or mutated with any level of ASNS expression. Dose escalation in combination with paclitaxel will be initiated at a dose level showing pharmacological activity (at least 50% inhibition of Glu:Gln ratio in PBMC at C_{trough} (12 hours postdose and predose for the following dose) on Day 14 of Cycle 1 in 66% of patients treated at this dose level) and good tolerability as identified in Part A. The IPN60090 dose being tested in Part C will always remain lower than that being tested in Part A (at least one dose level lower than the highest dose tested in Part A).

Three dose levels of IPN60090 are planned to be tested with an additional lower dose level (DL-1) if DL1 is not tolerated. The study will follow a BOIN design for dose escalation.

At all dose levels, IPN60090 will be administered orally BID starting from Day 1 of each 21-day cycle and paclitaxel will be administered as one i.v. infusion every 21 days (±1 day in Cycle 1 and ±3 days in all other cycles) starting from Day 1 of each cycle. The predefined dose escalation plan is described in Table 4.

Table 4 Dose Escalation Phase I-Part C in Combination with Paclitaxel

Dose level	Dose level -1	Dose level 1	Dose level 2	Dose level 3
Planned dose of IPN60090 [a]	80 mg BID	180 mg BID	320 mg BID	480 mg BID
Planned dose of paclitaxel	175 or 135 mg/m² Q3W [b]	175 or 135 mg/m² Q3W [b]	175 or 135 mg/m² Q3W [b]	175 or 135 mg/m² Q3W [b]

BID=bis in die (twice daily); Q3W=every three weeks (21 days)
a dose levels are examples; the actual starting dose will be determined by PD from the Part A dose escalation
b or according to the local label for particular tumour types

Dose finding will begin at DL1. The study will enrol in cohorts of three patients at the predefined dose levels until up to six cohorts have been enrolled. Following each cohort, the observed DLT data will be used to determine the dose level for the next cohort in accordance with the escalation and de-escalation rules for a local BOIN design using target toxicity rate of 30% with escalation and de-escalation thresholds of 23.6% and 35.9%, respectively. Following the completion of enrolment, the MTD will be estimated as the dose level at which the isotonic estimate of the DLT rate is closest to 30%.

If the first dose level of IPN60090 in combination with paclitaxel 175 or 135 mg/m² (or according to the local approved label for particular tumour types) given intravenously is not well tolerated, the dose of IPN60090 may be de-escalated and thus a new cohort may start with the DL-1.

At the end of each part, up to two dose levels may be repeated in order to reach a total of 18 patients at each dose level to collect more PK/PD information to better define the RD. The decision to repeat a dose level will be made by the SRC. Safety data from these additional patients will not be included in the BOIN design to determine the MTD but will be evaluated by the SRC and ultimately be taken into consideration for RD selection.

MTD Definition

The MTD is defined as the maximum dose of IPN60090 that may be administered BID for 21 days, in combination with an i.v. infusion of 175 or 135 mg/m² paclitaxel (or according to the local approved label for particular tumour types), so that no more than 30% of patients experience a DLT. The MTD will be determined by the dose for which the isotonic estimate of DLT rate is closest to 30% of patients experiencing a DLT.

DLT Assessment Period

The DLT assessment period will consist of the first 21 days of treatment (one cycle). The SRC will evaluate safety and available PK and PD data in order to make a decision on dose escalation, and to determine the MTD and the RD. The safety data reviewed by the SRC will include the safety findings and DLTs observed during the DLT assessment period from the

previous cohort. The SRC may decide to evaluate an intermediate, not predefined, previously evaluated or not previously evaluated dose or a less frequent dosing schedule that will not exceed the MTD level, if evaluation of toxicity at such a dose or schedule is desired.

DLT Criteria

The DLTs are defined for the IMP-related, probably related or possibly related AEs according to the NCI-CTCAE version 5.0 that occur during the defined DLT assessment period (over the 21 days following first the dose of IPN60090).

Other clinically significant or persistent toxicities may be considered a DLT following review by the SRC.

Transient infusion-related AEs that can be controlled with medical management (i.e. flu-like symptoms, fever) are not considered DLTs. Detailed DLT definitions are included in Section 3.1.2.3 of the protocol.

Patient Eligibility for Dose Escalation Decision

Any patient who does not complete the DLT assessment period for any reason other than a DLT will be considered nonevaluable for dose escalation decisions and MTD assessment and will be replaced by an additional patient at that same dose level. Moreover, patients will be considered eligible for the DLT assessment only if they are able to receive ≥75% of the total planned IPN60090 dose and one infusion of paclitaxel over the DLT assessment period. The SRC may decide to enrol additional patients based on the safety, PK or PD data.

Treatment Duration - Additional Cycles

Patients will be offered IPN60090 + paclitaxel treatment beyond Cycle 1 as long as they continue to experience clinical benefit, in the opinion of the investigator, until the earlier of disease progression, symptomatic deterioration, poor tolerability despite appropriate medical management or any of the other reasons for treatment discontinuation. Patients who experience a DLT (or other toxicities considered related, probably related or possibly related to the study treatment) will be permitted to continue to receive study treatment at a lower dose level than the dose at which the DLT was observed, at the discretion of the investigator and will be followed for safety. Patients who discontinue study treatment for reasons other than disease progression (for example toxicity) should continue to undergo scheduled tumour assessments approximately every 12 weeks until disease progression, or initiation of further systemic cancer therapy, death, or until the study closes, whichever occurs first.

Parts A, B and C Dose Escalation

In Parts A, B and C, when the RD is determined, if a patient is still in the study at a different dose, this patient can be moved to the RD at the discretion of the investigator.

In the event that operational/practical circumstances result in an over-enrolment (i.e. n>3) for a BOIN cohort, the next dose level decision would be based on the actual number of patients exposed in the cohort and the BOIN criteria.

Part D – Food Effect Assessment

Part D will start at the end of the Part A dose escalation. Patients in Part D will not be part of the dose escalation and MTD assessment.

Food effect evaluation will be conducted in patients with biomarker-positive and biomarker-negative advanced solid tumours.

These patients will not be selected for KEAP1/NRF2 mutation status and may be wild-type or mutated. Patients may have tumours with any level of ASNS expression. Eligibility criteria for Part D will be the same as the criteria for the Part A dose escalation.

After screening, eight patients will enter a run-in period of 7 days.

Full PK profiles will be obtained on Day -7 under fasting conditions and Day -3 after a moderate fat meal to assess the food effect on the IPN60090 PK profile.

In Part D, the moderate fat meal is defined as the following: total calories of 500 to 750 kCal

including 30 to 35% fat.
After the run-in period, patients will receive IPN60090 as a single agent administered orally BID (every 12 hours), during or after a meal, starting from Day 1 at the single agent RD.
Patients in Part D will follow the same schedule of assessments as described for Part A (with the exception of the urine sampling for PK).

Dose Expansion Cohorts

The multicohort dose expansion part of the study will further explore the safety and tolerability of IPN60090 in monotherapy and in combination; assess the preliminary anti-tumour activity of IPN60090 as a single agent and in combination with pembrolizumab or paclitaxel at the RD in biomarker positive and/or unselected patient population and will explore the potential of selected biomarkers as predictors of efficacy (candidate biomarkers will include, but will not be limited to, KEAP1/NRF2 mutation status, ASNS expression level, and known or new emerging predictive or prognostic markers of efficacy in selected tumour types).
Enrolment into dose expansion cohorts will occur independently of each other. Each cohort will follow a sequential 2-stage design and enrol ten patients in Stage 1 and up to a total of 18 patients (Stage 1 + Stage 2). Further expansion may be initiated in cohorts with observed efficacy signals.
The dose expansion cohorts that will be explored in each part of the study are defined as the following:

- Part A- IPN60090 monotherapy
  - Dose Expansion Cohort 1: KEAP1 or NRF2 mutant NSCLC
  - Dose Expansion Cohort 2: Other KEAP1 or NRF2 mutant tumours
  - Dose Expansion Cohort 3: $ASNS^{low}$ HGSOC
- Part B- IPN60090 + pembrolizumab:
  - Dose Expansion Cohort 4: KEAP1 or NRF2 mutant NSCLC
  - Dose Expansion Cohort 5: Other KEAP1 or NRF2 mutant tumours
  - Dose Expansion Cohort 6: KEAP1 or NRF2 wild-type tumours with any level of ASNS expression
- Part C- IPN60090 + paclitaxel:
  - Dose Expansion Cohort 7: Other KEAP1 or NRF2 mutant tumours
  - Dose Expansion Cohort 8: $ASNS^{low}$ HGSOC
  - Dose Expansion Cohort 9: KEAP1 or NRF2 wild-type tumours with any level of ASNS expression

Dose expansion cohorts (study populations and sample size) may be revised in light of the dose escalation data, resulting in a protocol amendment.
An independent safety assessment committee structured to assess safety in addition to efficacy will be established for dose expansion cohorts in order to make recommendations regarding protocol modifications to reduce risks to patients enrolled in the study. If preliminary clinical evidence in one or several dose expansion cohorts suggests a substantial improvement over available therapies on a clinically significant endpoint(s), further efficacy expansion cohorts may be initiated in the corresponding populations with the goal of assessing the anti-tumour activity of IPN60090 monotherapy or combination.
Patients enrolled in monotherapy Part A or Part D may receive combination treatment with either pembrolizumab or with paclitaxel upon progression on IPN60090 monotherapy at the discretion of the investigator and with the approval of the sponsor. These patients will need to satisfy eligibility criteria for combination therapy prior to initiating treatment and will be followed for safety and efficacy in a separate cohort.

Number of Patients Planned:

Dose Escalation

Part A (single agent): Approximately 30 patients for the dose escalation.

Part B (combination with pembrolizumab): Approximately 18 patients for the dose escalation.

Part C (combination with paclitaxel): Approximately 18 patients for the dose escalation.

Food Effect Assessment

Part D (single agent): Eight patients for preliminary food effect assessment.

Dose Expansion

Parts A, B, and C: Approximately 162 patients (90 patients in Stage 1 of dose expansion, and 72 patients in Stage 2).

Diagnosis and Criteria for Inclusion:

Inclusion Criteria

General Inclusion Criteria for All Parts

(1) Provision of written informed consent prior to any study related procedures.

(2) Male or female patients ≥18 years of age at the time of study entry who agree to participate by giving written informed consent prior to participation in any study-related activities.

(3) Histologically or cytologically confirmed advanced solid tumours including tumours known to harbour KEAP1 and/or NRF2 mutations or have low ASNS expression levels.

- In dose escalations of all parts, patients may be KEAP1 and NRF2 wild-type or mutated and have tumours with any level of ASNS expression. For dose expansions, see specific inclusion criteria per part below.

(4) Patients must have received at least one line of therapy for advanced stage disease and be refractory or ineligible to available existing therapy(ies) known to provide clinical benefit for their condition.

(5) Prior treatment with chemotherapy, radiotherapy, immunotherapy or any investigational therapies must have been completed at least 3 weeks or at least five half-lives before the study drug administration, and all AEs (excluding alopecia and peripheral neuropathy) have either returned to baseline or stabilised.

(6) Fresh and/or archival tumour tissue from the biopsy obtained between the completion of the most recent line of treatment until study entry must be available for mutation and biomarker analysis unless KEAP1/NRF2 mutations were present in any previous biopsy, in which case, no further biopsy is required. For ovarian cancer patients, both archival biopsies obtained between the completion of the most recent line of treatment until study entry and fresh biopsies must be available to evaluate the evolution of ASNS levels over time. Patients should not be put at undue risk to obtain fresh tumour biopsy. Procedures more invasive than core biopsy should not be used. Procedures to obtain biopsy should only be performed if the risk is minimal (no greater than 2% risk of serious or severe complications). If available, archival tumour tissue from time of initial diagnosis will be collected in addition to the most recent biopsy (archival and/or fresh).

(7) Measurable or non-measurable evaluable disease as defined per the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (or immune-related RECIST (iRECIST) for Part B only).

(8) Eastern Cooperative Oncology Group Performance Status ≤1.

(9) Adequate organ function as indicated by the following laboratory values:
- (a) Absolute neutrophil count ≥1500/mL
- (b) Platelets ≥100,000/mL
- (c) Haemoglobin ≥9 g/dL or ≥5.6 mmol/L
- (d) Serum creatinine ≤1.5×upper limit of normal (ULN) and/or creatinine clearance >40 mL/min. Actual body weight should be used for calculating creatinine clearance using the Cockroft-Gault equation (except for patients with body mass index >30 kg/m^2 when the lean body weight should be used).
- (e) Serum total bilirubin ≤1.5×ULN (with the exception of patients with known Gilbert's syndrome: serum total bilirubin must be <3×ULN in these patients)
- (f) Aspartate aminotransferase (serum glutamic oxaloacetic transaminase) and alanine aminotransferase (serum glutamic pyruvic transaminase) ≤2.5×ULN or ≤5×ULN for patients with liver metastases)

(10) Adequate cardiac function with a left ventricular ejection fraction ≥50%

(11) Female patients are eligible to enter and participate in the study if they are of:
- (a) Non-childbearing potential (physiologically incapable of becoming pregnant), including any female who:
  - has had a hysterectomy, OR
  - has had a bilateral oophorectomy, OR
  - has had a bilateral salpingectomy, OR
  - is postmenopausal (total cessation of menses for ≥2 years, or follicle-stimulating hormone ≥50 IU/L).
- (b) Childbearing potential, but with a negative serum pregnancy test at screening (within 7 days of the first IMP administration), is not breastfeeding, and uses highly effective contraception at study entry and throughout the study until 90 days after the last administration. Highly effective contraceptive methods include:
  - Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (for example oral, intravaginal, transdermal)
  - Progestogen-only hormonal contraception associated with inhibition of ovulation (for example oral, implantable, injectable)
  - Intrauterine device
  - Intrauterine hormone-releasing system
  - Bilateral tubal occlusion
  - Male partner has had a vasectomy

(12) Male patients are eligible to enter and participate in the study if they agree to use effective methods of contraception during the study treatment period and for at least 90 days after the last dose of investigational product.

Part A Specific Inclusion Criteria

There are no further inclusion criteria associated with Part A.

Dose Expansion ONLY:

(A1) Patients with the following tumour types will be recruited:
- (a) NSCLC KEAP1 and/or NRF2 mutant

(b) KEAP1 and/or NRF2 mutant other tumours

(c) HGSOC ASNS^{low}

Note: all biomarker mutations/expression levels must be confirmed prior to study treatment.

Part B Specific Inclusion Criteria

(B1) Patients may have received previous treatment with any programmed cell death protein 1 or programmed cell death ligand 1 (PD-L1) inhibitor

Dose Expansion ONLY:

(B2) Patients may have received previous treatment with any anti-programmed cell death protein 1 (PD-1)/PD-L1 monoclonal antibody (mAb) administered either as monotherapy, or in combination with other checkpoint inhibitors or other therapies. PD-1 treatment progression is defined by meeting all of the following criteria:

(a) Has received at least 2 doses of an approved anti-PD-1/L1 mAb.

(b) Has demonstrated disease progression after PD-1/L1 as defined by iRECIST v1.1. The initial evidence of disease progression is to be confirmed by a second assessment no less than four weeks from the date of the first documented disease progression, in the absence of rapid clinical progression.

(B3) Patients with the following tumour types will be recruited during the dose expansion only:

(a) NSCLC KEAP1 and/or NRF2 mutant

(b) Other KEAP1 and/or NRF2 mutant tumours

(c) KEAP1 and NRF2 wild-type tumours with any level of ASNS expression

Part C Specific Inclusion Criteria

(C1) Patients may have received previous treatment with any platinum- or taxane-based chemotherapy.

Dose Expansion ONLY:

(C2) Patients with the following tumour types will be recruited during dose expansion only:

(a) KEAP1 or NRF2 mutant tumours

(b) HGSOC ASNS^{low} tumours

(c) KEAP1 or NRF2 wild-type tumours with any level of ASNS expression

Part D Specific Inclusion Criteria

(D1) Patients must be able to consume a moderate fat meal.

Exclusion Criteria

General Exclusion Criteria for All Parts

(1) Prior malignancy within the previous 2 years except for locally curable cancers that have been cured, such as basal or squamous cell skin cancer, or carcinoma in situ of the cervix, breast or bladder.

(2) Known primary central malignancy or symptomatic central nervous system metastasis(es).

Note: Patients with stable, previously treated brain metastases may participate if neurologic symptoms have resolved, patients have been off steroids for at least 7 days, and there is no evidence of disease progression by imaging for at least 2 weeks before the first dose of study treatment.

(3) Patients should be excluded if they have a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other

immunosuppressive medications within 2 weeks of the first dose of study drug.

(4) Uncontrolled, significant intercurrent or recent illness including, but not limited to, the following cardiac conditions:

(a) Any unstable cardiac arrhythmia within 6 months prior to enrolment

(b) Prolongation of the Fridericia corrected QT interval defined as >450 ms for males and >470 ms for females

(c) History of any of the following cardiovascular conditions within 6 months of enrolment:

- cardiac angioplasty or stenting, myocardial infarction, unstable angina, coronary artery
- bypass graft surgery, symptomatic peripheral vascular disease, class III or IV congestive heart failure, as defined by the New York Heart Association.

(5) Major surgical intervention within 28 days before study drug administration.

(6) Significant acute or chronic infections.

(7) Any psychiatric condition that would prohibit the understanding or rendering of informed consent.

(8) Treatment with strong cytochrome P450 (CYP450) subtype 3A4 inducers (including St John's Wort) and inhibitors (including grapefruit juice) within 7 days of the first dose of study drug.

(9) Treatment with strong CYP450 subtype 2D6 inhibitors within 7 days of the first dose of study drug.

(10) Radiotherapy within 4 weeks prior to the start of study drug. Palliative radiotherapy for symptomatic control is acceptable if completed at least 2 weeks prior to study drug administration and no additional radiotherapy for the same lesion is planned.

(11) Underlying medical conditions that, in the investigator's opinion, will make the administration of study drug hazardous or obscure the interpretation of toxicity determination or AEs.

(12) History of allergic reactions attributed to compounds of similar chemical or biologic composition to any of the compounds in the study.

(13) Known alcohol or drug abuse.

(14) Legal incapacity or limited legal capacity.

(15) Inability to swallow oral medications (capsules and tablets) without chewing, breaking, crushing, opening or otherwise altering the product formulation. Patients should not have gastrointestinal illnesses that would preclude the absorption of IPN60090, which is an oral agent.

(16) Patients unwilling to comply with protocol requirements related to the assigned part.

Part A Specific Exclusion Criteria

There are no further exclusion criteria associated with Part A.

Part B Specific Exclusion Criteria

(B1) Autoimmune disease that might deteriorate when receiving an immune-stimulatory agent, or immunodeficiencies.

(B2) Known severe hypersensitivity reactions to monoclonal antibodies, any history of anaphylaxis, or uncontrolled asthma (that is, three or more features of partially

controlled asthma).

(B3) Prior organ transplantation, including allogeneic stem cell transplantation.

(B4) Patient has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are 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 are allowed; however, intranasal influenza vaccines (e.g. FluMist®) are live attenuated vaccines and are not allowed.

Part C Specific Exclusion Criteria

(C1) Treatment with strong CYP450 subtype 2C8 inhibitors and inducers within the 7 days of the paclitaxel infusion.

Part D Specific Exclusion Criteria

(D1) Treatment with drugs that can alter the absorption of IPN60090 by affecting gastrointestinal motility or by changing the gastric pH during the run-in period (Day -7 to Day -3) of Part D.

(D2) Patients suffering from conditions that are likely to adversely affect gastrointestinal motility and/or transit (for example, diarrhoea, vomiting or nausea, gastroparesis, irritable bowel syndrome and malabsorption) or patients with gastrointestinal resection (e.g. partial or total gastrectomy) likely to interfere with absorption of study treatment. Patients with Type 1 diabetes and hypercholesterolaemia are excluded.

(D3) Patients unable to fast for up to 14 hours.

Test Product, Dose, Mode of Administration:
IPN60090 will be administered as oral capsules of either 10, 60 or 240 mg BID during or after a meal over 21 days (1 cycle). IPN60090 capsules will be given every 12 hours corresponding to a BID regimen.

Part A dose escalation: tested doses of IPN60090 will range from 20 mg BID (40 mg total daily dose) (starting dose) to 720 mg BID (1,440 mg daily dose) (maximum dose).

Part B dose escalation: the starting dose of IPN60090 will be a dose showing pharmacological activity (at least 50% inhibition of Glu:Gln ratio in PBMC at C_{trough} (12 hours postdose) on Day 14 in 66% of patients at this dose level) and good tolerability as identified in Part A. IPN60090 intake should be performed at least 1 hour before the start of pembrolizumab infusion. The dose of pembrolizumab will be fixed at 200 mg every 21 days (±1 day in Cycle 1 and ±3 days in all other cycles) (or according to the local approved label for specific tumour types) as an i.v. infusion.

Part C dose escalation: the starting dose of IPN60090 will be a dose showing significant pharmacological activity (at least 50% inhibition of Glu:Gln ratio in PBMC at C_{trough} (12 hours postdose) on Day 14 in 66% of patients at this dose level) and good tolerability as identified in Part A. When histamine 2 receptor (H2) blockers are administered for paclitaxel premedication, they must be administered at least 30 minutes prior to paclitaxel infusion. IPN60090 intake should be performed at least 2.5 hours before the start of the paclitaxel infusion and at least 2 hours prior to H2 blocker administration.

The dose of paclitaxel will be fixed at 175 mg/m² or 135 mg/m^2 every 21 days (±1 day in Cycle 1 and ±3 days in all other cycles) (or according to the local approved label for specific tumour types) administered as an i.v. infusion.

The proposed dose levels may be further modified and additional doses may be considered based on the safety, tolerability and efficacy observed during dose escalation. An intermediate, not predefined, previously evaluated or not previously evaluated dose or a less

frequent dosing schedule that will not exceed the MTD level may be considered, if evaluation of toxicity at such a dose or schedule is desired.

Part D food effect assessment: single administration of IPN60090 at the RD (morning dose only), as defined by the SRC at the end of the Part A dose escalation, will be performed during the run-in period at Day -7 and Day -3. On Day -7, IPN60090 will be administered following an overnight fast of at least 10 hours. On Day -3, IPN60090 will be administered 30 minutes after the start of a moderate fat meal. The moderate fat meal should be eaten in 30 minutes or less. On both days, the patients should not consume any food for at least 4 hours after the dose. IPN60090 should be taken with 240 mL (i.e. 8 fluid ounces) of water. Additional water is permitted ad libitum except for the period 1 hour before to 1 hour after administration of the drug product. Substitutions to the test meal can be made after discussion with the sponsor. It is understood that some patients may not be able to consume the entire meal. Study staff should record the percent of the test meal breakfast and the time it takes to be consumed.

Then starting from Day 1, patients will receive IPN60090 BID (at the RD as defined by the SRC at the end of Part A) during or after a meal over 21 days (one cycle) as described in Part A.

Duration of Treatment: Approximately 6 months

Reference Therapy, Dose and Mode of Administration:
Not applicable.

Criteria for Evaluation (Endpoints):

Primary

- The safety and tolerability of IPN60090 as a single agent (Part A and Part D) and in combination with pembrolizumab (Part B) or paclitaxel (Part C) will be assessed by the rate of DLTs at each dose level in the dose escalation, and the rate of AEs and the rate of Grade 3 and higher AEs in the dose escalation and dose expansion. Continuous monitoring of AEs and serious AEs (SAEs), clinical laboratory test results, the presence of anti-pembrolizumab antidrug antibodies (ADA; Part B only), vital signs measurements, electrocardiogram (ECG) and physical examination results and concomitant medication usage will be performed.

For dose escalation only:

- Define MTD, if reached, as determined by the incidence and nature of DLTs, of:
  - single agent IPN60090 (Part A)
  - the combination of IPN60090 and pembrolizumab (Part B) or paclitaxel (Part C)
- Define RD, as determined by the PD, PK and safety of:
  - single agent IPN60090 (Part A)
  - the combination of IPN60090 and pembrolizumab (Part B) or paclitaxel (Part C)

Secondary

- Anti-tumour activity parameters assessed locally (for dose escalation) and centrally (for dose expansion) using RECIST v1.1 for Parts A, C and D and iRECIST for Part B only, including:
  - Clinical benefit rate (CBR) is defined as the proportion of patients in whom the Best Overall Response (BOR) is equal to complete response (CR), partial response (PR) or SD lasting at least 12 weeks for Parts A, C and D, and equal to immune CR (iCR), immune PR (iPR) or immune SD (iSD) lasting at least 12 weeks for Part B
  - Objective response rate (ORR) is defined as the proportion of patients in whom the BOR is equal to CR and PR for Parts A, C and D or iCR and iPR for Part B
  - Disease control rate (DCR) is defined as the proportion of patients in whom the

BOR is equal to CR, PR or SD for Parts A, C and D, and equal to iCR, iPR or iSD for Part B
- Progression free survival (PFS) is defined as the time from first dose of study medication to the first documented objective disease progression (for RECIST) or confirmed objective disease progression (for iRECIST) or death due to any cause, whichever occurs first (except for Part B where confirmation of progression is needed to determine the PFS to exclude pseudoprogression).
- Overall survival is defined as the time from first dose of study medication to death due to any cause.

• Pharmacokinetic parameters of IPN60090, including but not limited to maximum observed plasma drug concentration (C_{max}), time to C_{max} (T_{max}), C_{trough}, area under the plasma concentration time curve (AUC), elimination half-life ($t_{1/2}$), apparent total clearance from plasma (CL/F) and apparent volume of distribution (V/F) of IPN60090 (Parts A to D).
• Describe the PK of a single dose of IPN60090 administered in fed state (Day -3) relative to fasted state (Day -7) using the following PK parameters: C_{max}, AUC, T_{max}, $t_{1/2}$, CL/F and V/F (Part D).
• Assessment of concentrations of the combined product (Parts B and C)
• Assessment of potential ADA for pembrolizumab (Part B)
• Pharmacodynamic parameters and biomarkers evaluation:
  - Target engagement: Glu:Gln ratio in PBMC
  - Tumour mutation status (for example KEAP1/NRF2, serine/threonine kinase 11, Kirsten Rat Sarcoma Viral Oncogene Homolog and other mutations) and correlation with clinical outcome
  - Tumour ASNS expression

Exploratory

• Biomarkers of tumour biology evolution under treatment (e.g. immune profiling, PD-L1 expression, nuclear antigen Ki67, phosphorylation of histone variant H2AX, liver kinase B1, etc) may be evaluated and correlated with clinical outcome.
• Biobank samples will be collected for potential future analysis of biomarkers (optional, informed consent required)

Exploratory IPN60090 concentrations in urine will be assessed only in Part A of dose escalation. The following PK parameters will be calculated: the amount of IPN60090 excreted in urine and renal clearance.

Safety

The safety and tolerability of IPN60090 will be assessed by the rate of DLTs at each dose level in the dose escalation, and the rate of AEs and the rate of Grade 3 and higher AEs in the dose escalation and dose expansion. Continuous monitoring of AEs and SAEs, clinical laboratory test results, the presence of anti-pembrolizumab ADA (Part B only), vital signs measurements, ECG and physical examination results, and concomitant medication usage will be performed.

Statistical Methods:

The following populations will be defined during statistical analyses:
Screened population: All patients screened (i.e. who signed the informed consent).
Safety population: All patients who are exposed to (or started receiving) IPN60090 and/or the combination agents.
DLT evaluable population for the escalation phase only: All patients from the safety population who are evaluable for DLT (patients who have completed at least one cycle of treatment and have received ≥75% of the total planned dose of IPN60090 over the DLT

assessment period). Patients with noncompliance (<75% of total planned dose) due to DLT will be included in this population.
Efficacy population: All patients who receive at least one dose of IPN60090.
Pharmacokinetic population for noncompartmental analysis: All patients who have no major protocol deviation affecting the PK variables and who have a sufficient number of IPN60090 plasma concentrations to estimate the main PK parameters (C_{max}, T_{max}, AUC from time 0 to the last time point with quantifiable concentrations ($AUC_{0\text{-}last}$)).
Pharmacokinetic population for population PK modelling: All patients who receive at least one IPN60090 dose and who have at least one plasma IPN60090 concentration and who have no major protocol deviation affecting the PK variables.
Food effect population: All patients in Part D who have received IPN60090 under fasting and fed conditions (Day -7 and Day -3), have consumed ≥80% of the moderate fat meal in approximately 30 minutes on Day -3, and who have no major protocol deviation affecting the PK variables and who have a sufficient number of IPN60090 plasma concentrations to estimate the main PK parameters (C_{max}, T_{max} and $AUC_{0\text{-}last}$).
Pharmacodynamic population: All patients who have at least one PD endpoint measurement. PD endpoints refer to target engagement levels (Glu:Gln ratio in PBMC).
Data will be listed and summarised by dose level and part in the escalation phase; by cohort and part for safety and by cohort for efficacy in the expansion phase. Safety results will be presented for all the patients included in the study at the RD (dose escalation and expansion phases) by part and RD. Furthermore, all safety and efficacy results could be presented by group of patients depending on the interest there may be in these groups.
Categorical variables will be summarised by frequency distributions (number and percentages of patients). The 95% confidence interval (CI) will be calculated following the exact method. Continuous variables will be summarised by descriptive statistics (mean, standard deviation, median, minimum and maximum). Time-to-event variables will be summarised using the Kaplan-Meier method and the 95% CI of the median will be given.
Food effect assessment – Part D
The assessment of food effect will be based upon the ratio of the population geometric means (fed versus fasted, i.e. Day -3 versus Day -7) for the PK parameters (C_{max} and AUC). The data will be transformed prior to analysis using a logarithmic transformation. T_{max} between fed and fasted states will be compared using a non-parametric test such as the Wilcoxon test. Descriptive statistics of other PK parameters will be presented both in fasting and fed conditions.

Sample Size:
Monotherapy Dose Escalation – Part A
A BOIN design with target toxicity rate of 30% (with escalation and de-escalation thresholds of 23.6% and 35.9%, respectively) with maximum number of approximately 30 patients will be used to estimate the IPN60090 monotherapy MTD.
The design will proceed with accelerated titration up to DL3, i.e. cohorts of one will be enrolled until either the third dose level is evaluated, a Grade 2 AE that is at least possibly related to the study drug(s) occurs, or a DLT is observed (whichever occurs first). If a Grade 2 AE that is at least possibly related to the study drug(s) or a DLT is observed in a single patient cohort (i.e. in one of the first three dose levels), two additional patients will be added at this dose level with the same rules for escalation and de-escalation as the cohorts of three patients detailed below.
If the DLT rate within a cohort at a given dose level is less than the escalation boundary of 23.6% the rule is then to escalate, if the DLT rate is higher than the de-escalation boundary of 35.9% then the rule is either to de-escalate, or to retain the dose or to stop if the maximum

sample size is reached. Following the requisite follow-up in a cohort, the dose level for the next cohort will be determined using the following decision rules where ↑indicates the next cohort at one dose level higher, ↓ indicates the next dose level at one dose level lower and "Elim" indicates that the dose level (and all higher dose levels) is removed from further consideration:

	Number of patients at current dose level							
Action	3	4	5	6	7	8	9	10
↑if number of DLT ≤	0	0	1	1	1	1	2	2
Stay current dose if DLT	1	1	-	2	2	2	3	3
↓ if number of DLT ≥	2	2	2	3	3	3	4	4
Elim if number of DLT ≥	3	3	4	4	5	5	5	6

DLT=dose limiting toxicity; Elim=eliminate

If none of the actions is indicated, then the next cohort is enrolled at the same dose level as current. If the current dose level is the lowest dose level and the action indicated is de-escalation, then the next cohort is enrolled at the same dose level (i.e. the lowest dose level). Similarly, if the current dose level is the highest dose level and the action indicated is escalation then the next cohort is treated at the same dose level. When a dose is eliminated, the next cohort is enrolled at the next lower dose level. If the lowest dose is eliminated, then the study is stopped and none of the dose levels is selected as the MTD.

The study will continue until one of the following occurs:

(a) the maximum number of patients has been reached (approximately 30)

(b) the decision indicated by the table would result in adding patients to a dose level where at least 9 patients have already been treated

(c) the number of patients treated at the lowest dose level is ≥3 and the probability that the DLT rate at the lowest dose level exceeds the target is >0.90.

When (a) or (b) occurs, the MTD of IPN60090 will be estimated as the dose level at which the isotonic estimate of the DLT rate is closest to 30%. If there are ties, the MTD is selected as the higher dose level when the isotonic estimate is lower than the target toxicity rate and selected as the lower dose level when the isotonic estimate is greater than or equal to the target toxicity rate.

Combination Dose Escalation – Parts B and C

A BOIN design with target toxicity rate of 30% (with escalation and de-escalation thresholds of 23.6% and 35.9%, respectively) with maximum number of approximately 18 patients (for each combination dose finding) will be used to estimate the IPN60090 combination MTD. The design will enrol six cohorts of three patients. Patients in the first cohort will be treated at combination DL1. Because the escalation and de-escalation thresholds are the same as those used for the monotherapy, the escalation and de-escalation rules as a function of number of patients treated are the same as those presented for the monotherapy.

The study continues until one of the following occurs

(a) the maximum number of patients has been reached (approximately 18):

(b) the decision indicated by the table would result in the number of patients at a dose level exceeding nine patients.

(c) the number of patients treated at the lowest dose level is ≥3 and the probability that the DLT rate at the lowest dose level exceeds the target is greater than 0.90.

When (a) or (b) occurs, the MTD of IPN60090 will be estimated as the dose level at which the isotonic estimate of the DLT rate is closest to 30%. If there are ties, the MTD is selected as the higher dose level when the isotonic estimate is lower than the target toxicity rate and selected as the lower dose level when the isotonic estimate is greater than or equal to the target toxicity rate.

Food Effect Assessment - Part D

The sample size (n=8) is not based on statistical calculation. A sample size of eight patients allows for a preliminary assessment of the potential effect of food on the PK of IPN60090.

Dose Expansion Phase

Preliminary anti-tumour activity will be evaluated in each dose expansion cohort (each regimen and indication combination) according to a sequential two-stage design based on a fixed sample size with look at 10 and at 18. The first stage will enrol 10 patients and stop for futility if no patients or only one patient achieves the efficacy criterion defined by a BOR of CR, PR or SD lasting at least 12 weeks in Parts A and C cohorts; respectively iCR, iPR or iSD for 12 weeks for Part B cohorts. If an expansion cohort passes the first stage, then a total of 18 patients (eight additional patients) would be enrolled. Six or more patients achieving the efficacy criterion already defined would suggest promising anti-tumour activity in the corresponding expansion cohort. The table below shows the operating characteristics for a range of true CBRs.

True CBR rate	Pr(find encouraging)	Pr(stop at stage 1)
0.10	0.01	0.74
0.20	0.13	0.38
0.30	0.46	0.15
0.35	0.64	0.09
0.40	0.78	0.05
0.45	0.89	0.02
0.50	0.95	0.01

CBR=clinical benefit rate; Pr=probability

As this is a signal seeking study, no statistical adjustments are considered for the multiple comparisons.

All assumptions for this sequential two-stage design may be revised in light of the dose escalation data and will then be described in a protocol amendment.

Tumour response to treatment will be evaluated using RECIST v1.1 and iRECIST guideline (Part B only) per the investigator. ORR, CBR and DCR will be summarised descriptively by cohort with two-sided 95% CIs.

Within each expansion cohort, PFS will be summarised descriptively using the Kaplan-Meier method.

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ABBREVIATION	Wording Definition
ADA	antidrug antibodies
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
ASNS	asparagine synthetase
$ASNS^{low}$	low protein expression level of asparagine synthetase
AST	aspartate aminotransferase
AUC	area under the plasma concentration time curve
$AUC_{0\text{-}24h}$	area under the plasma concentration time curve from time 0 to 24 hours
$AUC_{0\text{-}last}$	area under the plasma concentration time curve from time 0 to the last time point with quantifiable concentrations
BOIN	Bayesian Optimal Interval
BOR	Best Overall Response
BID	bis in die (twice daily)
CA	Competent Authority
CBR	clinical benefit rate
CD8	cluster of differentiation 8
cfDNA	circulating free deoxyribonucleic acid
CFR	Code of Federal Regulations (United States of America)
CI	confidence interval
CL/F	apparent total clearance from plasma
C_{max}	maximum observed plasma drug concentration
C_{min}	minimum observed plasma concentration
CPI	checkpoint inhibitor
CR	complete response
CRO	contract research organisation
CSR	clinical study report
CT	computed tomography
C_{trough}	trough plasma concentration
CYP2C8	cytochrome P450 subtype 2C8

ABBREVIATION	Wording Definition
CYP2D6	cytochrome P450 subtype 2D6
CYP3A4	cytochrome P450 subtype 3A4
CYP450	cytochrome P450
DCR	disease control rate
DDI	drug-drug interactions
DL	dose level
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECLA	ElectroChemiLuminiscence
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EDTA	ethylenediaminetetraacetic acid
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EOS	end of study
EU	European Union
EW	early withdrawal
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GLP	Good Laboratory Practice
Glu:Gln	glutamate:glutamine
GLS1	glutaminase-1
H2	histamine 2 receptor
HCC	hepatocellular carcinoma
HCG	human chorionic gonadotrophin
HED	human equivalent dose
HGSOC	high-grade serous ovarian cancer
HNSCC	head and neck squamous cell carcinoma
HNSTD	highest non-severely toxic dose
HSNTD	highest severely non-toxic dose

ABBREVIATION	Wording Definition
IACS	Institute for Applied Cancer Sciences
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
IC_{90}	90% inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
iCPD	immune confirmed progressive disease
iCR	immune complete response
ID	identification
IEC	independent ethics committee
IMP	investigational medicinal product
iPR	immune partial response
IRB	institutional review board
iRECIST	immune-related Response Evaluation Criteria in Solid Tumors
irAE	immune-related adverse event
IRT	Interactive Response Technology
ISAC	independent safety assessment committee
iSD	immune stable disease
iUPD	immune unconfirmed progressive disease
i.v.	intravenous
KEAP1	Kelch-like ECH-associated protein 1
Ki67	nuclear antigen Ki67
KRAS	Kirsten Rat Sarcoma Viral Oncogene Homolog
LC	liquid chromatography
LKB1	liver kinase B1
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MS	mass spectrometry
MTD	maximum tolerated dose
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NOAEL	no-observed-adverse-effect-level

ABBREVIATION	Wording Definition
NOS	not otherwise specified
NRF2	nuclear factor erythroid 2–related factor 2
NSCLC	non-small cell lung cancer
ORR	objective response rate
PBMC	peripheral blood mononuclear cells
PD	pharmacodynamics
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PFS	progression free survival
PK	pharmacokinetics
PR	partial response
PT	preferred term
Q3W	every 3 weeks
QD	once daily
QTcF	Fridericia corrected QT interval
R & D	research and development
RCC	renal cell carcinoma
RD	recommended dose
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SmPC	Summary of Product Characteristics
SoC	standard of care
SOC	system organ class
SOP	Standard Operating Procedure
SRC	Safety Review Committee
STK11	serine/threonine kinase 11
$t_{½}$	elimination half-life
TEAE	treatment-emergent adverse event
TGI	tumour growth inhibition
T_{max}	time to maximum observed drug concentration

ABBREVIATION	Wording Definition
TNBC	triple-negative breast cancer
T_{reg}	regulatory T-cell
ULN	upper limit of normal
US	United States
USA	United States of America
V/F	apparent volume of distribution
WHO-DD	World Health Organization drug dictionary

1 BACKGROUND INFORMATION

1.1 Introduction

Altered metabolism is one of the main hallmarks of tumour biology, forming the conceptual basis for the development of metabolic therapies in cancer. Many tumour cells depend on glutamine for their growth and survival. Indeed, glutamine provides a main source of key bioenergetics and biosynthetic buildings blocks. The enzyme glutaminase-1 (GLS1) catalyses the conversion of glutamine into glutamate. This directly impacts on a number of other nutrients and cellular building blocks including nucleotides and glutathione. Glutaminase-1 inhibition has been shown to deprive tumour cells of their fuel, thus leading to tumour stasis. This inhibition was also associated with a decrease in the glutathione levels and an increase in the reactive oxygen species resulting in deoxyribonucleic acid (DNA) damage.

IPN60090 (also coded as IACS-06274) is a novel oral and potent selective GLS1 inhibitor developed by the MD Anderson Cancer Centre (part of the University of Texas), Institute for Applied Cancer Sciences (IACS). In May 2018, IACS and Ipsen entered into a research and development collaboration agreement to co-develop IPN60090.

Preclinical investigations have demonstrated a strong link between the Kelch-like ECH-associated protein 1 (KEAP1)/nuclear factor erythroid 2–related factor 2 (NRF2) mutation status in tumour cells and glutaminase dependency, as well as a synthetic lethal interaction between glutaminase inhibition and low protein expression levels of asparagine synthetase ($ASNS^{low}$ i.e. immunohistochemistry 0-1), an alternative source of glutamate. These data provide a rationale for the development plan described herein that is focused on biomarker-based selection of patients whose tumours have a high dependency on glutaminase.

IPN60090 is currently in clinical development and the first treatment in humans took place on 04 April 2019. Another GLS1 inhibitor developed by Calithera, CB-839, is currently in the phase II stage of clinical development. However, no biomarker strategy is currently established or being pursued with CB-839 in clinical studies. With the current biomarker-driven strategy (KEAP1/NRF2 mutant tumours or $ASNS^{low}$ tumours) defined for the novel GLS1 inhibitor IPN60090, it is thought that better anti-tumour activity may be expected in monotherapy.

The alterations in the metabolic networks necessary to fuel and sustain cellular growth have been linked to therapeutic resistance, which is frequently correlated with a very poor patient outcome. By targeting these sources of energy using a GLS1 inhibitor, resistant tumour cells can often be resensitised to anticancer therapies. Indeed, early compelling clinical activity was reported with CB-839 in combinatorial regimens, such as nivolumab, paclitaxel or cabozantinib in patients with aggressive tumour types, including triple-negative breast cancer (TNBC) and renal cell carcinoma (RCC) [1, 2]. These preliminary results suggest that GLS1 inhibitors, when combined with targeted therapies, immunotherapy or chemotherapy, present a pathway to overcome resistance within tumours that no longer respond to current standards of care (SoC).

This is a first in human study of IPN60090. The phase I study will generate safety, tolerability, and preliminary anti-tumour activity data in biomarker-selected and -unselected patients with advanced solid tumours. This study is also expected to provide a better understanding of the mechanism of action of IPN60090 and of the potential of selected biomarkers to predict the clinical outcome in monotherapy as well as in combination with other cancer therapies. The dose escalation part of the study will generate the first pharmacokinetic (PK), pharmacodynamic (PD) and safety data in humans, and will support the choice of the recommended dose (RD) for expansion. Dose expansion cohorts at the RD

will further define the safety and tolerability, and anti-tumour activity of IPN60090 monotherapy and combination therapy. The results observed in terms of anti-tumour activity during dose escalation and dose expansion will determine whether efficacy expansion cohorts will be conducted to further investigate the efficacy of IPN60090 in biomarker-selected or unselected populations and in combination with other anticancer agents.

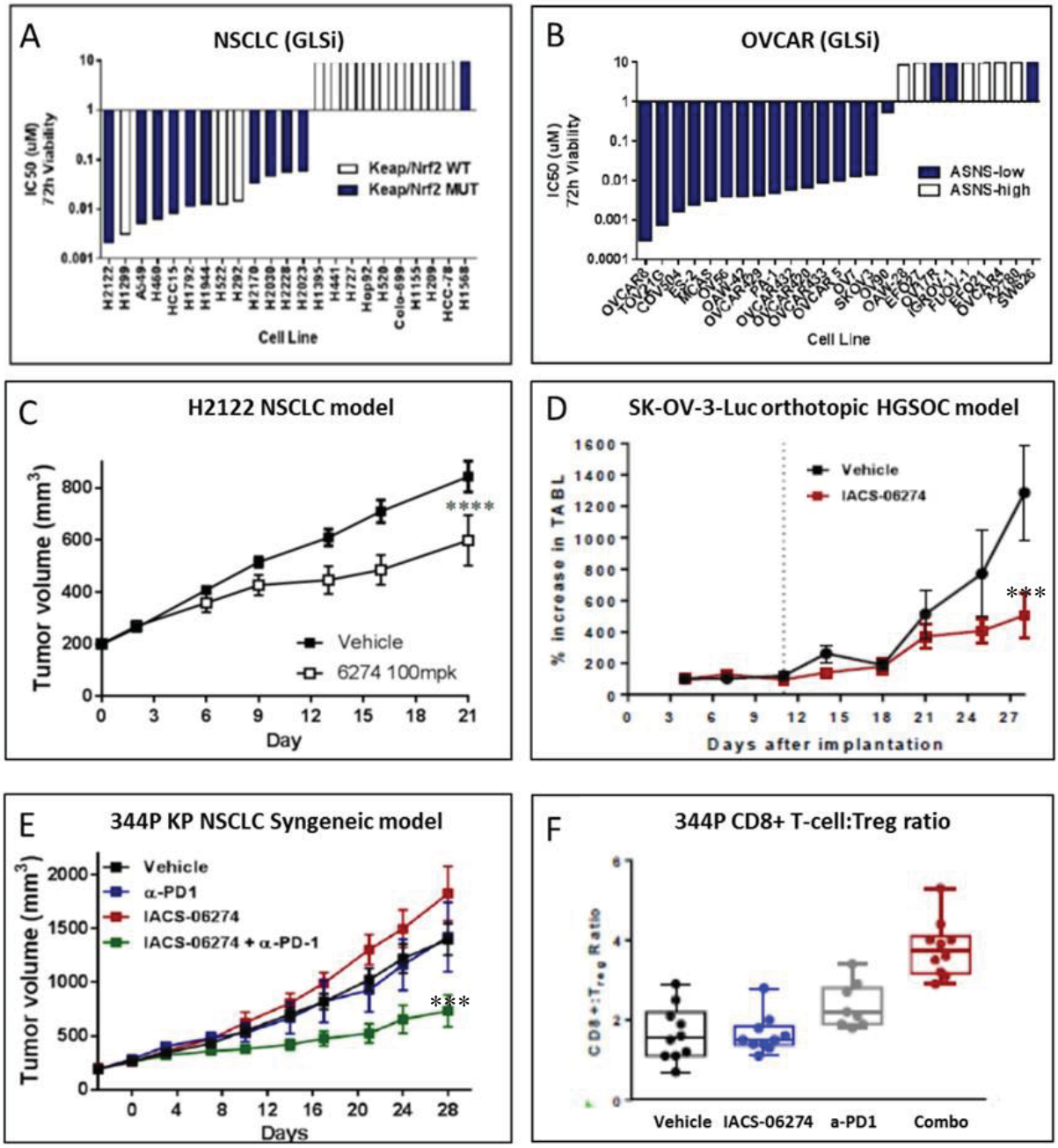
1.2 Study Rationale

1.2.1 Nonclinical Pharmacology Data

Preclinical data have shown that human non-small cell lung cancer (NSCLC) cells harbouring KEAP1/NRF2 mutations or high-grade serous ovarian cancer (HGSOC) cells with low expression levels of asparagine synthetase (ASNS) are highly sensitive to GLS1 inhibition. IPN60090 has shown a strong anti-proliferative activity in vitro across multiple NSCLC cell lines harbouring KEAP1 mutations (Figure 2, Panel A; Report IACS-6274-Pharm-001) and HGSOC cell lines with low levels of ASNS with half maximal inhibitory concentrations (IC_{50}) ranging from 45 nM to <1 µM (Figure 2, Panel B; Report IACS-6274-Pharm-002). In vivo investigations also confirm that IPN60090 exhibits significant tumour growth inhibition (TGI) in KEAP1 mutant NSCLC (Figure 2, Panel C; Report IACS-6274-Pharm-003) and $ASNS^{low}$ HGSOC (Figure 2, Panel D; Report IACS-6274-Pharm-003). These data provide strong evidence that in the context of these mutations/alterations in tumour cells, glutaminase dependence is observed.

It is known that within the tumour microenvironment, competition between tumour cells and immune cells for glutamine can lead to poor T-cell activation. IPN60090 synergises with anti-programmed cell death protein 1 (PD-1) in preclinical tumour models (Figure 2, Panel E). This synergy can be explained by the significant increase of cluster of differentiation 8 (CD8)/regulatory T-cells (T_{regs}) ratio in treated tumours (Figure 2, Panel F). These data highlight the ability of IPN60090 to modulate oncogenic pathways through actions on both tumour cells and T-cells within the tumour microenvironment.

Figure 2 Summary of Nonclinical Pharmacology Results



ASNS^{high}=high protein expression level of asparagine synthetase; ASNS^{low}=low protein expression level of asparagine synthetase; BID=bis in die (twice daily); CD8=cluster of differentiation 8; GLSi=glutaminase 1 inhibition; HGSOC=high-grade serous ovarian cancer; IACS-06274=IPN60090; IC_{50}=half maximal inhibitory concentration; KEAP1=Kelch-like ECH associated protein 1; KP=K-ras$^{LSL-G12D/+}$;p53$^{fl/fl}$; MUT=mutant; NRF2=nuclear factor erythroid 2-related factor 2; NSCLC=non-small cell lung cancer; OVCAR=ovarian cancer; PD-1=programmed cell death protein-1; T_{reg}=regulatory T-cells; WT=wild-type

***=p<0.001, ****=p<0.0001

Panel A: IC_{50} for the anti-proliferative activity of IPN60090 across multiple NSCLC cell lines over 72 hours

Panel B: IC_{50} for the anti-proliferative activity of IPN60090 across multiple HGSOC cell lines over 72 hours

Panel C: Anti-tumour activity in a subcutaneous KEAP1$_{mut}$ NSCLC model (H2122) treated with IPN60090 at 100 mg/kg BID for 21 days

Panel D: Anti-tumour activity in an orthototopic model of ASNS^{low} HGSOC treated with IPN60090 at 100 mg/kg BID for 27 days

Panel E: Anti-tumour activity of IPN60090 (100 mg/kg BID) in monotherapy or in combination with anti-PD-1 in a syngeneic model of NSCLC model (KRAS/P53$_{mut}$)

Panel F: The ratio of infiltrating CD8+/T_{regs} in tumours of mice treated with IPN60090 (100 mg/kg BID), anti-PD-1 or the combination of both drugs

IPN60090 was also shown to synergise with paclitaxel in ASNS^{low} tumours, potentially due to its capacity for decreasing glutathione pool levels and for increasing oxidative stress inside the tumours, thus, leading to tumour cell death.

These data all together provide strong evidence for evaluating IPN60090 in tumours harbouring KEAP1/NRF2 mutations or ASNS low levels in monotherapy. Preclinical data supporting anti-tumour activity in combination with anti-PD-1 and taxanes provide the rationale for exploring a combination therapy approach across a broad range of tumour types.

1.2.2 Unmet Medical Need

Lung cancer is the leading cause of cancer-related mortality world-wide. GLOBOCAN estimated worldwide incidence of lung cancer tumours in 2012 to be 1.8 million (12.9% of all cancers) with an age standardised rate of 23.1 per 100,000. Non-small cell lung cancer (NSCLC) accounts for 85% to 90% of all lung cancer cases [3]. When feasible, surgical resection remains the single most consistent and successful option for cure. However, close to 70% of patients with lung cancer present with locally advanced or metastatic disease at the time of diagnosis [4]. Combination chemotherapy modestly improves overall survival from approximately 6 months without chemotherapy to 10 to 12 months with chemotherapy. Molecular targeted therapy for a biomarker selected population with metastatic NSCLC allows long duration of disease control with acceptable toxicity for a subset of patients, extending median overall survival beyond 2 to 3 years [5, 6]. Given the global burden of NSCLC and despite a number of new therapies to treat advanced stage tumours, there is still a high unmet medical need for patients with NSCLC, especially for those harbouring these KEAP1 and NRF2 mutations. Expression of KEAP1/NRF2 mutations in NCSLC, and several advanced solid tumours, is indeed associated with higher malignant biological behaviour and poor prognosis [7]. NSCLC is the most common tumour type expressing these mutations with approximately 20% and 10% of patients expressing KEAP1/NRF2 mutations, respectively.

Additionally, these mutations can commonly be found in head and neck squamous cell carcinoma (HNSCC) (5% and 13%), urothelial carcinoma (7% and 3%) and hepatocellular carcinoma (HCC) (5% and 4%), among others.

It has been demonstrated that KEAP1/NRF2 mutations drive increased dependency on glutamine in human lung adenocarcinoma [7]. A significant increased sensitivity to IPN60090 was also demonstrated across multiple KEAP1/NRF2 mutant cell lines as well as in in vivo tumour models harbouring these alterations, making tumours harbouring KEAP1/NRF2 mutation good candidates for treatment with IPN60090.

Significant unmet medical need exists for subsets of NSCLC like those with co-occurring genomic alterations in Kirsten Rat Sarcoma Viral Oncogene Homolog (KRAS) and serine/threonine kinase 11 (STK11)/liver kinase B1 (LKB1) (KL cluster) representing about 30% of KRAS-mutant NSCLC. These genomic alterations are associated with a “cold” tumour immune microenvironment with reduced density of infiltrating CD8+ T lymphocytes but also lower levels of programmed death-ligand 1 (PD-L1) expression and thus very poor response to checkpoint inhibitor (CPI) alone (objective response rate (ORR): 0%; 0/6 in CheckMate-057 study) [8]. A significant co-occurrence of KEAP1 mutation was reported in this KL cluster making this subset good candidate for treatment with IPN60090 [9]. The combination of IPN60090 with CPI may thus be a way to revert CPI resistance in this subset of NSCLC since IPN60090 was shown to synergize with CPI (see Section 1.2.1).

Preclinical activity of IPN60090 was observed in ASNS^{low} HGSOC cell lines and xenograft models. Acquired or de-novo resistance to platinum-based chemotherapy represents a significant challenge in the treatment of advanced ovarian cancer. Platinum-resistant tumours have been shown to have a significant dependency on glutamine, with an upregulated

expression of glutamine transporter ASCT2 and glutaminase [10]. Targeting a subset of ASNS^{low} HGSOC with a GLS1 inhibitor such as IPN60090 may provide a way to overcome resistance to platinum-based therapies.

Therefore, for these patients, a biomarker-driven approach with IPN60090 in monotherapy may provide previously unseen benefit in the second or later line setting. Preclinical data also supports studying IPN60090 in combination with SoC anticancer therapies (anti PD-1 and taxanes).

1.2.3 Current Clinical Data Available on Glutaminase Inhibitors

A GLS1 inhibitor, CB-839 developed by Calithera, is currently in the phase II stage of development. To date, CB-839 monotherapy demonstrated one partial response (PR) and eight stable disease (SD) among 15 patients with RCC (ORR=7%) [11]. This would suggest the need for identification of the patient subpopulation carrying specific mutations or genetic alterations that render cancers glutaminase-dependent to potentiate anti-tumour efficacy in monotherapy.

CB-839 was also tested in combination with different standard therapies, such as nivolumab, paclitaxel and cabozantinib. Early phase I efficacy results were reported with these combinatorial regimens:

- combination with nivolumab: 44% disease control rate (DCR) and 19% ORR in 16 patients with melanoma previously treated with a CPI,
- combination with paclitaxel: 80% DCR and 40% ORR in TNBC patients at the RD of 600 mg twice daily (BID) of CB-839 [1],
- combination with cabozantinib: 100% DCR and 33% of ORR in 12 patients with clear cell and papillary advanced or metastatic RCC at a dose of 800 mg BID of CB-839 [2].

These preliminary results suggest that GLS1 inhibitors, when combined with other therapies, may present a pathway to overcome resistance within cancers that no longer respond to current SoC.

1.3 Name and Description of Investigational Medicinal Product

IPN60090 is an oral potent and selective small molecule inhibitor of GLS1. IPN60090 will be supplied as hard capsules containing either 10 mg, 60 mg or 240 mg of active substance. A more detailed description of the product is provided in Section 3.5.

1.4 Known and Potential Risks and Benefits to Human Patients

Anti-tumour efficacy of IPN60090 in monotherapy may be potentiated by identifying and selecting patients with specific mutational profiles that render cancer glutaminase dependent. Indeed, preclinical investigations have shown that IPN60090 inhibits glutamine metabolism in NSCLC and HGSOC cell lines in vitro and shows anti-proliferative effects on biomarker-defined subsets of KEAP1/NRF2 mutant NSCLC cells and ASNS^{low} HGSOC cells in vitro. In animal models using KEAP1/NRF2 mutant NSCLC and ASNS^{low} HGSOC human tumour cell lines, IPN60090 inhibited tumour growth, with TGI of 38% to 55%. Upon orthotopic implantation of an ASNS^{low} model of HGSOC in the intraperitoneal cavity, IPN60090 caused an even more significant inhibition of tumour growth (TGI=67%).

Combinatorial regimens of CB-839 with standard therapies such as nivolumab or paclitaxel showed preliminary clinical efficacy results in different types of tumours. Nonclinical investigations have shown that IPN60090 sensitises taxane-resistant KEAP1/NRF2 mutant NSCLC and ASNS^{low} HGSOC models to taxane-based therapies. These data suggest that for indications in which taxane-based chemotherapy is the front-line SoC, IPN60090 has the potential to enhance clinical response, especially in patients with NSCLC whose tumours

have mutations in KEAP1/NRF2 and patients with HGSOC whose tumours are characterised as $ASNS^{low}$. In addition, glutamine metabolism has been shown to play important roles within the immune system, including roles in T-cell activation and T-cell effector functions. In a syngeneic model of $KRAS^{mut}$, $TP53^{mut}$ NSCLC, co-administration of IPN60090 and αPD-1 monoclonal antibodies (mAb) induced an overall TGI of 65% whereas neither agent alone showed anti-tumour activity. The mechanism of how IPN60090 treatment enhances checkpoint blockade is likely due to the statistically significant increase in CD8+ T-cells and concurrent reduction in T_{regs} present in tumours treated with IPN60090 in combination with an anti-PD-1 mAb. These findings demonstrate that IPN60090 treatment enhances the activity of checkpoint blockade agents through actions both on tumour cells and on T-cells within the tumour microenvironment.

Based on the clinical data generated with a related compound and based on the nonclinical data generated with IPN60090, evaluating the investigational new drug in the selected populations is justified.

The known and potential risks in humans from nonclinical toxicology studies are haematotoxicity observed in dog and hepatotoxicity observed in both rat and dog. IPN60090 was well tolerated in male rats up to 300 mg/kg/day but reversible increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), total bilirubin, total cholesterol, and triglycerides were observed in two female rats administered 300 mg/kg/day. These changes correlated with mild bile duct hyperplasia (also present in one recovery female animal), minimal focal necrosis of the liver, necrosis of the pancreatic duct and/or mild to moderate lymphoid necrosis of the thymus. The dog was the more sensitive species in the 4-week Good Laboratory Practice (GLP) toxicology studies. Both male and female dogs in the high dose group (100 mg/kg/day) were terminated early after only 8 days of dosing due to adverse clinical signs of inappetence, prostration, salivation, thinness, decreased activities, vomitus, dilated pupils, yellowish eye discolouration and significantly decreased body weight and food consumption. Treatment-related findings in this group included: reversible decreased reticulocyte count that correlated with reversible bone marrow hypocellularity and/or decreased erythropoiesis in bone marrow; increased ALT, AST, total bilirubin, alkaline phosphatase (ALP), total cholesterol, triglyceride, creatine kinase, and GGT that were correlated with bile duct hyperplasia, periportal fibrosis, periportal mixed cell infiltration, canalicular cholestasis, Kupffer cell pigmentation, hepatocellular necrosis and/or hepatocellular vacuolation. These adverse liver findings were partially reversible at the end of the 28-day recovery period. Consequently, biochemistry and haematology parameters will be carefully monitored during the phase I study with laboratory assessments performed on Days 1, 2, 8, 14, 22, 29 and then every 21 days.

The target GLS1 is also known to be expressed in organs such as the brain, kidney, cardiac muscle and pancreas [12, 13]. Regarding the brain, there were no treatment-related effects on neurobehavioral functional observational battery tests in rats. Potential central effects in humans will be carefully monitored by neurological examination. Monitoring of kidney function is part of the biochemistry assessments with creatinine serum levels and estimated glomerular filtration rate (eGFR) calculation. Regarding cardiac function, in both the non-GLP and GLP human ether-a-go-go-related gene assays, the IC_{50} was >30 µM indicating negligible risk for corrected QT interval prolongation and there were no treatment-related effects on cardiovascular parameters in dogs (based on the electrocardiogram (ECG) measurements in the GLP 4-week toxicology studies). Repeated ECG measurements will nevertheless be performed during the first days of treatment in this study. Pancreatic function will be monitored as part of the regular laboratory assessments.

The starting dose has been selected using a conservative approach as approximately 1/8.4 (or 0.12) of the human equivalent dose (HED) associated with the highest severely non-toxic dose (HSNTD) in the most sensitive species with consideration of the Food and Drug Administration (FDA) Guidance for estimating the maximum safe starting dose in initial clinical studies for therapeutics in adult healthy volunteers [14, 15]. Moreover, the dose of IPN60090 will be carefully escalated using a Bayesian Optimal Interval (BOIN) design [16, 17] with target dose limiting toxicity (DLT) rate of 30% in monotherapy and combination dose escalations.

Based on all the available data, the sponsor believes that the potential benefits of IPN60090 will outweigh the potential risks in this phase I study conducted in patients with serious and advanced diseases for which no curative therapies are available. In addition, patients enrolled in this study will be closely monitored for potential safety risks. The sponsor will ensure that a safety surveillance plan is put into place to disseminate new safety information to investigators, institutional review boards (IRBs) and regulatory authorities in a timely manner.

1.5 Selection of Investigational Medicinal Products and Dosages

1.5.1 Starting Dose

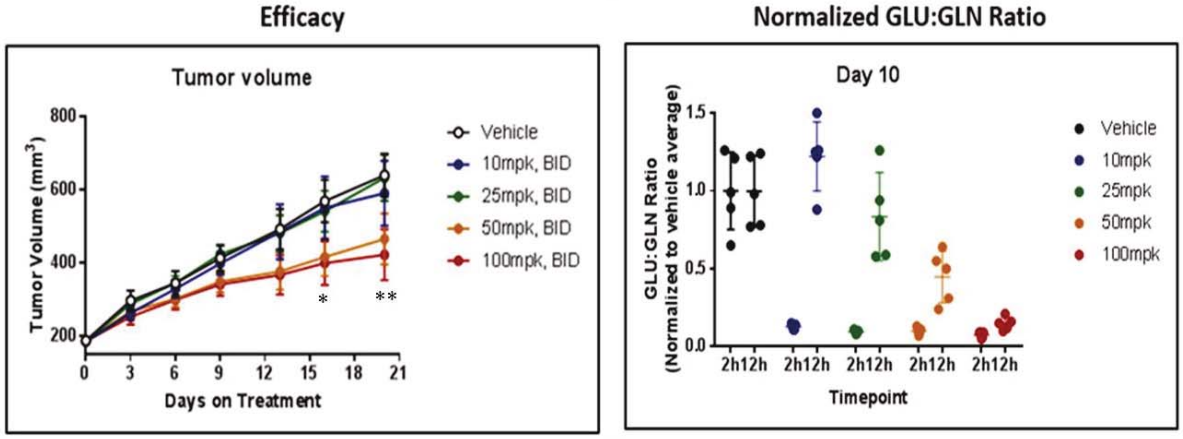
Nonclinical efficacy, toxicology and PK data were used to define a starting dose in humans and to support preliminary projections of potentially pharmacologically active doses. The estimations of HEDs for the starting dose and the projected pharmacologically active doses were based on the methods proposed in the International Council for Harmonisation (ICH) Guidance for Industry S9 [ICH 2009] and in the FDA Guidance for Industry "Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers" [14].

A no-observed-adverse-effect-level (NOAEL) was determined for rats and dogs in the pivotal 28-day oral toxicity studies. The NOAEL in rats was 300 mg/kg/day in males and 100 mg/kg/day in females. Associated exposure to IPN60090 in female rats was 142 µg/mL (maximum observed plasma drug concentration (C_{max})) and 2280 µg*h/mL (area under the plasma concentration time curve (AUC) from time 0 to 24 hours (AUC_{0-24h})). In dogs, the NOAEL was 30 mg/kg/day in males and 10 mg/kg/day in females. The lower NOAEL for female dogs was mainly due to one animal in the 30 mg/kg/day group that had test article-related adverse findings in the liver (for example increased liver enzymes, bile duct hyperplasia, hepatocellular necrosis) and bone marrow (for example decreased erythropoiesis and hypocellularity of the bone marrow) like those observed in the 100 mg/kg/day group. This one female dog exhibited much higher exposures to the drug than the other animals in the group. Consequently, the highest non-severely toxic dose (HNSTD) in this study (for the female dog) was equivalent to the NOAEL (i.e. 10mg/kg/day). Associated exposure to IPN60090 at the HNSTD was 11.6 µg/mL (C_{max}) and 138 µg*h/mL (AUC_{0-24h}). Using the HNSTD for the female dog (the more sensitive species), the calculated HED for a 60 kg human is 5.4 mg/kg. Based on this calculated HED and after applying a safety factor of 6, the starting dose in the clinic is estimated to be approximately 54 mg/day (i.e. 27 mg BID). However, because of limited capsule strengths availability (10 mg, 60 mg and 240 mg), a starting dose in humans of 40 mg/day (0.67 mg/kg/day for a 60 kg human patient), dosed as 20 mg every 12 hours (i.e. 20 mg BID), was selected. This proposed starting dose provides about 8.4-fold safety margins below the HED associated with the HNSTD in the dog GLP toxicology studies.

The dose escalation studies in combination with pembrolizumab and paclitaxel (Parts B and C, respectively) will start at the first dose level showing pharmacological activity (i.e. at least 50% inhibition of glutamate:glutamine (Glu:Gln) ratio in peripheral blood mononuclear cells

(PBMCs) at trough plasma concentration (C_{trough}; i.e. 12 hours postdose) on Day 14 in 66% of patients treated at this dose level) with good tolerability identified in Part A. This threshold of 50% inhibition of the PD marker at 12 hours was selected since data from a mouse model of NSCLC (H2122) suggest that maintaining at least 50% inhibition of the Glu:Gln ratio in PBMC over a dosing interval (i.e. 12 hours for BID dosing) is correlated with TGI (Report IACS-6274-Pharm-005, see Figure 3) that is expected to be further potentiated in combination with other agents. Indeed, the two doses that showed anti-tumour efficacy in terms of TGI (50 and 100 mg/kg BID) were able to maintain from 50% up to 96% inhibition of Glu:Gln ratio in PBMC up to the end of the dosing interval.

Figure 3 Effect of IPN60090 Doses (from 10 to 100 mg/kg BID) on Tumour Growth Inhibition



BID=bis in die (twice daily); GLU:GLN= glutamate:glutamine; PBMC=peripheral blood mononuclear cell
*=p<0.05, **=p<0.01
Effect of different IPN60090 doses (from 10 to 100 mg/kg BID) on tumour growth inhibition in H2122 mouse model (left panel) and corresponding normalised Glu:Gln ratio in PBMC at 2 and 12 hours on Day 10 (right panel)

1.5.2 Dosing Regimen

Most nonclinical pharmacology experiments on which dose extrapolations were based were performed with a BID regimen. Moreover, at the same daily dose, a BID regimen allows a reduction in C_{max} compared to a once daily (QD) regimen, thus decreasing the risk of potential C_{max}-related adverse effects. In addition, nonclinical pharmacology experiments seemed to show that significant anti-tumour activity is reached when minimum IPN60090 concentration and thus PD marker inhibition (Glu:Gln ratio inhibition) are maintained over a dosing interval (Report IACS-6274-Pharm-005). A BID regimen allows maintenance of a higher minimum observed plasma concentration (C_{min}) over a dosing interval compared to a QD regimen at the same daily dose. For these reasons, a BID regimen has been selected.

1.5.3 Projections of Pharmacologically Active Range

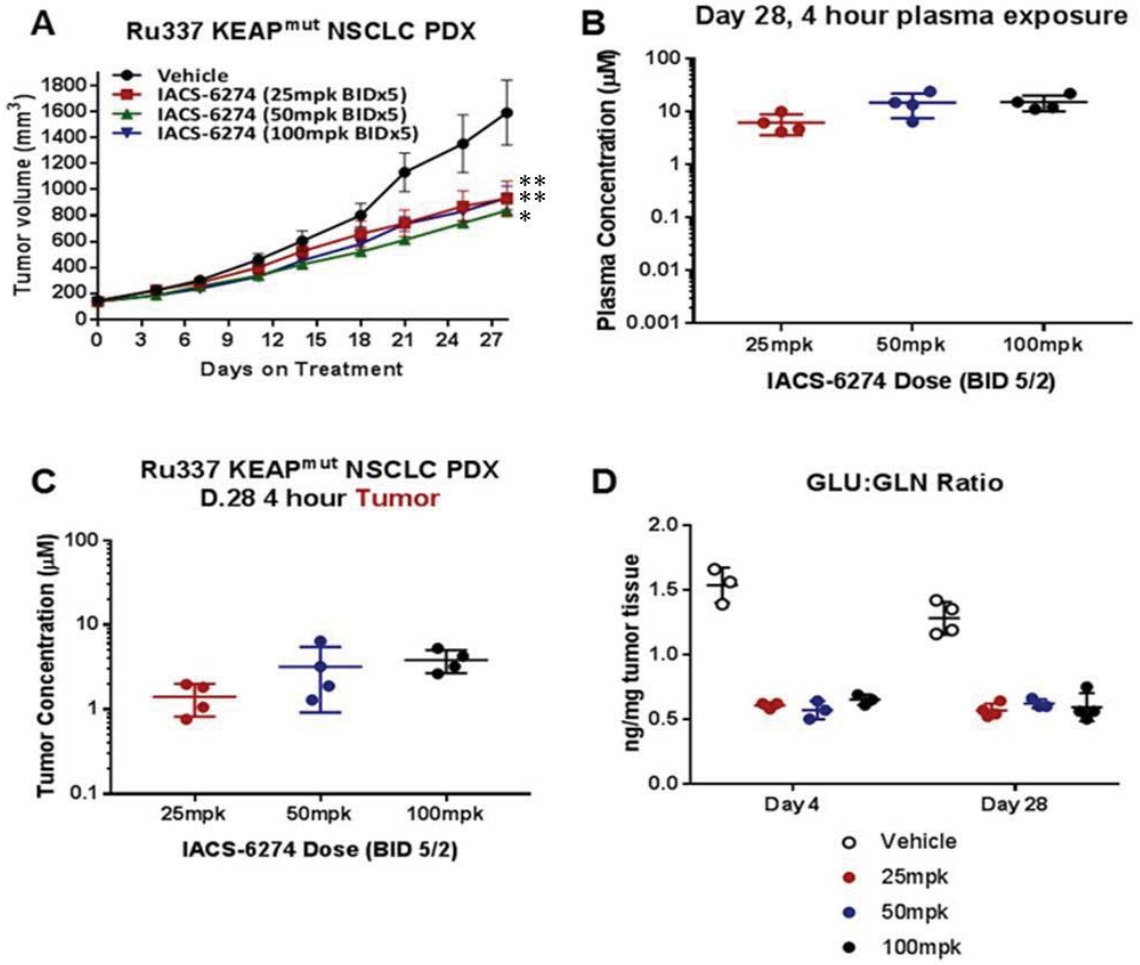
In in vitro pharmacology studies, IPN60090 inhibited the conversion of glutamine to glutamate in an A549 lung cancer cell line with an IC_{50} of approximately 14 nM. In addition, IPN60090 demonstrated a potent anti-proliferative effect across a panel of NSCLC and HGSOC human tumour cell lines with 90% inhibitory concentrations (IC_{90s}) ranging from 0.4 µM to 6.8 µM. IPN60090 treatment was also associated with a reduction in glutathione levels and an increase in reactive oxygen species production and DNA damage accumulation in tumour cells at 1 µM, a dose that is consistent with the aforementioned range of IC_{90} required for inhibition of tumour cell proliferation. In addition, the ability of IPN60090 to inhibit GLS1 activity, measured as the conversion of $^{13}C_5$-GLN to $^{13}C_5$-GLU, was evaluated in PBMCs from human donors in vitro. In these studies, IPN60090 had an IC_{90} of 2.56 µM (1.36 µg/mL), consistent with the concentrations required to inhibit tumour cell proliferation

(0.4 µM to 6.8 µM; i.e. 0.213 µg/mL to 3.62 µg/mL). Thus, the in vitro activity of IPN60090 in both mechanistic glutaminase inhibition and tumour cell proliferation assays supports target trough plasma levels in the range of approximately 1 µg/mL to 4 µg/mL.

In in vivo pharmacology studies, IPN60090 inhibited the growth of biomarker-defined subsets of both NSCLC and HGSOC in monotherapy and enhanced anti-tumour response to taxanes and immune CPIs in several tumour models. A potent anti-tumour effect was achieved with an oral dosing of IPN60090 at 100 mg/kg BID or 200 mg/kg QD in a NSCLC model. The dose of 100 mg/kg BID was selected for multiple preclinical in vivo studies. This dose achieves the maximal potent target engagement of GLS1, as measured both in vitro and ex vivo and is associated with a C_{max} of 52.7 µg/mL, an $AUC_{0\text{-}24h}$ of 319 µg*h/mL and a C_{trough} of 11.34±3.60 µM (6.03 µg/mL) in the mouse.

The minimally effective dose of IPN60090 was explored in a dose-ranging study (Report IACS-6274-Pharm-005). IPN60090 inhibited tumour growth in a KEAP1 mutant patient derived xenograft model of NSCLC (Ru337 model). The effect on tumour growth was similar at doses ranging from 25 mg/kg BID to 100 mg/kg BID (see Figure 5) suggesting that doses less than 100 mg/kg BID may be potentially associated with a clinical benefit. Indeed, the maximal potent target engagement in tumours (Glu:Gln ratio inhibition) was already achieved at the dose of 25 mg/kg BID and was similar across the different doses tested up to 100 mg/kg BID. In addition, the concentrations of IPN60090 that were achieved in plasma and the tumours of treated animals (Day 28, 4 hours post-treatment) were between 1 µM and 10 µM at 25 mg/kg BID. These values are consistent with the IC_{90} of anti-proliferative effect of IPN60090 in vitro (0.4 µM to 6.8 µM) and with the IC_{90} of the compound observed in human PBMC assay (2.56 µM). In addition, the inhibition of Glu:Gln ratio evaluated in mouse PBMCs at 2 hours post-treatment with IPN60090 reached a plateau at the doses between 10 mg/kg and 30 mg/kg. These doses corresponded to more than 90% of inhibition of GLS1 activity with a 90% effective concentration around 1.4 µM.

Figure 4 PK/PD/Efficacy Study in a KEAP1 Mutant PDX Model of NSCLC (Ru337)



BID=bis in die (twice daily); GLU:GLN=glutamate:glutamine; IACS-6274=IPN60090; KEAP1=Kelch-like ECH-associated protein 1; NSCLC=non-small cell lung cancer; PD=pharmacodynamic; PDX=patient derived xenograft; PK=pharmacokinetic

*=p<0.05, **=p<0.01

Panel A: Anti-tumour efficacy of IPN60090 in Ru337 model by oral BID dosing at 25, 50 and 100 mg/kg. Panels B and C: Concentrations levels of IPN60090 achieved in plasma (panel B) and in tumours (Panel C) of animals treated with IPN60090 at the different doses tested (4 hours post-treatment on Day 28). Panel D: The ratio of Glu:Gln in tumours of treated animals at Day 4 and Day 28.

All together, these data strongly support the consideration of the dose of 25 mg/kg BID as the minimal active dose in mice. Thus, the projected HED associated with the range of pharmacologically active doses in mice models (25 to 100 mg/kg BID) is 230 mg BID to 900 mg BID, when corrected by the unbound fraction being different across species (0.9% in human and 1.7% in mouse).

1.5.4 Proposed Dosing Strategy and Dose Escalation Scheme

Table 5 summarises the projected human starting dose and potentially pharmacologically active doses.

Table 5 Summary Table of Projected Human Doses

Projected human dose	Extrapolated from	Human equivalent dose (HED)[a]	
		Total	Corrected by unbound fraction[b]
Dose associated with HNSTD	HNSTD in female dog: 10 mg/kg/day (5 mg/kg BID)	336 mg/day (168 mg BID)[c]	~860 mg/day (430 mg BID)
Starting dose in human	HNSTD in female dog: 10 mg/kg/day (5 mg/kg BID)	Starting dose of 40 mg/day (20 mg BID) corresponding to a safety factor of 8.4 in dog	~100 mg/day (50 mg BID)
Projected range of pharmacologically active doses in human	25 mg/kg BID in mouse model	120 mg BID	230 mg BID[d]

BID=bis in die (twice daily); HED=human equivalent dose; HNSTD=highest non-severely toxic dose
a assuming a 60 kg human
b dose yielding similar unbound concentration in human and animal
c the low HNSTD (10 mg/kg/day) is due to one single animal with high exposure. If 30 mg/kg/day had been selected as the HNSTD, the dose associated with the HNSTD and the corresponding starting dose would be 972 mg/day (486 mg BID) and about 160 mg/day (80 mg BID), respectively.
d computed using HED conversion factor and correction by fu (0.9 % in human, 1.7 % in mouse, 2.3% in dog)

The proposal in dose escalation Part A (monotherapy) is to use an accelerated titration with single-patient cohorts and 100% dose increments up to 80 mg BID. Single-patient cohorts will only be used for doses projected to be below the dose associated with the HNSTD and thus expected to produce low or no toxicity (20, 40 and 80 mg BID with safety factors of 8.4, 4.2 and 2.1, respectively). Then, from 180 mg BID (human dose associated with the HNSTD), the number of patients in each cohort will be increased to three. The dose escalation will continue with 100% increments until the range of projected pharmacologically active doses is reached (i.e. 320 mg BID) then dose increments will be decreased to 50%.

Table 6 Projected Escalation Scheme

Dose level 1	Dose level 2	Dose level 3	Dose level 4	Dose level 5	Dose level 6	Dose level 7
20 mg BID	**40 mg BID**	**80 mg BID**	**180 mg BID[a]**	**320 mg BID**	**480 mg BID**	**720 mg BID**
N=1 patient	N=1	N=1	N=3	N=3	N=3	N=3
2×10 mg capsules	4×10 mg	1×60 mg + 2×10 mg	3×60 mg	1×240 mg + 1×60 mg + 2×10 mg	2×240 mg	3×240 mg

BID=bis in die (twice daily)
a 180 mg BID was selected instead of 160 mg BID to reduce the number of capsules and therefore reduce the burden for patients. The dose of 160 mg BID would correspond to six capsules BID (2×60 mg+4×10 mg) whereas the dose of 180 mg corresponds to three capsules BID (3x60 mg).

This is a projected escalation scheme that may be revised on an ongoing basis since the escalation will be guided by a BOIN design using a target DLT rate of 30%.

Beside the safety data (DLTs), other parameters, such as PK and PD parameters, will be looked at during the escalation to evaluate the levels of target engagement and compound exposure. The Glu:Gln ratio in PBMCs will be the PD parameter used to analyse the target engagement potency at each dose level. In addition to DLT considerations, the PK and PD parameters will also help to refine the escalation levels if needed.

Further details on study treatments are presented in Section 6.2.

1.5.5 Food Effect Assessment Rationale

Part D will explore the effect of food on a single administration of IPN60090 (patients will receive the treatment under fed and fasted conditions). A moderate fat meal has been selected since patients with late stage cancer may have difficulties eating a high-fat meal as described in the FDA Guidance for Industry *Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations.* For ethical reasons, after the run-in period designed to evaluate the effect of food on the IPN60090 PK profile, patients will be allowed to receive IPN60090 BID as described in Part A.

1.6 Population to be Studied

Emerging studies highlight the determinant role of the metabolic heterogeneity and plasticity to potentially influence the clinical outcome of molecules targeting cancer metabolism. Thus, patients whose tumours are highly dependent on glutamine catabolism should be in principle more susceptible to glutaminase inhibition, both in monotherapy and in combination. Thus, the clinical development strategy for IPN60090 will be focusing on a biomarker driven approach in monotherapy to select glutamine-dependent tumours harbouring a high frequency of either KEAP1/NRF2 mutations or low level of ASNS such as:

- NSCLC: ~20% and 10% KEAP1 and NRF2 mutations respectively. NSCLC patient selection will also allow exploring the predictive role of co-occurring mutations such as KRAS and LKB1 status (mutant versus wild-type)
- Other tumour types that express KEAP1/NRF2 mutations including, but not limited to: HNSCC (approximately 5% of KEAP1 mutations and 12% to 14% of NRF2 mutations), urothelial cancer (7% and 3% KEAP1 and NRF2 mutations respectively), and HCC (approximately 5% of KEAP1 mutations and 4 % of NRF2 mutations)
- HGSOC with low expression levels of ASNS (approximatively 15% of HGSOC tumours). Tumours will be classified as ASNS low using a qualitative analysis of ASNS staining in tumour biopsies with a score of 0 or 1+ depending on the intensity (negative or weak) and pervasiveness of staining [18]. A quantitative method of ASNS staining using H-SCORE may also be explored to evaluate the optimal range of H-SCORE that would be associated with a clinical benefit.

The dose escalation study and the food assessment study will be performed in biomarker unselected patients with solid tumours to establish the RD of IPN60090. Patients will be actively screened for putative predictive biomarkers of response to IPN60090, for example KEAP1 and NRF2 mutations, and low ASNS expression levels for this study. A retrospective analysis of the correlation between KEAP1/NRF2 mutations versus wild-type or $ASNS^{low}$ versus $ASNS^{high}$ tumours and the sensitivity to IPN60090 will be performed. Patients will be enrolled in four separate parts either:

- Part A: IPN60090 monotherapy, or
- Part B: IPN60090 + pembrolizumab, or
- Part C: IPN60090 + paclitaxel, or
- Part D: IPN60090 monotherapy, food effect part

The dose expansion portions will aim to further assess safety and tolerability, and preliminary anti-tumour activity of IPN60090 in monotherapy and the combination of IPN60090 with pembrolizumab or paclitaxel.

Patients must have received at least one line of therapy for advanced stage disease and be refractory or ineligible to available existing therapy(ies) known to provide clinical benefit for their condition.

Patients in Part A (IPN60090 monotherapy) dose expansion must be KEAP1/NRF2 mutation carriers or have $ASNS^{low}$ levels.

Patients enrolled in the Part B expansion portion may have received previous treatment with any PD-1 or PD-L1 inhibitor, to evaluate if adding IPN60090 can increase response rate or reverse resistance to CPI.

Patients enrolled in the Part C expansion portion must have received at least one line of therapy for metastatic disease (including platinum- or taxane-based chemotherapy) and may be refractory or resistant to platinum and/or -taxane chemotherapies (for example HGSOC, TNBC).

Patients enrolled in Parts B (IPN60090 + pembrolizumab) and C (IPN60090 + paclitaxel) dose expansion portions may be KEAP1/NRF2 mutant or KEAP1/NRF2 wild-type, or may have different levels of ASNS.

Further details on administration procedures and dosage are provided in Section 6.2.

1.7 Compliance Statement

The study will adhere to all local regulatory requirements and relevant company policies. The sponsor will ensure that the countries where the data are transferred provide an adequate level of protection to the data.

In case of data transfer outside the European Union (EU), the sponsor will either ensure that the countries where the data are transferred provide an adequate level of data protection or that the company receiving the data has joined the EU-United States (US) of America (USA) Privacy Shield Framework or will put in place a contract including standard contractual clauses adopted by the European Commission to ensure that the transfer of study information complies with applicable data protection legislation. Such a contract can be made available upon request.

Before initiating the study, the investigator/institution will have: written and dated approval/favourable opinion from the independent ethics committee (IEC)/IRB for the study protocol/amendment(s), written informed consent form, any consent form updates, patient emergency study contact cards, patient recruitment procedures (for example advertisements), any written information to be provided to patients and a statement from the IEC/IRB that they comply with Good Clinical Practice (GCP) requirements. The IEC/IRB approval must identify the protocol version as well as the documents reviewed.

2 PURPOSE OF THE STUDY AND STUDY OBJECTIVES

2.1 Purpose of the Study

Preclinical studies provide strong evidence for evaluating IPN60090 in tumours harbouring KEAP1/NRF2 mutations or ASNS low levels in monotherapy, and in combination with different therapeutic agents, including anti-PD-1 and taxanes across a variety of tumour types (see Section 1.2.1).

This is a phase I, first in human, dose escalation study with multiple expansion cohorts of IPN60090. The dose escalation part will investigate the safety and tolerability and provide a better understanding of the mechanism of action of IPN60090 and of the potential of selected biomarkers to predict the clinical outcome in monotherapy as well as in combination with other cancer therapies. This study will also generate the first PK data in humans and PK/PD correlation data that will support the choice of the RD. An additional cohort will explore the effect of food on the IPN60090 PK profile. The dose expansion part will further define the safety and tolerability of IPN60090 alone and in combination and investigate the preliminary anti-tumour activity.

2.2 Study Objectives

This study will evaluate the safety, PK, PD and anti-tumour activity of IPN60090 as a single agent (Part A) and in combination with pembrolizumab (Part B) or paclitaxel (Part C) in patients with advanced solid tumours. Part D will evaluate the safety of IPN60090 as a single agent and explore the effect of food on the IPN60090 PK profile. Specific objectives and corresponding endpoints for the study are outlined below.

2.2.1 Primary

- To assess the safety and tolerability of oral IPN60090 as a single agent (Part A and Part D) and in combination therapy with pembrolizumab (Part B) or paclitaxel (Part C).

For Dose Escalation Only:

- To determine the maximum tolerated dose (MTD), if reached, and the RD of IPN60090 as a single agent (Part A) and in combination therapy with pembrolizumab (Part B) or paclitaxel (Part C).

2.2.2 Secondary

- To assess the preliminary anti-tumour activity of IPN60090 as a single agent (Part A and Part D) and in combination with pembrolizumab (Part B) or paclitaxel (Part C) in patients with or without biomarker selected specific tumour types.
- To characterise the PK and PD profile of IPN60090 as a single agent (Part A and Part D) and in combination with pembrolizumab (Part B) or paclitaxel (Part C).
- To assess the effect of food on the PK profile of a single administration of IPN60090 (Part D).
- To document the concentrations of pembrolizumab and paclitaxel (Parts B and C).
- To document the potential development of antibodies against pembrolizumab (Part B)
- To evaluate biomarkers of patient stratification and correlate them with clinical outcome.

2.2.3 Exploratory

- To analyse exploratory biomarkers in archival and fresh biopsy samples, including biomarkers of response or resistance to the treatment, and associate them with clinical outcome.

- To collect biobank samples for potential future analysis of biomarkers (optional, informed consent required).

2.3 Study Hypothesis

IPN60090 will have a manageable safety profile to permit further clinical development as a single agent or in combination with pembrolizumab or paclitaxel in patients with advanced solid tumours and will demonstrate preliminary efficacy and anti-tumour effects as a monotherapy and/or in combination with pembrolizumab or paclitaxel across KEAP1/NRF2 mutant solid tumours and in $ASNS^{low}$ solid tumours.

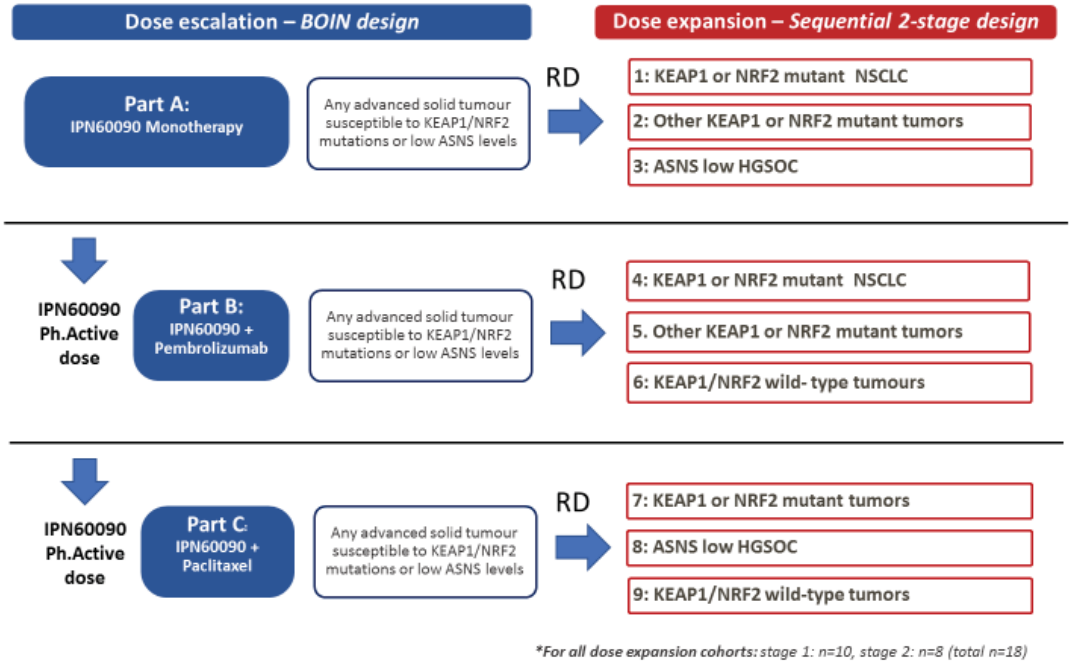
3 STUDY DESIGN

3.1 General Design and Study Schema

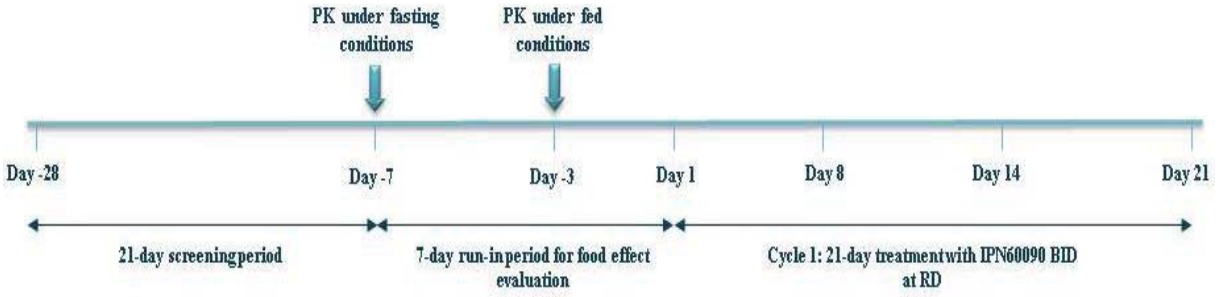
This is a phase I, first in human, open-label, dose escalation and dose expansion study of IPN60090 as a single agent or in combination in patients with advanced solid tumours. The study will be conducted from one centre in the USA to approximately 50 sites worldwide over the dose escalation and expansion parts of the study.

As summarised in Figure 5, the study will be divided into four parts.

Figure 5 IPN60090: Summary of Early Clinical Development



PART D



ASNS=asparagine synthetase; BID=bis in die (twice daily); BOIN=Bayesian Optimal Interval; HGSOC=high-grade serous ovarian cancer; KEAP1=Kelch-like ECH-associated protein 1; NRF2=nuclear factor erythroid 2-related factor 2; NSCLC=non-small cell lung cancer; Ph.=pharmacologically; RD=recommended dose

Part A: The dose escalation will explore the safety profile and establish the MTD (if reached), the target engagement or PD levels (Glu:Gln ratio in PBMC) and the RD of single agent IPN60090 in biomarker unselected patient populations. During the dose expansion portion, safety and tolerability at the RD will be assessed further, and the preliminary anti-tumour activity of IPN60090 will be explored in three different cohorts (NSCLC KEAP1 or NRF2 mutant, other KEAP1 or NRF2 mutant tumours and HGSOC $ASNS^{low}$). The scientific rationale for conducting these cohorts is provided in Section 1.2.1 and described below:

Dose Expansion Cohort 1: NSCLC KEAP1 or NRF2 Mutant: Due to the inherent heterogeneity of NSCLC and despite recent advances in targeted and combination treatment approaches, management of advanced NSCLC in the absence of targetable mutation, such as epidermal growth factor receptor, anaplastic lymphoma kinase, or BRAF, represents an unmet medical need as these patients inevitably relapse post each subsequent line of chemotherapy and have limited response to CPI blockade. KEAP1 and NRF2 mutations may represent novel markers of GLS1 inhibition. These mutations are present in about 20% of NSCLC, and often co-occur with KRAS mutations, for which no available targeted treatment option exists.

Dose Expansion Cohort 2: Other KEAP1 or NRF2 Mutant Tumours: KEAP1 and NRF2 mutations are present in about 6% of HNSCC, 5% of HCC and 3% to 5% of urothelial carcinomas, respectively, and convey tumour dependence on glutaminase and sensitivity to GLS1 inhibition, which warrants further exploration as there may be a potential to induce sensitivity to conventional therapy by including a tumour metabolism altering agent in the treatment paradigm.

Dose Expansion Cohort 3: HGSOC ASNS^{low}: Treatment of advanced recurrent HGSOC represents a highly unmet medical need, especially in the platinum resistant/refractory setting. By the time patients are determined to be platinum resistant or refractory, treatment options available to them become extremely limited. Targeting a specific subset of patients with low ASNS expression and sensitivity to GLS1 inhibition will explore the therapeutic potential of IPN60090 in this highly unmet medical need population.

Part B: The dose escalation will explore the safety profile and establish the MTD (if reached) and the RD of IPN60090 in combination with pembrolizumab. During the dose expansion portion, safety and tolerability at the RD will be assessed further, and preliminary anti-tumour activity of this combination will be explored.

In general, response to CPI blockade monotherapy is limited; however, those responses are durable. There is a need to explore treatment strategies that will increase response or overcome resistance to PD-1 inhibition.

Dose Expansion Cohort 4: KEAP1 or NRF2 Mutant NSCLC: Preclinical data indicates that adding a GLS1 inhibitor to anti-PD-1 therapy has the potential to boost response via an increase in the CD8/T_{reg} ratio. Dose expansion Cohort 4 will focus on KEAP1/NRF2 mutant NSCLC. Within that patient population, patients with co-occurring KRAS/KEAP1/LKB1 mutations are of particular interest, as presence of this cluster mutation may convey resistance to CPI therapy.

Dose Expansion Cohort 5: Other KEAP1 or NRF2 Mutant Tumours: A similar approach is applied in Cohort 5 in additional biomarker positive KEAP1/NRF2 mutant tumour types for which pembrolizumab is approved as SoC to explore if addition of IPN60090 would prevent or reverse resistance to CPI.

Dose Expansion Cohort 6: KEAP1 or NRF2 Wild-type Tumours with any level of ASNS Expression: In addition, the combination of IPN60090 and pembrolizumab will be explored in KEAP1/NRF2 wild-type tumours, as there are early clinical data from CB-839 that indicate preliminary anti-tumour activity of the combination in the biomarker-unselected patient population.

Part C: The dose escalation will explore the safety profile and establish the MTD (if reached) and the RD of IPN60090 in combination with paclitaxel. During the dose expansion portion, safety and tolerability at the RD will be assessed further, and preliminary anti-tumour activity of this combination will be explored.

Dose Expansion Cohort 7: KEAP1 or NRF2 Mutant Tumours and Dose Expansion Cohort 8: ASNS^{low} HGSOC: Preclinical data for the combination of IPN60090 and paclitaxel

provides rationale for the synergistic activity of the combination in HGSOC and NSCLC models. Given the high unmet medical need in treatment of these tumour types, dose expansion Cohorts 7 and 8 will look into this combination in KEAP1/NRF2 mutant tumours and ASNS^{low} HGSOC, respectively, to explore if adding a glutaminase inhibitor may enhance response to treatment.

Dose Expansion Cohort 9: KEAP1 or NRF2 Wild-type Tumours with any level of ASNS Expression: In addition, Cohort 9 will explore the combination of IPN60090 and paclitaxel in the biomarker-unselected patient population across approved tumour types, based on early clinical data from CB-839 that indicate the potential synergy of IPN60090 and paclitaxel.

Parts B and C: These dose escalations in combination with pembrolizumab or paclitaxel will be initiated at the first dose with pharmacological activity (at least 50% inhibition of Glu:Gln ratio in PBMCs at C_{trough} (12 hours postdose) on Day 14 in 66% of patients treated at this dose level) and with good tolerability as identified in Part A. The threshold of 50% inhibition of the PD marker has been selected since in a mouse model of NSCLC (H2122), maximum TGI (at 50 and 100 mg/kg BID) was observed when at least 50% up to 96% inhibition of the PD marker in PBMC was maintained over a dosing interval (i.e. 12 hours).

Part D: This cohort will evaluate the safety of IPN60090 administered as a single agent and explore the effect of a moderate fat meal on the PK profile of IPN60090 administered as a single dose under fasting and fed conditions at the RD as defined by the Safety Review Committee (SRC).

3.1.1 Number of Patients

Number of Patients Planned:

Dose Escalation

Part A (single agent): Approximately 30 patients for the dose escalation.

Part B (combination with pembrolizumab): Approximately 18 patients for the dose escalation.

Part C (combination with paclitaxel): Approximately 18 patients for the dose escalation.

Food Effect Assessment

Part D: Eight patients for preliminary food effect assessment.

Dose Expansion

Parts A, B and C: Approximately 162 patients (90 patients in Stage 1 of dose expansion and 72 patients in Stage 2).

3.1.2 Dose Escalations

3.1.2.1 Part A – Dose Escalation with IPN60090 as a Single Agent

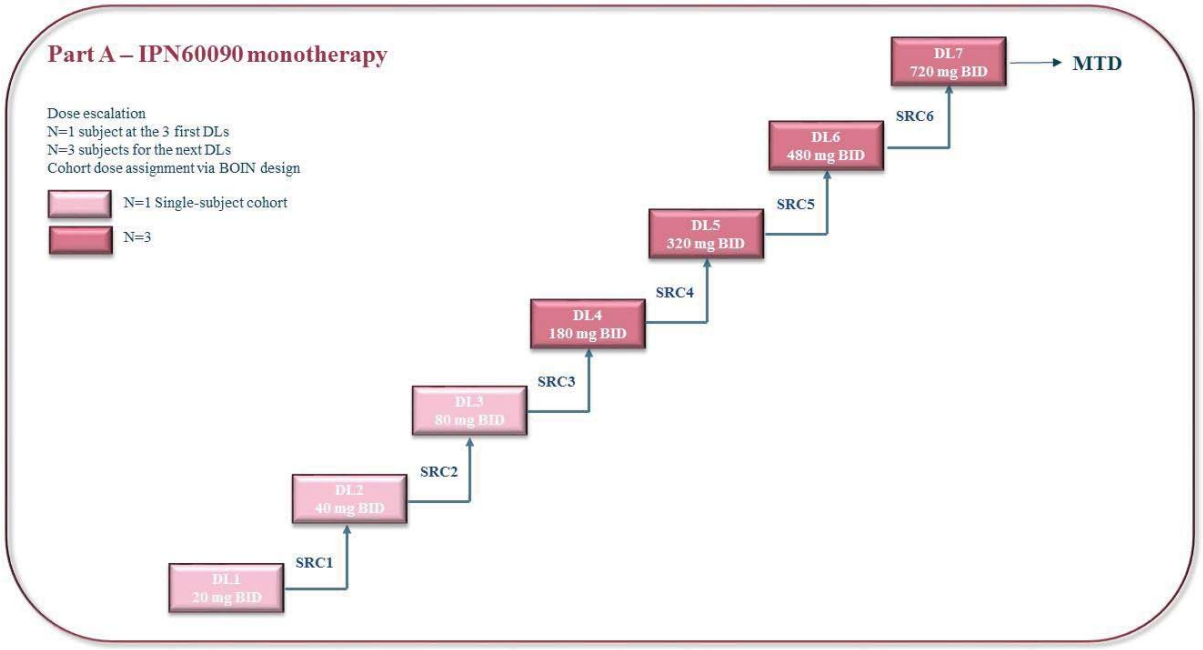
The dose escalation portion of Part A is to evaluate the safety, tolerability, PK and PD of IPN60090 given as a BID oral dose (every 12 hours), during or after a meal, over a 21-day cycle.

Dose escalation of IPN60090 will be conducted in patients with biomarker-positive and biomarker-negative advanced solid tumours.

These patients will not be selected for KEAP1/NRF2 mutation status and may be wild-type or mutated. Patients may have tumours with any level of ASNS expression.

Seven dose levels are planned to be tested (as presented in Figure 6). The study will follow a BOIN design for dose escalation [16, 17]. Dose levels provided are examples and after the starting dose, the dose level will be determined by the SRC. After each SRC meeting, the tested dose level can be escalated, de-escalated or extended as indicated per the BOIN design.

Figure 6 Part A-IPN60090 Monotherapy - Predefined Escalation and De-escalation Scheme



BOIN=Bayesian Optimal Interval; DL=dose level; MTD=maximum tolerated dose; SRC=Safety Review Committee

At all dose levels, IPN60090 will be administered orally BID starting from Day 1 of each 21-day cycle. The predefined dose escalation plan is described in Table 7.

Table 7 Dose Escalation Phase I-Part A

DL1	DL2	DL3	DL4	DL5	DL6	DL7
20 mg BID	40 mg BID	80 mg BID	180 mg BID[a]	320 mg BID	480 mg BID	720 mg BID

BID=bis in die (twice daily); DL=dose level

a 180 mg BID was selected instead of 160 mg BID to reduce the number of capsules and therefore reduce the burden for patients. The dose of 160 mg BID would correspond to six capsules BID (2×60 mg+4×10 mg) whereas the dose of 180 mg corresponds to three capsules BID (3×60 mg).

The Part A monotherapy dose escalation will enrol single-patient cohorts for the first three dose levels (if no Grade 2 adverse event (AE) that is at least possibly related to the study drug(s) or DLT is observed) and then cohorts of three patients each at the predefined dose levels. If a Grade 2 AE that is at least possibly related to the study drug(s) or a DLT is observed in a single patient cohort (first three dose levels), two additional patients will be added at this dose level with the same rules for escalation and de-escalation as the cohorts of three patients. At any point, additional patients may be enrolled as required for safety assessment and/or biomarker analysis. Following each cohort DLT assessment period, the observed DLT data will be used to determine the dose level for the next cohort in accordance with the escalation and de-escalation rules for a local BOIN design using a target toxicity rate of 30% with escalation and de-escalation thresholds of 23.6% and 35.9%, respectively. Following the completion of enrolment, the MTD will be estimated at the dose level at which the isotonic estimate of the DLT rate is closest to 30%.

At the end of each part, up to two dose levels may be repeated in order to reach a total of 18 patients at each dose level to collect more PK/PD information to better define the RD. The decision to repeat a dose level will be made by the SRC. Safety data from these additional patients will not be included in the BOIN design to determine the MTD but will be evaluated by the SRC and ultimately be taken into consideration for RD selection.

MTD Definition

The MTD is defined as the maximum dose of IPN60090 that may be administered BID for 21 days, so that no more than 30% of patients experience a DLT. The MTD will be determined by the dose for which the isotonic estimate of DLT rate is closest to 30% of patients experiencing a DLT.

DLT Assessment Period

The DLT assessment period will consist of the first 21 days of treatment (one cycle). The SRC will evaluate safety and available PK and PD data after patients have completed at least one cycle of treatment in order to make a decision on dose escalation, and to determine the MTD and the RD. The SRC may decide to evaluate an intermediate, not predefined, previously evaluated or not previously-evaluated dose or a less frequent dosing schedule that will not exceed the MTD level, if evaluation of toxicity at such a dose or schedule is desired. More details about the SRC are included in Section 4.3.1 and will be described in the SRC charter.

DLT Criteria

The DLTs for Part A are defined for any of the following investigational medicinal product (IMP)-related, probably related or possibly related AEs according to National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 that occur during the defined DLT assessment period (over the 21 days following the first dose of IPN60090):

- Grade 4 neutropenia lasting >7 days
- Febrile neutropenia of any grade (absolute neutrophil count (ANC) <1000/mm^3 with a single temperature episode of 38.3°C or a sustained temperature of 38°C for >1 hour).
- Grade 3 or 4 neutropenia with infection.
- Grade 3 thrombocytopenia with bleeding and Grade 4 thrombocytopenia.
- Grade 4 life threatening anaemia.
- ALT/AST ≥3×upper limit of normal (ULN) with total bilirubin ≥2×ULN without elevation of ALP and no other reasonable explanation for the abnormality (Hy's law criteria).
- Grade 3 lasting more than 7 days or Grade 4 laboratory abnormalities of ALT/AST and/or bilirubin, with the following exceptions:
  - for patients with Grade 1 ALT/AST at baseline (>ULN to 3×ULN), an ALT/AST value of >7.5×ULN will be considered a DLT.
  - for patients with Grade 2 ALT/AST at baseline (>3×ULN to 5×ULN), an ALT/AST value >10×ULN will be considered a DLT.
- Grade 3 or higher non-haematological toxicity excluding:
  - Grade 3 nausea, vomiting or diarrhoea for less than 72 hours with adequate supportive care.
  - Grade 3 fatigue lasting less than a week.
  - Grade 3 or higher electrolyte abnormality that lasts for less than 72 hours, that is not clinically complicated and resolves spontaneously or with conventional medical interventions.
  - Grade 3 or higher amylase or lipase lasting less than 72 hours and not associated with clinical manifestations of pancreatitis.
- Grade 5 (death).

Other clinically significant or persistent toxicities may be considered a DLT following review by the SRC.

Patient Eligibility for Dose Escalation Decision

Any patient who does not complete the DLT assessment period for any reason other than a DLT will be considered nonevaluable for dose escalation decisions and MTD assessment and will be replaced by an additional patient at that same dose level. Patients will be considered eligible for the DLT assessment only if they are able to receive ≥75% of the total planned IPN60090 dose over the DLT assessment period. Noncompliant patients will also be replaced. The SRC may decide to enrol additional patients based on the safety, PK or PD data.

Treatment Duration - Additional Cycles

Patients will be offered IPN60090 treatment beyond Cycle 1 as long as they continue to experience clinical benefit, in the opinion of the investigator, until the earlier of disease progression, symptomatic deterioration, poor tolerability despite appropriate medical management or any of the other reasons for treatment discontinuation. Patients who experience a DLT (or other toxicities considered related, probably related or possibly related to the study treatment) will be permitted to continue to receive study treatment at a lower dose level than the dose at which the DLT was observed, at the discretion of the investigator (see Section 6.4.4) and will be followed for safety. Biomarker-positive patients who are enrolled and receive study treatment at initial dose levels below the pharmacologically active range for at least two cycles with good tolerability, and achieve and maintain at least SD, may be escalated to a higher dose level that has been tested and proven to be well tolerated, at the recommendation of the SRC. These patients will be treated outside of the BOIN design. Patients who discontinue study treatment for reasons other than disease progression (for example toxicity) should continue to undergo scheduled tumour assessments approximately every 12 weeks until disease progression, initiation of further systemic cancer therapy, death, or until the study closes, whichever occurs first.

3.1.2.2 Part B – Pembrolizumab Combination Dose Escalation

The dose escalation portion of Part B is to evaluate the safety, tolerability, PK and PD of IPN60090 given as a BID oral dose (every 12 hours) during or after a meal in combination with pembrolizumab, over a 21-day cycle. The intake of IPN60090 will be made before the start of the pembrolizumab infusion.

Dose escalation of IPN60090 in combination with pembrolizumab will be conducted in patients with biomarker-positive and biomarker-negative advanced solid tumours.

These patients will be unselected for KEAP1/NRF2 mutation status and may be KEAP1/NRF2 wild-type or mutated. The same applies for ASNS expression levels; patients may have tumours with any level of ASNS expression. Previous treatment with CPI therapy is allowed.

This dose escalation in combination with pembrolizumab will be initiated at a dose level showing pharmacological activity (at least 50% inhibition of Glu:Gln ratio in PBMCs at C_{trough} (12 hours postdose and predose for the following dose) on Day 14 of Cycle 1 in 66% of patients treated at this dose level) and with good tolerability as identified in Part A. The IPN60090 dose being tested in the dose escalation of Part B will always remain lower than that being tested in the dose escalation of Part A (at least one dose level lower than the highest dose tested in Part A).

Three dose levels of IPN60090 are planned to be tested with an additional lower dose level (DL-1) if DL1 is not tolerated. The study will follow a BOIN design for dose escalation.

At all dose levels, IPN60090 will be administered orally BID starting from Day 1 of each 21-day cycle and pembrolizumab will be administered as one intravenous (i.v.) infusion every 21 days (±1 day in Cycle 1 and ±3 days in all other cycles) starting from Day 1 of each cycle. The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumour type. The predefined dose escalation plan is described in Table 8.

Table 8 Dose Escalation Phase I-Part B in Combination with Pembrolizumab

Dose level	Dose level -1	Dose level 1	Dose level 2	Dose level 3
Planned dose of IPN60090 [a]	80 mg BID	180 mg BID	320 mg BID	480 mg BID
Planned dose of pembrolizumab	200 mg Q3W [b]	200 mg Q3W [b]	200 mg Q3W [b]	200 mg Q3W [b]

BID=bis in die (twice daily); Q3W=every 3 weeks (21 days)
a dose levels are examples; the actual starting dose will be determined by PD from the Part A dose escalation
b or according to the local approved label for particular tumour types

Dose finding will begin at DL1. The study will enrol in cohorts of three patients at the predefined dose levels until up to six cohorts have been enrolled. Following each cohort, the observed DLT data will be used to determine the dose level for the next cohort in accordance with the escalation and de-escalation rules for a local BOIN design using a target toxicity rate of 30% with escalation and de-escalation thresholds of 23.6% and 35.9%, respectively. Following the completion of enrolment, the MTD will be estimated as the dose level at which the isotonic estimate of the DLT rate is closest to 30%.

If the first dose level of IPN60090 in combination with 200 mg pembrolizumab is not well tolerated, upon the decision of the SRC, the dose of IPN60090 may be de-escalated and thus a new cohort may start with DL-1.

At the end of each part, up to two dose levels may be repeated in order to reach a total of 18 patients at each dose level to collect more PK/PD information to better define the RD. The decision to repeat a dose level will be made by the SRC. Safety data from these additional patients will not be included in the BOIN design to determine the MTD but will be evaluated by the SRC and ultimately be taken into consideration for RD selection.

MTD Definition

The MTD is defined as the maximum dose of IPN60090 that may be administered BID for 21 days in combination with an i.v. infusion of 200 mg pembrolizumab (or according to the local approved label for particular tumour types), so that no more than 30% of patients experience a DLT. The MTD will be determined by the dose for which the isotonic estimate of DLT rate is closest to 30% of patients experiencing a DLT.

DLT Assessment Period

The DLT assessment period for IPN60090 in combination with pembrolizumab (Part B) will consist of the first 21 days of treatment (one cycle). An additional safety assessment for delayed onset AEs will be performed at 6 weeks (42 days), and at 12 weeks (84 days). The SRC will evaluate safety and available PK and PD data in order to make a decision on dose escalation, and to determine the MTD and the RD. The safety data reviewed by the SRC will include the safety findings and DLTs observed during the DLT assessment period from the previous cohort. The SRC may decide to evaluate an intermediate, not predefined, previously evaluated or not previously-evaluated dose of IPN60090 or a less frequent dosing schedule that will not exceed the MTD level if evaluation of toxicity at such a dose or schedule is desired.

DLT Criteria

The DLTs for Part B are defined for any of the following IMP-related, probably related or possibly related AEs according to NCI-CTCAE version 5.0 that occur during the defined DLT assessment period (over the 21 days following the first dose of IPN60090 combined with pembrolizumab):

- Grade 4 neutropenia lasting >7 days
- Febrile neutropenia of any grade (ANC <1000/mm^3 with a single temperature episode of 38.3°C or a sustained temperature of 38°C for >1 hour)
- Grade 3 or 4 neutropenia with infection.
- Grade 3 thrombocytopenia with bleeding and Grade 4 thrombocytopenia.
- Grade 4 life threatening anaemia.
- ALT/AST ≥3×ULN with total bilirubin ≥2×ULN without elevation of ALP and no other reasonable explanation for the abnormality (Hy's law criteria).
- Grade 3 lasting more than 7 days or Grade 4 laboratory abnormalities of ALT/AST and/or bilirubin, with the following exceptions:
  - for patients with Grade 1 ALT/AST at baseline (>ULN to 3×ULN, an ALT/AST value of >7.5×ULN will be considered a DLT.
  - for patients with Grade 2 ALT/AST at baseline (>3×ULN to 5×ULN), an ALT/AST value >10×ULN will be considered a DLT.
- Grade 3 or Grade 4 pneumonitis, hepatitis, colitis, nephritis, encephalitis, etc
- Grade 3 or Grade 4 rash lasting more than 72 hours with adequate supportive care.
- Grade 3 or higher non-haematological toxicity excluding:
  - Grade 3 nausea, vomiting or diarrhoea lasting less than 72 hours with adequate supportive care.
  - Grade 3 fatigue lasting less than a week.
  - Grade 3 or higher electrolyte abnormality that lasts for less than 72 hours, that is not clinically complicated and resolves spontaneously or with conventional medical interventions.
  - Grade 3 or higher amylase or lipase lasting less than 72 hours and not associated with clinical manifestations of pancreatitis.
- Grade 5 (death)

Other clinically significant or persistent toxicities may be considered a DLT following review by the SRC.

Transient infusion-related AEs that can be controlled with medical management (i.e. flu-like symptoms, fever) are not considered DLTs.

Patient Eligibility for Dose Escalation Decision

Any patient who does not complete the DLT assessment period for any reason other than a DLT will be considered nonevaluable for dose escalation decisions and MTD assessment and will be replaced by an additional patient at that same dose level. Moreover, patients will be considered eligible for the DLT assessment only if they received ≥75% of the total planned IPN60090 dose and one infusion of pembrolizumab over the DLT assessment period. Noncompliant patients will also be replaced. The SRC may decide to enrol additional patients based on the safety, PK or PD data.

Treatment Duration - Additional Cycles

Patients will be offered IPN60090 + pembrolizumab treatment beyond Cycle 1 as long as they continue to experience clinical benefit, in the opinion of the investigator, until the earlier of confirmed disease progression, symptomatic deterioration, poor tolerability despite appropriate medical management or any of the other reasons for treatment discontinuation. Patients who experience a DLT (or other toxicities considered related, probably related or possibly related to the study treatment) will be permitted to continue to receive study treatment at a lower dose level than the dose at which the DLT was observed, at the discretion of the investigator (see Section 6.4.4) and will be followed for safety. Patients who discontinue study treatment for reasons other than disease progression (for example toxicity) should continue to undergo scheduled tumour assessments approximately every 12 weeks until confirmed disease progression, or initiation of further systemic cancer therapy, death, or until the study closes, whichever occurs first.

3.1.2.3 Part C – Paclitaxel Combination Dose Escalation

The dose escalation portion of Part C is to evaluate the safety, tolerability, PK and PD of IPN60090 given as a BID oral dose (every 12 hours) in combination with paclitaxel, during or after a meal, over a 21-day cycle. The intake of IPN60090 will be made before the paclitaxel infusion.

Dose escalation of IPN60090 in combination with paclitaxel will be conducted in patients with biomarker-positive and biomarker-negative advanced solid tumours.

These patients will be unselected for KEAP1/NRF2 mutation and may be KEAP1/NRF2 wild-type or mutated. The same applies for ASNS expression levels, patients may have tumours with any level of ASNS expression. Dose escalation in combination with paclitaxel will be initiated at a dose level showing pharmacological activity (at least 50% inhibition of Glu:Gln ratio in PBMC at C_{trough} (12 hours postdose and predose for the following dose) on Day 14 of Cycle 1 in 66% of patients treated at this dose level) and good tolerability as identified in Part A. The IPN60090 dose being tested in Part C will always remain lower than that being tested in Part A (at least one dose level lower than the highest dose tested in Part A).

Three dose levels of IPN60090 are planned to be tested with an additional lower dose level (DL-1) if DL1 is not tolerated. The study will follow a BOIN design for dose escalation.

At all dose levels, IPN60090 will be administered orally BID starting from Day 1 of each 21-day cycle and paclitaxel will be administered as one i.v. infusion every 21 days (±1 day in Cycle 1 and ±3 days in all other cycles) starting from Day 1 of each cycle. The predefined dose escalation plan is described in Table 9.

Table 9 Dose Escalation Phase I-Part C in Combination with Paclitaxel

Dose level	DL-1	DL1	DL2	DL3
Planned dose of IPN60090 [a]	80 mg BID	180 mg BID	320 mg BID	480 mg BID
Planned dose of paclitaxel	175 or 135 mg/m² Q3W [b]	175 or 135 mg/m² Q3W [b]	175 or 135 mg/m² Q3W [b]	175 or 135 mg/m² Q3W [b]

BID=bis in die (twice daily); DL=dose level; Q3W=every 3 weeks (21 days)
a dose levels are examples; the actual starting dose will be determined by PD from the Part A dose escalation
b or according to the local approved label for particular tumour types

Dose finding will begin at DL1. The study will enrol in cohorts of three patients at the predefined dose levels until up to six cohorts have been enrolled. Following each cohort, the observed DLT data will be used to determine the dose level for the next cohort in accordance with the escalation and de-escalation rules for a local BOIN design using a target toxicity rate

of 30% with escalation and de-escalation thresholds of 23.6% and 35.9%, respectively. Following the completion of enrolment, the MTD will be estimated as the dose level at which the isotonic estimate of the DLT rate is closest to 30%.

If the first dose level of IPN60090 in combination with paclitaxel 175 or 135 mg/m² (or according to the local approved label for particular tumour types) given intravenously is not well tolerated, the dose of IPN60090 may be de-escalated and thus a new cohort may start with the DL-1.

At the end of each part, up to two dose levels may be repeated in order to reach a total of 18 patients at each dose level to collect more PK/PD information to better define the RD. The decision to repeat a dose level will be made by the SRC. Safety data from these additional patients will not be included in the BOIN design to determine the MTD but will be evaluated by the SRC and ultimately be taken into consideration for RD selection.

MTD Definition

The MTD is defined as the maximum dose of IPN60090 that may be administered BID for 21 days in combination with an i.v. infusion of 175 or 135 mg/m² paclitaxel (or according to the local approved label for particular tumour types), so that no more than 30% of patients experience a DLT. The MTD will be determined by the dose for which the isotonic estimate of DLT rate is closest to 30% of patients experiencing a DLT.

DLT Assessment Period

The DLT assessment period will consist of the first 21 days of treatment (one cycle). The SRC will evaluate safety and available PK and PD data in order to make a decision on dose escalation, and to determine the MTD and the RD. The safety data reviewed by the SRC will include the safety findings and DLTs observed during the DLT assessment period from the previous cohort. The SRC may decide to evaluate an intermediate, not predefined, previously evaluated or not previously evaluated dose or a less frequent dosing schedule that will not exceed the MTD level, if evaluation of toxicity at such a dose or schedule is desired.

DLT Criteria

The DLTs for Part C are defined for any of the following IMP-related, probably related or possibly related AEs according to NCI-CTCAE version 5.0 that occur during the defined DLT assessment period (over the 21 days following the first dose of IPN60090 combined with paclitaxel):

- Grade 4 neutropenia lasting >7 days
- Febrile neutropenia of any grade (ANC <1000/mm^3 with a single temperature episode of 38.3°C or a sustained temperature of 38°C for >1 hour.
- Grade 3 or 4 neutropenia with infection.
- Grade 3 thrombocytopenia with bleeding and Grade 4 thrombocytopenia.
- Grade 4 life threatening anaemia.
- ALT/AST ≥3×ULN with total bilirubin ≥2×ULN without elevation of ALP and no other reasonable explanation for the abnormality (Hy's law criteria).
- Grade 3 lasting more than 7 days or Grade 4 laboratory abnormalities of ALT/AST and/or bilirubin, with the following exceptions:
  - for patients with Grade 1 ALT/AST at baseline >ULN to 3×ULN, an ALT/AST value of >7.5×ULN will be considered a DLT.
  - for patients with Grade 2 ALT/AST at baseline (>3×ULN to 5×ULN), an ALT/AST value >10×ULN will be considered a DLT.
- Grade 3 or Grade 4 rash lasting more than 72 hours with adequate supportive care.

- Grade 3 or higher non-haematological toxicity excluding:
  - Grade 3 nausea, vomiting or diarrhoea for less than 72 hours with adequate supportive care.
  - Grade 3 fatigue lasting less than 1 week.
  - Grade 3 or higher electrolyte abnormality that lasts for less than 72 hours, that is not clinically complicated and resolves spontaneously or with conventional medical interventions.
  - Grade 3 or higher amylase or lipase lasting less than 72 hours and not associated with clinical manifestations of pancreatitis.
- Grade 5 (death).

Other clinically significant or persistent toxicities may be considered a DLT following review by the SRC.

Transient infusion-related AEs that can be controlled with medical management (i.e. flu-like symptoms, fever) are not considered DLTs.

Patient Eligibility for Dose Escalation Decision

Any patient who does not complete the DLT assessment period for any reason other than a DLT will be considered nonevaluable for dose escalation decisions and MTD assessment and will be replaced by an additional patient at that same dose level. Moreover, patients will be considered eligible for the DLT assessment only if they are able to receive ≥75% of the total planned IPN60090 dose and one infusion of paclitaxel over the DLT assessment period. Noncompliant patients will also be replaced. The SRC may decide to enrol additional patients based on the safety, PK or PD data.

Treatment Duration - Additional Cycles

Patients will be offered IPN60090 + paclitaxel treatment beyond Cycle 1 as long as they continue to experience clinical benefit, in the opinion of the investigator, until the earlier of disease progression, symptomatic deterioration, poor tolerability despite appropriate medical management or any of the other reasons for treatment discontinuation. Patients who experience a DLT (or other toxicities considered related, probably related or possibly related to the study treatment) will be permitted to continue to receive study treatment at a lower dose level than the dose at which the DLT was observed, at the discretion of the investigator (see Section 6.4.4) and will be followed for safety. Patients who discontinue study treatment for reasons other than disease progression (for example toxicity) should continue to undergo scheduled tumour assessments approximately every 12 weeks until disease progression, or initiation of further systemic cancer therapy, death, or until the study closes, whichever occurs first.

3.1.2.4 Transition to Recommended Dose or Different Regimen

In Parts A, B and C, when the RD is determined, if a patient is still in the study at a different dose, this patient can be moved to the RD, at the discretion of the investigator.

In Part A, biomarker-positive patients who are enrolled and receive study treatment at initial dose levels below the pharmacologically active range for at least two cycles with good tolerability, and achieve and maintain at least SD, may be escalated to a higher dose level that has been tested and proven to be well tolerated at the recommendation of the SRC. These patients will be treated outside of the BOIN design.

Patients enrolled in monotherapy Part A may receive combination treatment with either pembrolizumab or with paclitaxel upon progression on IPN60090 monotherapy, at the discretion of the investigator, and with the approval of the sponsor, once the safe dose level

for the combination is determined. These patients will need to satisfy the eligibility criteria for combination therapy prior to initiating treatment (see Section 4.1) and will be followed for safety and efficacy in a separate cohort.

3.1.3 Food Effect Assessment – Part D

Part D will start at the end of the Part A dose escalation. Patients in Part D will not be part of the dose escalation and MTD assessment.

Food effect evaluation will be conducted in patients with biomarker-positive and biomarker-negative advanced solid tumours.

These patients will not be selected for KEAP1/NRF2 mutation status and may be wild-type or mutated. Patients may have tumours with any level of ASNS expression. Eligibility criteria for Part D will be the same as the criteria for the Part A dose escalation.

After screening, eight patients will enter a run-in period of 7 days:

- At Day -7, patients will receive a single administration of IPN60090 at the RD (as defined by the SRC at the end of the Part A dose escalation) following an overnight fast of at least 10 hours. The patients should not consume any food for at least 4 hours after the dose. IPN60090 should be taken with 240 mL (i.e. 8 fluid ounces) of water. Additional water is permitted ad libitum except for the period 1 hour before to 1 hour after administration of the drug product.
- At Day -3, patients will receive a single administration of IPN60090 at the RD (morning dose only, as defined by the SRC at the end of the Part A dose escalation) 30 minutes after the start of a moderate fat meal. The moderate fat meal should be eaten in 30 minutes or less. The patients should not consume any food for at least 4 hours after the dose. IPN60090 should be taken with 240 mL (i.e. 8 fluid ounces) of water. Additional water is permitted ad libitum except for the period 1 hour before to 1 hour after administration of the drug product. Substitutions to the test meal can be made after discussion with the sponsor. It is understood that some patients may not be able to consume the entire meal. Study staff should record the percent of the test meal breakfast and the time it takes to be consumed.

Full PK profiles will be obtained on Day -7 and Day -3 to assess the effect of a moderate fat meal on the IPN60090 PK profile. Blood samples will be collected on Day -7 and Day -3 for the evaluation of haematology and serum chemistry, and AEs will be reported.

In Part D, the moderate fat meal is defined as the following: total calories of 500 to 750 kCal including 30 to 35% fat (see Table 13).

After the run-in period, patients will receive IPN60090 as a single agent administered orally BID (every 12 hours), during or after a meal, starting from Day 1 at the single agent RD. Patients in Part D will follow the same schedule of assessments as described for Part A (with the exception of the urine sampling for PK).

Patients enrolled in monotherapy Part D may receive combination treatment with either pembrolizumab or with paclitaxel upon progression on IPN60090 monotherapy, at the discretion of the investigator, and with the approval of the sponsor, once the safe dose level for the combination is determined. These patients will need to satisfy the eligibility criteria for combination therapy prior to initiating treatment (see Section 4.1), and will be followed for safety and efficacy in a separate cohort.

3.1.4 Dose Expansion Cohorts

The multicohort dose expansion part of the study will further explore the safety and tolerability of IPN60090 in monotherapy and in combination; assess the preliminary

anti-tumour activity of IPN60090 as a single agent and in combination with pembrolizumab or paclitaxel at the RD in biomarker positive and/or unselected patient population and will explore the potential of selected biomarkers as predictors of efficacy (candidate biomarkers will include, but will not be limited to, KEAP1/NRF2 mutation status, ASNS expression level and known or new emerging predictive or prognostic markers of efficacy in selected tumour types).

Enrolment into dose expansion cohorts will occur independently of each other. Each cohort will follow a sequential 2-stage design and enrol ten patients in Stage 1 and up to a total of 18 patients (Stage 1 + Stage 2).

The dose expansion cohorts that will be explored in each part of the study are defined as the following (which may be further expanded if an efficacy signal is observed):

- Part A- IPN60090 monotherapy
  - Dose Expansion Cohort 1: KEAP1 or NRF2 mutant NSCLC
  - Dose Expansion Cohort 2: Other KEAP1 or NRF2 mutant tumours
  - Dose Expansion Cohort 3: $ASNS^{low}$ HGSOC
- Part B- IPN60090 + pembrolizumab:
  - Dose Expansion Cohort 4: KEAP1 or NRF2 mutant NSCLC
  - Dose Expansion Cohort 5: Other KEAP1 or NRF2 mutant tumours
  - Dose Expansion Cohort 6: KEAP1 or NRF2 wild-type tumours with any level of ASNS expression
- Part C- IPN60090 + paclitaxel:
  - Dose Expansion Cohort 7: KEAP1 or NRF2 mutant tumours
  - Dose Expansion Cohort 8: $ASNS^{low}$ HGSOC
  - Dose Expansion Cohort 9: KEAP1 or NRF2 wild-type tumours with any level of ASNS expression

Dose expansion cohorts (study populations and sample size) may be revised in light of the dose escalation data and would then be described in a protocol amendment.

An independent safety assessment committee (ISAC) structured to assess safety in addition to efficacy will be established for dose expansion cohorts in order to make recommendations regarding protocol modifications to reduce risks to patients enrolled in the study. If preliminary clinical evidence in one or several dose expansion cohorts suggests a substantial improvement over available therapies on a clinically significant endpoint(s), further efficacy expansion cohorts may be initiated in the corresponding populations with the goal of assessing the anti-tumour activity of IPN60090 monotherapy or combination.

Patients enrolled in monotherapy Part A may receive combination treatment with either pembrolizumab or with paclitaxel upon progression on IPN60090 monotherapy, at the discretion of the investigator, and with the approval of the sponsor. These patients will need to satisfy the eligibility criteria for combination therapy prior to initiating treatment, and will be followed for safety and efficacy in a separate cohort.

3.2 Primary and Secondary Endpoints and Evaluations

3.2.1 Primary

- The safety and tolerability of IPN60090 as a single agent (Part A and Part D) and in combination with pembrolizumab (Part B) or paclitaxel (Part C) will be assessed by the rate of DLTs at each dose level in the dose escalation, and the rate of AEs and the rate of Grade 3 and higher AEs in the dose escalation and dose expansion. Continuous

monitoring of AEs and serious AEs (SAEs), clinical laboratory test results, the presence of anti-pembrolizumab antidrug antibodies (ADA; Part B only), vital signs measurements, ECG and physical examination results and concomitant medication usage will be performed.

For dose escalation only:

- Define MTD, if reached, as determined by the incidence and nature of DLTs, of:
  - single agent IPN60090 (Part A)
  - the combination of IPN60090 and pembrolizumab (Part B) or paclitaxel (Part C).
- Define RD, as determined by the PD, PK and safety of:
  - single agent IPN60090 (Part A)
  - the combination of IPN60090 and pembrolizumab (Part B) or paclitaxel (Part C).

3.2.2 Secondary

- Anti-tumour activity parameters assessed locally (for dose escalation) and centrally (for dose expansion) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 for Parts A, C and D and immune-related RECIST (iRECIST) for Part B only, including:
  - Clinical benefit rate (CBR) is defined as the proportion of patients in whom the Best Overall Response (BOR) is equal to complete response (CR), PR or SD lasting at least 12 weeks for Parts A, C and D, and equal to immune CR (iCR), immune PR (iPR) or immune SD (iSD) lasting at least 12 weeks for Part B
  - ORR is defined as the proportion of patients in whom the BOR is equal to CR and PR for Parts A, C and D or iCR and iPR for Part B
  - DCR is defined as the proportion of patients in whom the BOR is equal to CR, PR or SD for Parts A, C and D, and equal to iCR, iPR or iSD for Part B
  - Progression free survival (PFS) is defined as the time from first dose of study medication to the first documented objective disease progression (for RECIST) or confirmed objective disease progression (for iRECIST) or death due to any cause, whichever occurs first (except for Part B where confirmation of progression is needed to determine the PFS to exclude pseudoprogression).
  - Overall survival (OS) is defined as the time from first dose of study medication to death due to any cause.
- Pharmacokinetic parameters of IPN60090, including but not limited to C_{max}, time to C_{max} (T_{max}), C_{trough}, area under the plasma concentration-time curve (AUC), elimination half-life ($t_{1/2}$), apparent total clearance from plasma (CL/F) and apparent volume of distribution (V/F) of IPN60090 (Parts A to D).
- Describe the PK of a single dose of IPN60090 administered in fed state (Day -3) relative to fasted state (Day -7) using the following PK parameters: C_{max}, AUC, T_{max}, $t_{1/2}$, CL/F and V/F (Part D).
- Assessment of concentrations of the combined product (Parts B and C).
- Assessment of potential ADA for pembrolizumab (Part B)

- Pharmacodynamic parameters and biomarkers evaluation:
  - Target engagement: Glu:Gln ratio in PBMC
  - Tumour mutation status (for example KEAP1/NRF2, STK11, KRAS and other mutations) and correlation with clinical outcome
  - Tumour ASNS expression

3.2.3 Exploratory

- Biomarkers of tumour biology evolution under treatment (e.g. immune profiling, PD-L1 expression, nuclear antigen Ki67 (Ki67), phosphorylation of histone variant H2AX (γH2AX), LKB1, etc) may be evaluated and correlated with clinical outcome.
- Biobank samples will be collected for potential future analysis of biomarkers (optional, informed consent required)

Exploratory IPN60090 concentrations in urine will be assessed only in Part A of dose escalation. The following PK parameters will be calculated: the amount of IPN60090 excreted in urine and renal clearance.

3.2.4 Safety Endpoints and Evaluations

The safety and tolerability of IPN60090 will be assessed by the rate of DLTs at each dose level in the dose escalation, and the rate of AEs and the rate of Grade 3 and higher AEs in the dose escalation and dose expansion. Continuous monitoring of AEs and SAEs, clinical laboratory test results, the presence of anti-pembrolizumab ADA (Part B only), vital signs measurements, ECG and physical examination results, and concomitant medication usage will be performed.

3.2.5 Biobanking

For patients participating in the optional research biobanking program, who consent to optional informed consent form (ICF) procedures, the samples listed below will be biobanked for potential future exploratory biomarkers evaluation:

PBMC, plasma, serum, circulating free DNA (cfDNA), paxgene DNA, paxgene ribonucleic acid (RNA), stools and remaining material from tumour biopsies.

Analysis of biobank samples will be performed outside the scope of the main study and reported separately.

Instructions for collection, processing, handling and shipment of the biobanking samples will be outlined in the laboratory manual.

3.3 Randomisation and Blinding

This is a nonrandomised, open-label study.

3.4 Maintenance of Randomisation and Blinding

Not applicable.

3.5 Study Treatments and Dosage

IPN60090 will be administered as oral capsules of either 10, 60 or 240 mg BID during or after a meal over 21 days (1 cycle). IPN600900 capsules will be taken every 12 hours corresponding to a BID regimen. Table 10 outlines the defined dose levels and the number of capsules in the dose escalation portion of the study. The RD for dose expansion, and number of capsules, will be determined at the completion of the dose escalation.

Patients will be instructed to swallow IPN60090 capsules with a glass of water without biting, breaking or opening the capsules, or attempting to dissolve the content in water prior to taking them. For patients in Part B, on the days of infusion, patients should take the capsules before

the start of the pembrolizumab infusion. For patients in Part C, on the days of infusion, when histamine 2 receptor (H2) blockers are administered for paclitaxel premedication, they must be administered at least 30 minutes prior to paclitaxel infusion. IPN60090 intake should be performed at least 2.5 hours before the start of the paclitaxel infusion and at least 2 hours prior to H2 blocker administration.

Table 10 IPN60090 Dose Level and Corresponding Number of Capsules to be Administered

DL	DL1	DL2	DL3	DL4	DL5	DL6	DL7
Dose	20 mg BID	40 mg BID	80 mg BID	180 mg BID[a]	320 mg BID	480 mg BID	720 mg BID
Number of capsules	2×10 mg	4×10 mg	1×60 mg + 2×10 mg	3×60 mg	1×240 mg + 1×60 mg + 2×10 mg	2×240 mg	3×240 mg

BID=bis in die (twice daily); DL=dose level

a 180 mg BID was selected instead of 160 mg BID to reduce the number of capsules and therefore reduce the burden for patients. The dose of 160 mg BID would correspond to six capsules BID (2×60 mg+4×10 mg) whereas the dose of 180 mg corresponds to three capsules BID (3×60 mg).

In Part B, the dose of pembrolizumab will be fixed at 200 mg administered as an i.v. infusion over 30 minutes every 21 days (±1 day in Cycle 1 and ±3 days in all other cycles) (Day 1 of every cycle), consistent with the pembrolizumab prescribing information. Premedication with an antipyretic and antihistamine should be considered. The table below outlines the defined dose levels and the number of capsules in the dose escalation portion of the study. The RD for dose expansion, and number of capsules, will be determined at the completion of the dose escalation.

Table 11 Pembrolizumab and IPN60090 Dose Level and Corresponding Number of Capsules to be Administered

Dose level	Dose level -1	Dose level 1	Dose level 2	Dose level 3
Planned dose of IPN60090	80 mg BID	180 mg BID	320 mg BID	480 mg BID
Number of IPN60090 capsules	1×60 mg + 2×10 mg	3×60 mg	1×240 mg + 1×60 mg + 2×10 mg	2×240 mg
Planned dose of pembrolizumab	200 mg [a] i.v. Q3W	200 mg [a] i.v.Q3W	200 mg [a] i.v.Q3W	200 mg [a] i.v.Q3W

BID=bis in die (twice daily); i.v.=intravenous; Q3W=every three weeks (21 days)

a or according to the local approved label for particular tumour types

In Part C, the dose of paclitaxel will be fixed at 175 or 135 mg/m² (or according to the local approved label for particular tumour types) administered as an i.v. infusion as per standard practice or at the approved RD per indication every 21 days (±1 day in Cycle 1 and ±3 days in all other cycles) (Day 1 of each cycle), consistent with the paclitaxel prescribing information. Premedication (e.g. dexamethasone, diphenhydramine, histamine H2 blockers) to prevent hypersensitivity reactions should be considered. H2 blockers may decrease absorption of the drugs given orally, such as IPN60090, therefore decreasing the exposure. When H2 blockers are administered for paclitaxel premedication, they must be administered at least 30 minutes prior to paclitaxel infusion. IPN60090 intake should be performed at least 2.5 hours before the start of the paclitaxel infusion and at least 2 hours prior to H2 blocker administration. Table 12 outlines the defined dose levels and the number of capsules in the dose escalation portion of the study. The RD for dose expansion, and number of capsules, will be determined at the completion of the dose escalation.

Table 12 Paclitaxel and IPN60090 Dose Level and Corresponding Number of Capsules to be Administered

Dose level	Dose level -1	Dose level 1	Dose level 2	Dose level 3
Planned dose of IPN60090	80 mg BID	180 mg BID	320 mg BID	480 mg BID
Number of IPN60090 capsules	1×60 mg + 2×10 mg	3 × 60 mg	1×240 mg + 1×60 mg + 2×10 mg	2×240 mg
Planned dose of paclitaxel	175 or 135 mg/m^2[a] i.v.	175 or 135 mg/m^2[a] i.v.	175 or 135 mg/m^2[a] i.v.	175 or 135 mg/m^2 [a] i.v.

BID=bis in die (twice daily); i.v.=intravenous
a or according to the local approved label for particular tumour types

The proposed dose levels may be further modified and additional doses may be considered based on the safety, tolerability and efficacy observed during dose escalation. An intermediate, not predefined, previously evaluated or not previously evaluated dose or a less frequent dosing schedule that will not exceed the MTD level may be considered, if evaluation of toxicity at such a dose or schedule is desired.

In Part D, single administration of IPN60090 at the RD (morning dose only), as defined by the SRC at the end of the Part A dose escalation, will be performed during the run-in period at Day -7 and Day -3. On Day -7, IPN60090 will be administered following an overnight fast of at least 10 hours. On Day -3, IPN60090 will be administered 30 minutes after the start of a moderate fat meal (see Table 13). The moderate fat meal should be eaten in 30 minutes or less. On both days, the patients should not consume any food for at least 4 hours after the dose. IPN60090 should be taken with 240 mL (i.e. 8 fluid ounces) of water. Additional water is permitted ad libitum except for the period 1 hour before to 1 hour after administration of the drug product. Substitutions to the test meal can be made after discussion with the sponsor. It is understood that some patients may not be able to consume the entire meal. Study staff should record the percent of the test meal breakfast eaten and the time it takes to be consumed.

Table 13 Composition of the Moderate Fat Meal

Type of meal	Total calories (Kcal)	Calories from fat (%)	Calories from carbohydrates (%)	Calories from proteins (%)
Moderate fat	500-750	30-35	≥55%	≥12-14

Then, starting from Day 1, patients will receive IPN60090 BID (at the RD as defined by the SRC at the end of Part A) during or after a meal over 21 days (one cycle) as described in Part A.

Investigational Product

The IPN60090 capsules will be manufactured, packaged and labelled by WuXi AppTec (Shanghai, China) and delivered to an interim storage facility. A sufficient quantity of IMP will be supplied with an acknowledgement of receipt form.

The sponsor's representative will receive a Certificate of Analysis for which batch of IMP has been used under their study, Material Data Safety Sheets for IMP and a Packaging Order that reflects the product release statement.

The core label texts for all packaging units will be translated and/or adjusted, to be in compliance with applicable regulatory requirements (for example Good Manufacturing Practice guidelines (Volume 4 Annex 13)), national laws in force and in accordance with the local languages.

The investigator or designee will only dispense IMPs to patients included in this study. Each patient will only be given the IMP carrying his/her number. An Interactive Response

Technology (IRT) system will be used to track and allocate IMP to the patients. Dispensation will be documented in the electronic case report form (eCRF).

The treatment kits will be allocated by IRT each time drug is dispensed, according to the cohort. The IRT will also manage all the logistical aspects of treatments (for example drug supplies and replacement of lost, damaged, quarantined, expiring and expired kits).

This service provides investigators, site coordinators and project team members with a 24-hour per day, 7-day per week service. In case of medical or technical dispensation queries, a 24-hour helpline is available. See supporting information in the IRT reference manual

3.6 Study Duration

During dose escalation, for each patient the study duration will consist of an up to 28-day screening period (up to 21 days in Part D), followed by the DLT assessment period, which will consist of the first 21 days of treatment (one cycle). Patients will be offered IPN60090 and combination treatment (as defined in Parts B and C) beyond Cycle 1 as long as they continue to experience clinical benefit, in the opinion of the investigator, until the earlier of disease progression, symptomatic deterioration, poor tolerability despite appropriate medical management or any of the other reasons for treatment discontinuation. Patients will then be followed up for safety and survival during follow-up visits as per the schedule of assessments (Table 14). Patients who experience a DLT (or other toxicities considered related, probably related or possibly related to the study treatment) will be permitted to continue to receive study treatment at a lower dose level than the dose at which the DLT was observed, at the discretion of the investigator (see Section 6.4.4), and will be followed for safety.

During dose expansion, for each patient the study duration will consist of an up to 28-day screening period, followed by a treatment period of 21 days per cycle. Patients will be offered IPN60090 and combination treatment (as defined in Parts B and C) as long as they continue to experience clinical benefit, in the opinion of the investigator, until the earlier of unacceptable toxicity, symptomatic deterioration attributed to disease progression, or any of the other reasons for treatment discontinuation. Patients will then be followed up for safety and survival during follow-up visits as per the schedule of assessments (Table 14).

Any patient in this study who continues to demonstrate objective clinical benefit at the end of a 2-year treatment duration may continue study treatment after agreement between the sponsor and treating investigator.

All patients will then be followed post end of treatment at 30 days ±3 days (for Parts A, C and D) and 90±3 days (for Part B) for the end of treatment visit, at 180 days ±14 days for the safety follow-up visit and then every 3 months ±14 days for survival until the end of the study.

The overall duration of the study will be approximately 3 years. The study will be considered to have started when the first patient has provided signed informed consent.

The study will be considered to have ended after the last patient has completed the last follow-up period in the study.

3.7 Source Data Recorded on the Case Report Form

Data will be collected in the eCRF in compliance with FDA 21 Code of Federal Regulations (CFR) Part 11. As required by GCP guidelines, the sponsor assigned monitor will verify, by direct reference to the source documents, that the data required by the protocol are accurately reported on the eCRF.

The source documents must, at a minimum, contain a statement that the patient is included in a clinical study, the date that informed consent was obtained prior to participation in the

study, the identity of the study, diagnosis and eligibility criteria, visit dates, IMP administration and any AEs and associated concomitant medication.

As required by ICH-E6, if some items are recorded directly on the eCRF and are considered as source data, the identification of these data must be documented and agreed between the investigator and the sponsor.

Definition for source data and source documents are given below:

- **Source data:** All original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).
- **Source documents:** Original documents, data and records (for example hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, X-rays, patient files and records kept at the pharmacy, at the laboratories and at medicotechnical departments involved in the clinical study).

The patient must have consented to their medical records being viewed by the sponsor's authorised personnel and by local and possibly foreign, Competent Authorities (CAs). This information is included in the informed consent.

4 SELECTION AND WITHDRAWAL OF PATIENTS

4.1 Inclusion Criteria

4.1.1 General Inclusion Criteria for All Parts

(1) Provision of written informed consent prior to any study related procedures.

(2) Male or female patients ≥18 years of age at the time of study entry who agree to participate by giving written informed consent prior to participation in any study-related activities.

(3) Histologically or cytologically confirmed advanced solid tumours including tumours known to harbour KEAP1 and/or NRF2 mutations or have low ASNS expression levels.

- In dose escalations of all parts, patients may be KEAP1 and NRF2 wild-type or mutated and have tumours with any level of ASNS expression. For dose expansions, see specific inclusion criteria per part below.

(4) Patients must have received at least one line of therapy for advanced stage disease and be refractory or ineligible to available existing therapy(ies) known to provide clinical benefit for their condition.

(5) Prior treatment with chemotherapy, radiotherapy, immunotherapy or any investigational therapies must have been completed at least 3 weeks or at least five half-lives before the study drug administration, and all AEs (excluding alopecia and peripheral neuropathy) have either returned to baseline or stabilised.

(6) Fresh and/or archival tumour tissue from the biopsy obtained between the completion of the most recent line of treatment until study entry must be available for mutation and biomarker analysis unless KEAP1/NRF2 mutations were present in any previous biopsy, in which case, no further biopsy is required. For ovarian cancer patients, both archival biopsies obtained between the completion of the most recent line of treatment until study entry and fresh biopsies must be available to evaluate the evolution of ASNS levels over time. Patients should not be put at undue risk to obtain fresh tumour biopsy. Procedures more invasive than core biopsy should not be used. Procedures to obtain biopsy should only be performed if the risk is minimal (no greater than 2% risk of serious or severe complications). If available, archival tumour tissue from time of initial diagnosis will be collected in addition to the most recent biopsy (archival and/or fresh).

(7) Measurable or non-measurable evaluable disease as defined per the RECIST v1.1 (or iRECIST for Part B only).

(8) Eastern Cooperative Oncology Group (ECOG) Performance Status ≤1.

(9) Adequate organ function as indicated by the following laboratory values:

(a) ANC ≥1500/mL

(b) Platelets ≥100,000/mL

(c) Haemoglobin ≥9 g/dL or ≥5.6 mmol/L

(d) Serum creatinine ≤1.5×ULN and/or creatinine clearance >40 mL/min. Actual body weight should be used for calculating creatinine clearance using the Cockroft-Gault equation (except for patients with body mass index >30 kg/m^2 when the lean body weight should be used).

(e) Serum total bilirubin ≤1.5×ULN (with the exception of patients with known Gilbert's syndrome: serum total bilirubin must be <3×ULN in these patients).

(f) AST (serum glutamic oxaloacetic transaminase) and ALT (serum glutamic pyruvic transaminase) ≤2.5×ULN or ≤5×ULN for patients with liver metastases)

(10) Adequate cardiac function with a left ventricular ejection fraction (LVEF) ≥50%

(11) Female patients are eligible to enter and participate in the study if they are of:

(a) Non-childbearing potential (physiologically incapable of becoming pregnant), including any female who:

- has had a hysterectomy, OR
- has had a bilateral oophorectomy, OR
- has had a bilateral salpingectomy, OR
- is postmenopausal (total cessation of menses for ≥2 years, or follicle-stimulating hormone ≥50 IU/L)

(b) Childbearing potential, but with a negative serum pregnancy test at screening (within 7 days of the first IMP administration), is not breastfeeding, and uses highly effective contraception at study entry and throughout the study until 90 days after the last administration. Highly effective contraceptive methods include:

- Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (for example oral, intravaginal, transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (for example oral, implantable, injectable)
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Male partner has had a vasectomy

(12) Male patients are eligible to enter and participate in the study if they agree to use effective methods of contraception during the study treatment period and for at least 90 days after the last dose of investigational product.

4.1.2 Part A Specific Inclusion Criteria

There are no further inclusion criteria associated with Part A.

Dose Expansion ONLY:

(A2) Patients with the following tumour types will be recruited:

(a) NSCLC KEAP1 and/or NRF2 mutant

(b) KEAP1 and/or NRF2 mutant other tumours

(c) HGSOC $ASNS^{low}$

Note: all biomarker mutations/expression levels must be confirmed prior to study treatment.

4.1.3 Part B Specific Inclusion Criteria

(B1) Patients may have received previous treatment with any PD-1 or PD-L1 inhibitor.

Dose Expansion ONLY:

(B2) Patients may have received previous treatment with any anti-PD-1/PD-L1 mAb administered either as monotherapy, or in combination with other checkpoint inhibitors or other therapies. PD-1 treatment progression is defined by meeting all of the following criteria:

(a) Has received at least 2 doses of an approved anti-PD-1/L1 mAb.

(b) Has demonstrated disease progression after PD-1/L1 as defined by iRECIST v1.1. The initial evidence of disease progression is to be confirmed by a second assessment no less than four weeks from the date of the first documented disease progression, in the absence of rapid clinical progression.

(B3) Patients with the following tumour types will be recruited during the dose expansion only:

(a) NSCLC KEAP1 and/or NRF2 mutant

(b) Other KEAP1 and/or NRF2 mutant tumours

(c) KEAP1 and NRF2 wild-type tumours with any level of ASNS expression

4.1.4 Part C Specific Inclusion Criteria

(C1) Patients may have received previous treatment with any platinum- or taxane-based chemotherapy.

Dose Expansion ONLY:

(C2) Patients with the following tumour types will be recruited during the dose expansion only:

(a) KEAP1 or NRF2 mutant tumours

(b) HGSOC $ASNS^{low}$ tumours

(c) KEAP1 or NRF2 wild-type tumours with any level of ASNS expression

4.1.5 Part D Specific Inclusion Criteria

(D1) Patients must be able to consume a moderate fat meal.

4.2 Exclusion Criteria

4.2.1 General Exclusion Criteria for All Parts

(1) Prior malignancy within the previous 2 years except for locally curable cancers that have been cured, such as basal or squamous cell skin cancer, or carcinoma in situ of the cervix, breast or bladder.

(2) Known primary central malignancy or symptomatic central nervous system metastasis(es).

Note: Patients with stable, previously treated brain metastases may participate if neurologic symptoms have resolved, patients have been off steroids for at least 7 days, and there is no evidence of disease progression by imaging for at least 2 weeks before the first dose of study treatment.

(3) Patients should be excluded if they have a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 2 weeks of the first dose of study drug.

(4) Uncontrolled, significant intercurrent or recent illness including, but not limited to, the following cardiac conditions:

(a) Any unstable cardiac arrhythmia within 6 months prior to enrolment

(b) Prolongation of the Fridericia corrected QT (QTcF) interval defined as >450 ms for males and >470 ms for females

(c) History of any of the following cardiovascular conditions within 6 months of enrolment:

- cardiac angioplasty or stenting, myocardial infarction, unstable angina, coronary artery
- bypass graft surgery, symptomatic peripheral vascular disease, class III or IV congestive heart failure, as defined by the New York Heart Association.

(5) Major surgical intervention within 28 days before study drug administration.

(6) Significant acute or chronic infections.

(7) Any psychiatric condition that would prohibit the understanding or rendering of informed consent.

(8) Treatment with strong cytochrome P450 (CYP450) subtype 3A4 (CYP3A4) inducers (including St John's Wort) and inhibitors (including grapefruit juice) within 7 days of the first dose of study drug.

(9) Treatment with strong CYP450 subtype 2D6 (CYP2D6) inhibitors within 7 days of the first dose of study drug.

(10) Radiotherapy within 4 weeks prior to the start of study drug. Palliative radiotherapy for symptomatic control is acceptable if completed at least 2 weeks prior to study drug administration and no additional radiotherapy for the same lesion is planned.

(11) Underlying medical conditions that, in the investigator's opinion, will make the administration of study drug hazardous or obscure the interpretation of toxicity determination or AEs.

(12) History of allergic reactions attributed to compounds of similar chemical or biological composition to any of the compounds in the study.

(13) Known alcohol or drug abuse.

(14) Legal incapacity or limited legal capacity.

(15) Inability to swallow oral medications (capsules and tablets) without chewing, breaking, crushing, opening or otherwise altering the product formulation. Patients should not have gastrointestinal illnesses that would preclude the absorption of IPN60090, which is an oral agent.

(16) Patients unwilling to comply with protocol requirements related to the assigned part.

4.2.2 Part A Specific Exclusion Criteria

There are no further exclusion criteria associated with Part A

4.2.3 Part B Specific Exclusion Criteria

(B1) Autoimmune disease that might deteriorate when receiving an immune-stimulatory agent, or immunodeficiencies.

(B2) Known severe hypersensitivity reactions to monoclonal antibodies, any history of anaphylaxis, or uncontrolled asthma (that is, three or more features of partially controlled asthma).

(B3) Prior organ transplantation, including allogeneic stem cell transplantation.

(B4) Patient has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are 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 are allowed; however, intranasal influenza vaccines (e.g. FluMist®) are live attenuated vaccines and are not allowed.

4.2.4 Part C Specific Exclusion Criteria

(C1) Treatment with strong CYP450 subtype 2C8 (CYP2C8) inhibitors and inducers within the 7 days of the paclitaxel infusion.

4.2.5 Part D Specific Exclusion Criteria

(D1) Treatment with drugs that can alter the absorption of IPN60090 by affecting gastrointestinal motility or by changing the gastric pH during the run-in period (Day -7 to Day -3) of Part D.

(D2) Patients suffering from conditions that are likely to adversely affect gastrointestinal motility and/or transit (for example, diarrhoea, vomiting or nausea, gastroparesis, irritable bowel syndrome and malabsorption) or patients with gastrointestinal resection (e.g. partial or total gastrectomy) likely to interfere with absorption of study treatment. Patients with Type 1 diabetes and hypercholesterolaemia are excluded.

(D3) Patients unable to fast for up to 14 hours.

4.3 Stopping Rules, Discontinuation and Withdrawal Criteria and Procedures

4.3.1 Discontinuation of a Cohort

The safety and preliminary anti-tumour activity profile of IPN60090 will be explored in the dose escalation portion of the study and will inform the decisions for the dose expansion.

In the dose escalation, safety will be monitored on an ongoing basis by the SRC, which will be comprised of participating investigators and medical monitors of the sponsor. Cohort stopping rules are defined by the DLT criteria outlined in Section 3.1.2.1 for Part A, Section 3.1.2.2 for Part B, and Section 3.1.2.3 for Part C, and the DLT rate described in Section 11.2.1.

The decision to halt enrolment at a specific dose level, or to discontinue a cohort may be made by the SRC at any point if a safety signal or unacceptable toxicity is observed.

The dose escalations will be stopped once the MTD has been established. The SRC may also decide to stop the escalation before the MTD is reached if no safety signals (DLTs) are seen but consecutive escalating doses (covering a 2- and 3-fold dose range) showed significant PD effect (90% inhibition of Glu:Gln ratio in PBMCs in 66% of patients).

Both the safety and anti-tumour activity of IPN60090 in patients in the dose expansion cohorts, as well as of patients from the dose escalation receiving additional cycles of IPN60090 treatment, will continue to be monitored by the SRC, and by the ISAC on an ongoing basis. The ISAC will meet 1 year after the start of the study or at the end of the dose escalation, whichever occurs first. The decision to halt enrolment or to discontinue a patient or a cohort may be made by the SRC and ISAC at any point if a safety signal or unacceptable toxicity is observed. The anti-tumour activity of IPN60090 will be assessed by the SRC and ISAC after Stage I of the sequential two-stage design, and if the study treatment does not demonstrate sufficient anti-tumour activity in any given cohort(s) as defined in Section 11.3.1 (CBR at 12 weeks in at least one patient out of 10), then the cohort(s) will be discontinued.

4.3.2 Discontinuation of a Site or Study Termination

A specific site or a given cohort can be discontinued or the entire study may be terminated at any time, if the sponsor judges it necessary for any reason. In such a case, all scheduled procedures and assessments for patients who are still in the study will be performed. Some possible reasons for the closure of a study site may include:

- failure of the investigator staff to comply with the protocol or with the GCP guidelines;
- safety concerns;

- inadequate patient recruitment.

In the case of premature discontinuation of a site or early termination of the study, depending on the reason(s) for the discontinuation or termination, the sponsor will notify the investigator(s) affected in writing as to whether the ongoing patients should continue the remaining IMP dose administration(s).

4.3.3 Individual Discontinuation Rules

A patient may discontinue participation in the study at any time for any reason (for example lack of efficacy, withdrawal of consent, AE). The investigator and/or sponsor can withdraw a patient from the study at any time for any reason (for example protocol violation or deviation as defined in Section 13.1.2, noncompliance with the protocol conditions or AEs). All cases of discontinuation will be discussed between the investigator and the sponsor.

If a stopping rule is met at any dose level, the safety data will be reviewed by the SRC and, on the basis of the evaluation of the safety data, a recommendation will be made. Determining an AE to be a potential DLT is independent of the investigator's causality assessment, but the event must be at least possibly related to IMP administration (i.e. after IMP administration through the follow-up visit), clinically significant, in the opinion of the investigator, and of at least moderate severity. In addition, a medically plausible alternative explanation for the AE should not be apparent.

Each patient will be allowed a maximum of two dose reductions for IPN60090 to manage severe adverse reactions.

Patients who experience a DLT will be allowed to continue to receive study treatment at a lower dose level at the discretion of the investigator and will be closely monitored for safety. The SRC may consider additional sparse PK samples for DLT assessment. The criteria for DLTs are described in Section 3.1.2.1 for Part A, Section 3.1.2.2 for Part B, and Section 3.1.2.3 for Part C.

If a patient decides to withdraw from the study after administration of IMP, or should the investigator decide to withdraw the patient, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation at the time of the patient's withdrawal should be made and an explanation given for why the patient is withdrawing or being withdrawn from the study.

The reason for and date of withdrawal from the study must be recorded on the eCRF. If a patient withdraws consent, every attempt will be made to determine the reason. If the reason for withdrawal is an AE or a clinically significant laboratory test abnormality, monitoring will continue until the event has resolved or stabilised, until the patient is referred to the care of a local health care professional, or until determination of a cause unrelated to the IMP or study procedure is made. The specific AE or test result(s) must be recorded on the eCRF. All evaluations should be performed, according to the protocol, on the last day the patient receives IMP, or as soon as possible thereafter.

Patients participating in the optional research biobanking programme have the right to withdraw their consent at any time and for any reason during the study or during the period of sample storage (i.e. the entire 15 years during which samples are kept). If a patient wishes to withdraw their consent for biobanking and the samples are still at the investigator site or at the central laboratory at the time, the investigator must inform the study monitor in writing of the patient's decision and destroy the samples. If the samples are at the sponsor's central biorepository, the investigator must inform the sponsor directly using the e-mail address, CCI [redacted], mentioning only the patient identification (ID) in this e-mail. The sponsor will ensure destruction of the samples and all corresponding aliquots and issue

confirmation of the destruction, which will be forwarded to the investigator. Analyses conducted before the withdrawal will not be affected.

5 STUDY PROCEDURES

5.1 Study Schedule

The schedule of procedures and assessments during the study is summarised in Table 14 (Parts A to C) and Table 15 (Part D).

Table 14 Study Procedures and Assessments (Parts A to C)

Procedures and assessments	Protocol section	Screening	Treatment																	Follow-up		
			Cycle 1					Cycle 2			Cycle 3			Cycle 4			All Cycles after Cycle 4			EOS/EW	Safety FU	Survival FU
		D -28 to -1	D1	D2	D8	D14	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	30 days (Parts A and C) or 90 days (Part B) after last dose	Up to 180 days after last dose	Every 3 months after safety FU
		D1	D2	D8	D14	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	Dx	Dx	Dx			
Visit window (days)		N/A	N/A	±1			±3			±3			±3			±3			±3	±14	±14
Baseline documentation and physical examination																						
Informed consent		X																				
Medical and disease history		X																				
Demographics and height		X																				
Physical examination		X	X[a]		X	X		X			X			X			X			X		
Body weight		X	X[a]		X	X		X			X			X			X			X		
Vital signs		X	X[a]		X	X		X			X			X			X			X		
ECOG performance status		X	X[a]					X			X			X			X			X		
Ophthalmological examination		X																				
Enrolment																						
Inclusion/exclusion criteria		X	X																			
End of phase disposition		X	X																	X		X
Safety/Laboratory assessments																						
Haematology		X	X[a]	X	X	X		X	X		X			X			X			X		
Chemistry (including liver function tests)		X	X[a]	X	X	X		X	X		X			X			X			X		
INR		X	X[a]								Day 1 of every 3rd cycle starting with Day 1 (i.e. Day 1, Cycle 6 Day 1, etc.)									X		
TSH (Part B only)		X	X[a]								Day 1 of every 3rd cycle starting with Day 1 (i.e. Day 1, Cycle 6 Day 1, etc.)									X		
Urinalysis		X	X[a]					X			X			X			X			X		
Serum pregnancy test		X																				
Urine pregnancy test								X			X			X			X			X		
ECHO/MUGA		X																		X		
Triplicate ECG (12-lead)		X	X[b]					X [b] [c]			X[c]			X[c]			As clinically indicated			X		

Procedures and assessments	Protocol section	Screening	Treatment																	Follow-up		
			Cycle 1					Cycle 2			Cycle 3			Cycle 4			All Cycles after Cycle 4			EOS/EW	Safety FU	Survival FU
		D -28 to -1	D1	D2	D8	D14	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	30 days (Parts A and C) or 90 days (Part B) after last dose	Up to 180 days after last dose	Every 3 months after safety FU
			D1	D2	D8	D14	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	Dx	Dx	Dx			
Visit window (days)		**N/A**	**N/A**			**±1**		**±3**			**±3**			**±3**			**±3**			**±3**	**±14**	**±14**
PK/Biomarkers																						
Blood sampling for PK of IPN60090			X[d]	X[c]		X[d]	X[e]	X[f]			X[f]			X[f]			X[f]			X		
Blood sampling for PK of combined drug: pembrolizumab (Part B only)			X[c]					X[c]			X[c]			X[c]			X[c]					
Blood sampling for PK of combined drug: paclitaxel (Part C only)			X[g]					X[g]			X[g]											
Urine sampling for PK (Part A dose escalation only)			X[h]			X[h]																
Blood/PBMC samples for PD biomarker[i]			X[j]			X[j]	X[e]															
Serum Ca-125			X[k]								X[k]						X[k]					
cfDNA		X[c]					X[c]				X[c]						X[c] [l]			X		
Fresh tumour biopsy[m]		X[n][o]					X[n][p]													X[n][q]		
Archival tumour biopsies[r]		X																				
ADA samples for pembrolizumab (binding and neutralising) (Part B only)		X									X[c]						X[c]			X		
Biobanking (optional)																						
Biobanking serum[s]			X[t]				X	X			X			X			X			X		
Biobanking PBMC[s]			Remaining and not used PBMC for PD biomarker should be biobanked																			
Biobanking plasma[s]			X[t]				X	X			X			X			X			X		
Biobanking paxgene RNA[s]			X[t]				X	X			X			X			X			X		
Biobanking paxgene DNA[s]			X[c]																			
Biobanking stools[s]			X[c]				X[c]													X		

Procedures and assessments	Protocol section	Screening	Treatment																	Follow-up		
			Cycle 1					Cycle 2			Cycle 3			Cycle 4			All Cycles after Cycle 4			EOS/EW	Safety FU	Survival FU
		D -28 to -1	D1	D2	D8	D14	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	30 days (Parts A and C) or 90 days (Part B) after last dose	Up to 180 days after last dose	Every 3 months after safety FU
			D1	D2	D8	D14	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	Dx	Dx	Dx			
Visit window (days)		N/A	N/A		±1			±3			±3			±3			±3			±3	±14	±14
Biobanking cfDNA[s]			X[c]				X[c]	Blood collection for cfDNA should occur at the same time as efficacy assessments. Every 6 weeks from Cycle 1 Day 1[c].												X[c]		
Biobanking leftover tissue material and additional biopsies obtained from fresh frozen biopsies[s]		Remaining biopsies from biomarkers collection should be biobanked along with any additional tumour material collected at these visits (archival and/or fresh).																				
Tumour assessments																						
CT/MRI chest, abdomen, pelvis, or other (if clinically indicated)		X	Images required every 6 weeks (±1 week) from Cycle 1 Day 1 for the first 24 weeks of treatment, and every 12 weeks (±2 weeks) thereafter. To ensure image consistency, the same imaging modalities and acquisition protocols used at screening are to be used for subsequent tumour assessments.																	X	X	
CT/MRI brain			Required in patients with documented, treated brain metastasis. As clinically indicated for patients with suspected brain metastasis. Images required every 6 weeks (±1 week) from Cycle 1 Day 1 for the first 24 weeks of treatment, and every 12 weeks (±2 weeks) thereafter. To ensure image consistency, the same imaging modalities and acquisition protocols used at screening are to be used for subsequent tumour assessments.																	X (if applicable)	X	
Other clinical assessments																						
Adverse events			Document new or worsening AEs from informed consent through 30 days after the date of the decision to permanently discontinue study treatment. AE information will be collected at study visits and may also be collected at any time over the phone or by spontaneous patient report. Certain AEs and all SAEs that are ongoing 30 days after of the date of the decision to permanently discontinue study treatment are to be followed until resolution or determination by the investigator that the event is stable or irreversible.																			
Prior and concomitant medication/procedures/non-drug therapies			Document prior and concomitant medication taken from 28 days before first dose of study treatment through 30 days after the date of the decision to discontinue study treatment.																			
Further anti-tumour treatment																				X	X	X
IPN60090			Daily BID starting on Cycle 1 Day 1. Dose will be determined by phase and cohort.																			

Procedures and assessments	Protocol section	Screening	Treatment																Follow-up		
			Cycle 1					Cycle 2			Cycle 3			Cycle 4			All Cycles after Cycle 4			EOS/EW	Safety FU	Survival FU
		D -28 to -1	D1	D2	D8	D14	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	30 days (Parts A and C) or 90 days (Part B) after last dose	Up to 180 days after last dose	Every 3 months after safety FU
			D1	D2	D8	D14	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	Dx	Dx	Dx			
Visit window (days)		**N/A**	**N/A**		**±1**			**±3**			**±3**			**±3**			**±3**			**±3**	**±14**	**±14**
Pembrolizumab			200 mg (or per approved label) every 21 days (Day 1 of every cycle) as i.v. infusion.																		
Paclitaxel			175 mg/m^2 or 135 mg/m^2 (or per approved label) every 21 days (Day 1 of every cycle) i.v. infusion.																		

ADA=antidrug antibodies; AE=adverse event; BID=bis in die (twice daily); cfDNA=circulating free DNA; CT=computed tomography; D=day; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; EOS=end of study; EW=early withdrawal; FU=follow-up; HGSOC=high-grade serous ovarian cancer; INR=international normalised ratio; i.v.=intravenous; MRI=magnetic resonance imaging; MUGA=multigated acquisition; N/A=not applicable; PBMC=peripheral blood mononuclear cells; PD=pharmacodynamics; PK=pharmacokinetics; RNA=ribonucleic acid; SAE=serious adverse event; TSH=thyroid stimulating hormone

a assessment does not need to be repeated if done within 3 days of first dose.
b 30 minutes (±15 minutes), 1 hour (±15 minutes), 2 hours (±15 minutes), 4 hours (±15 minutes), 8 hours (±15 minutes) and 12 hours (±15 minutes) postdose.
c predose.
d predose, 30 minutes (±5 minutes), 1 hour (±5 minutes), 2 hours (±5 minutes), 4 hours (±10 minutes), 8 hours (±30 minutes) and 12 hours (±1 hour) postdose.
e predose, and between 2 to 4 hours postdose.
f predose, 2 hours (±5 minutes) postdose.
g two time points: immediately before paclitaxel infusion and at the end of the paclitaxel infusion i.e. 3 hours after the start of the infusion.
h 0-12 h urine time collection interval (only performed for Part A Dose Escalation).
i see Table 34 for more details on collection timepoints and volumes.
j predose, 2 and 12 hours postdose.
k serum Ca-125 assessments will be performed at baseline, on Day 1 of Cycle 3 and then on Day 1 of every other cycle. This assessment will be performed in patients with HGSOC only.
l cfDNA sample on Day 1 of every other cycle after Cycle 3.
m remaining tumour materials should be biobanked.
n cfDNA should be collected at the same day of biopsy, if feasible.
o fresh tumour must be available for mutation and biomarker analysis unless KEAP1/NRF2 mutations were present in any previous biopsy, in which case, no further biopsy is required. For ovarian cancer patients, fresh biopsies must be collected in addition to the archival biopsies. Procedures to obtain biopsy should only be performed if the risk is minimal (no greater than 2% risk of serious or severe complications).
p performed 2 to 4 hours postdose.
q the EOS fresh biopsy is optional.
r archival biopsies collected after the completion of the last line of treatment until study entry and archival biopsies from initial diagnosis if available.
s biobanking samples will only be collected for patients who have signed the optional biobanking informed consent form.
t predose and 12 hours postdose.

Table 15 Study Procedures and Assessments (Part D)

Procedures and assessments	Protocol section	Screening	Run-in		Treatment																		Follow-up		
					Cycle 1					Cycle 2			Cycle 3			Cycle 4			All cycles after Cycle 4					
		D -28 to D -8	D -7	D -3	D1	D2	D8	D14	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	EOS/EW	Safety FU	Survival FU
					D1	D2	D8	D14	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	Dx	Dx	Dx	30 days after last dose	Up to 180 days after last dose	Every 3 months after safety FU
Visit windows (days)		N/A	N/A	N/A	N/A		±1			±3			±3			±3			±3			±3	±14	±14
Baseline documentation and physical examination																								
Informed consent		X																						
Medical and disease history		X																						
Demographics and height		X																						
Physical examination		X			X[a]		X	X		X			X			X			X			X		
Body weight		X			X[a]		X	X		X			X			X			X			X		
Vital signs		X			X[a]		X	X		X			X			X			X			X		
ECOG performance status		X			X[a]					X			X			X			X			X		
Ophthalmological examination		X																						
Enrolment																								
Inclusion/exclusion criteria		X			X																			
End of phase disposition		X			X																	X		X
Safety/Laboratory assessments																								
Haematology		X	X	X	X[a]	X	X	X		X	X		X			X			X			X		
Chemistry (including liver function tests)		X	X	X	X[a]	X	X	X		X	X		X			X			X			X		
INR		X			X[a]								Day 1 of every 3rd cycle starting with Day 1 (i.e. Day 1, Cycle 6 Day 1, etc.)									X		
Urinalysis		X			X[a]					X			X			X			X			X		
Serum pregnancy test		X																						
Urine pregnancy test										X			X			X			X			X		
ECHO/MUGA		X																				X		
Triplicate ECG (12-lead)		X	X[b]	X[b]	X[c]					X[c] [d]			X[d]			X[d]			As clinically indicated			X		
PK/Biomarkers																								
Blood sampling for PK of IPN60090			X[e]	X[e]	X[f]	X[d]		X[f]	X[g]	X[h]			X[h]			X[h]			X[h]			X		

Procedures and assessments	Protocol section	Screening	Run-in		Treatment																		Follow-up		
					Cycle 1					Cycle 2			Cycle 3			Cycle 4			All cycles after Cycle 4					
		D -28 to D -8	D -7	D -3	D1	D2	D8	D14	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	EOS/EW	Safety FU	Survival FU
					D1	D2	D8	D14	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	Dx	Dx	Dx	30 days after last dose	Up to 180 days after last dose	Every 3 months after safety FU
Visit windows (days)		**N/A**	**N/A**	**N/A**	**N/A**			**±1**			**±3**			**±3**			**±3**			**±3**		**±3**	**±14**	**±14**
Blood/PBMC samples for PD biomarker[i]					X[j]			X[j]	X[g]															
Serum Ca-125					X[k]								X[k]						X[k]					
cfDNA		X[d]							X[d]				X[d]						X[d] [l]			X		
Fresh tumour biopsy[m]		X[n][o]							X[n] [p]													X[n][q]		
Archival tumour biopsies[r]		X																						
Biobanking (optional)																								
Biobanking serum[s]					X[t]				X	X			X			X			X			X		
Biobanking PBMC[s]					Remaining and not used PBMC for PD biomarker should be biobanked																			
Biobanking plasma[s]					X[t]				X	X			X			X			X			X		
Biobanking paxgene RNA[s]					X[t]				X	X			X			X			X			X		
Biobanking paxgene DNA[s]					X[d]																			
Biobanking stools[s]					X[d]				X[d]													X		
Biobanking cfDNA[s]					X[d]				X[d]	Blood collection for cfDNA should occur at the same time as efficacy assessments. Every 6 weeks from Cycle 1 Day 1[d].												X[d]		
Biobanking leftover material and additional biopsies obtained from fresh frozen biopsies[s]		Remaining biopsies from biomarkers collection should be biobanked along with any additional tumour material collected at these visits (archival and/or fresh)																						
Tumour assessments																								
CT/MRI chest, abdomen, pelvis, or other (if clinically indicated)		X			Images required every 6 weeks (±1 week) from Cycle 1 Day 1 for the first 24 weeks of treatment, and every 12 weeks (±2 weeks) thereafter. To ensure image consistency, the same imaging modalities and acquisition protocols used at screening are to be used for subsequent tumour assessments.																	X	X	

Procedures and assessments	Protocol section	Screening	Run-in		Treatment																	Follow-up		
					Cycle 1					Cycle 2			Cycle 3			Cycle 4			All cycles after Cycle 4					
		D -28 to D -8	D -7	D -3	D1	D2	D8	D14	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	EOS/EW	Safety FU	Survival FU
					D1	D2	D8	D14	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	Dx	Dx	Dx	30 days after last dose	Up to 180 days after last dose	Every 3 months after safety FU
Visit windows (days)		N/A	N/A	N/A	N/A		±1			±3			±3			±3			±3			±3	±14	±14
CT/MRI brain					Required in patients with documented, treated brain metastasis. As clinically indicated for patients with suspected brain metastasis. Images required every 6 weeks (±1 week) from Cycle 1 Day 1 for the first 24 weeks of treatment, and every 12 weeks (±2 weeks) thereafter. To ensure image consistency, the same imaging modalities and acquisition protocols used at screening are to be used for subsequent tumour assessments.																X (if applicable)	X	
Other clinical assessments																								
Adverse events			Document new or worsening AEs from informed consent through 30 days after the date of the decision to permanently discontinue study treatment. AE information will be collected at study visits and may also be collected at any time over the phone or by spontaneous patient report. Certain AEs and all SAEs that are ongoing 30 days after of the date of the decision to permanently discontinue study treatment are to be followed until resolution or determination by the investigator that the event is stable or irreversible.																				
Prior and concomitant medication/procedures/non-drug therapies					Document prior and concomitant medication taken from 28 days before first dose of study treatment through 30 days after the date of the decision to discontinue study treatment.																			
Further anti-tumour treatment																						X	X	X
IPN60090			X[u]	X[u]	Daily BID starting on Cycle 1 Day 1. Dose will be at the RD (as defined by the SRC at the end of the Part A dose escalation)																			

Procedures and assessments	Protocol section	Screening	Run-in		Treatment																	Follow-up		
					Cycle 1					Cycle 2			Cycle 3			Cycle 4			All cycles after Cycle 4					
		D -28 to D -8	D -7	D -3	D1	D2	D8	D14	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	EOS/EW	Safety FU	Survival FU
					D1	D2	D8	D14	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	Dx	Dx	Dx	30 days after last dose	Up to 180 days after last dose	Every 3 months after safety FU
Visit windows (days)		N/A	N/A	N/A	N/A		±1			±3			±3			±3			±3			±3	±14	±14
Pembrolizumab					200 mg (or per approved label) every 21 days (Day 1 of every cycle) as i.v. infusion.																			
Paclitaxel					175 mg/m^2 or 135 mg/m^2 (or per approved label) every 21 days (Day 1 of every cycle) i.v. infusion.																			

AE=adverse event; BID=bis in die (twice daily); cfDNA=circulating free DNA; CT=computed tomography; D=day; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; EOS=end of study; EW=early withdrawal; FU=follow-up; HGSOC=high-grade serous ovarian cancer; INR=international normalised ratio; i.v.=intravenous; MRI=magnetic resonance imaging; MUGA=multigated acquisition; N/A=not applicable; PBMC=peripheral blood mononuclear cells; PD=pharmacodynamics; PK=pharmacokinetics; RNA=ribonucleic acid; SAE=serious adverse event

a assessment does not need to be repeated if done within 3 days of first dose.
b 1 hour (±15 minutes), 2 hours (±15 minutes) and 4 hours (±15 minutes) postdose.
c 30 minutes (±15 minutes), 1 hour (±15 minutes), 2 hours (±15 minutes), 4 hours (±15 minutes), 8 hours (±15 minutes) and 12 hours (±15 minutes) postdose.
d predose.
e predose, 30 minutes (±5 minutes), 1 hour (±5 minutes), 2 hours (±5 minutes), 4 hours (±10 minutes), 8 hours (±30 minutes), 12 hours (±1 hour), 24 hours (±2 hours), 48 hours (±2 hours) and 72 hours (±2 hours) postdose.
f predose, 30 minutes (±5 minutes), 1 hour (±5 minutes), 2 hours (±5 minutes), 4 hours (±10 minutes), 8 hours (±30 minutes) and 12 hours (±1 hour) postdose.
g predose, and between 2 to 4 hours postdose.
h predose, 2 hours (±5 minutes) postdose.
i see Table 34 for more details on collection timepoints and volumes.
j predose, 2 and 12 hours postdose.
k serum Ca-125 assessments will be performed at baseline, on Day 1 of Cycle 3 and then on Day 1 of every other cycle. This assessment will be performed in patients with HGSOC only.
l cfDNA sample on Day 1 of every other cycle after Cycle 3.
m remaining tumour materials should be biobanked.
n cfDNA should be collected at the same day of biopsy, if feasible.
o fresh tumour must be available for mutation and biomarker analysis unless KEAP1/NRF2 mutations were present in any previous biopsy, in which case, no further biopsy is required. For ovarian cancer patients, fresh biopsies must be collected in addition to the archival biopsies. Procedures to obtain biopsy should only be performed if the risk is minimal (no greater than 2% risk of serious or severe complications).
p performed 2 to 4 hours postdose.
q the EOS fresh biopsy is optional.
r archival biopsies collected after the completion of the last line of treatment until study entry and archival biopsies from initial diagnosis if available.
s biobanking samples will only be collected for patients who have signed the optional biobanking informed consent form.
t predose and 12 hours postdose.
u morning dose only.

5.2 Study Visits

The schedule of visits and main procedures at each visit are summarised in Table 14 (Parts A to C) and Table 15 (Part D).

5.2.1 Procedures for Screening and Enrolment

A signed and dated ICF will be obtained from each patient before any screening procedures are conducted. Evaluations obtained as part of routine medical care and performed during the screening period may be used in place of the study specific evaluations as long as they are consistent with the protocol requirements. Patients will acknowledge and agree to the possible use of this information for the study by giving informed consent. Computed tomography (CT)/magnetic resonance imaging (MRI) scans performed within 28 days prior the start of study treatment are acceptable. Otherwise they are to be repeated.

Patients will be offered to participate in an optional research biobanking programme. Patients who agree to participate will be requested to sign a separate ICF.

After informed consent is obtained, patients who are screened will be allocated a patient number. All screened patients must be identifiable throughout the study. The investigator will maintain a list of patient numbers and names to enable records to be found at a later date, if required.

Patients may be re-screened once. The reason for prior screening failure will be recorded in the eCRF.

Following confirmation of eligibility for the study, patients will be allocated to one of the dosing groups specified in Section 6.1.

Each investigator will also maintain a record of all patients screened in the study (i.e. who signed the ICF). In the event that the patient was not receiving IMP, the primary reason will be recorded in the eCRF.

5.3 Laboratory Assessments

Blood samples will be tested locally for safety clinical laboratory evaluations. During dose expansion, blood samples will also be tested centrally.

The total volume of blood collected for all evaluations throughout this study varies depending on the study part, and will reach a maximum of approximately 278.0 mL per month for any one patient (in Part D) (Table 16 and Table 17). An additional 60.5 mL of blood will be collected from patients who have signed the optional biobanking ICF.

Therefore, the maximum total blood volume collected per month from any one patient will not reach more than 338.5 mL per patient over the study duration.

Table 16 Total Blood Volume for All Evaluations (Parts A to C)

Assessments	Volume per sample (mL)	Max number of samples/month	Total max volume/month (mL)
Laboratory assessments			
Haematology	2	6	12
Chemistry (including liver function tests)	5	6	30
INR	2	2	4
TSH (Part B only)	2	2	4
Serum pregnancy test	2	1	2
PK and Biomarkers			
Blood sampling for PK of IPN60090	2	17	34
Blood sampling for PK of paclitaxel (Part C only)	2	2	4
Blood sampling for PK of pembrolizumab (Part B only)	2	1	2
Blood sampling for ADA against pembrolizumab (Part B only)	6	1	6
Blood sampling for Ca-125 (HGSOC only)	2	2	4
Blood/PBMC samples	6	18	108
cfDNA	10	3	30
Total volume Part A			**224**
Total volume Part B			**236**
Total volume Part C			**228**
Biobanking (optional)			
Biobanking serum	2.5	4	10
Biobanking plasma	2	4	8
Biobanking paxgene RNA	2.5	4	10
Biobanking paxgene DNA	2.5	1	2.5
Biobanking cfDNA	10	3	30
Total biobanking			**60.5**
Maximum Total			**296.5**

ADA=antidrug antibody; cfDNA=circulating free deoxyribonucleic acid; DNA=deoxyribonucleic acid; HGSOC=high-grade serous ovarian cancer; INR=international normalised ratio; max=maximum; PBMC=peripheral blood mononuclear cells; PK=pharmacokinetic; RNA=ribonucleic acid; TSH=thyroid stimulating hormone

Table 17 Total Blood Volume for All Evaluations (Part D)

Assessments	Volume per sample (mL)	Max number of samples/month	Total max volume/month (mL)
Laboratory assessments			
Haematology	2	8	16
Chemistry (including liver function tests)	5	8	40
INR	2	2	4
Serum pregnancy test	2	1	2
PK and Biomarkers			
Blood sampling for PK of IPN60090	2	37	74
Blood sampling for Ca-125 (HGSOC only)	2	2	4
Blood/PBMC samples	6	18	108
cfDNA	10	3	30
Total volume Part D			**278**
Biobanking (optional)			
Biobanking serum	2.5	4	10
Biobanking plasma	2	4	8
Biobanking paxgene RNA	2.5	4	10
Biobanking paxgene DNA	2.5	1	2.5
Biobanking cfDNA	10	3	30
Total biobanking			**60.5**
Maximum Total			**338.5**

cfDNA=circulating free deoxyribonucleic acid; DNA=deoxyribonucleic acid; HGSOC=high-grade serous ovarian cancer; INR=international normalised ratio; max=maximum; PBMC=peripheral blood mononuclear cells; PK=pharmacokinetic; RNA=ribonucleic acid

Technical instructions will be provided in a separate laboratory manual. During dose escalation (Parts A to C) and during Part D, all samples will be analysed locally, except PK samples for pembrolizumab and paclitaxel analyses and anti-pembrolizumab ADA samples. During the dose expansion, all samples will be sent for central analysis (with the exception of laboratory safety tests for clinical decision making, which will be analysed locally).

5.4 Disease Evaluation

Tumour assessments will be performed at screening and every 6 weeks (±1 week) from Cycle 1, Day 1 using the RECIST v1.1 or iRECIST (Part B only).

Tumour evaluations will be assessed locally during the dose escalation and centrally during the dose expansion phase. Additionally, during the dose expansion part of the study, safety and supportive efficacy data will be reviewed and evaluated by an Independent Radiology Review Committee and ISAC to ensure that the continuation of the study is appropriate and to make recommendations to the sponsor. A specific scope of work and procedures will be described in an ISAC Charter and ISAC statistical analysis plan (SAP), to be established prior to the start of recruitment of the dose expansion phase.

The tumour assessments at screening are:

- CT/MRI (chest/abdomen and pelvis if indicated),
- brain MRI if clinically indicated.

Baseline tumour assessments performed per SoC within 28 days of enrolment are acceptable as long they are consistent with protocol requirements, and imaging data are available to transmit for central review (for the dose expansion only).

The tumour assessment will be conducted every 6 weeks (±1 week) from Cycle 1, Day 1, for the first 6 months, then every 12 weeks. Patients who discontinue study treatment for reasons other than progressive disease should continue tumour evaluations per the visit schedule until progression.

For patients who are allergic to i.v. contrast or cannot tolerate i.v. contrast due to impaired renal function or other issues, a regular CT or MRI is acceptable. Each follow-up tumour assessment should use the same assessment method as performed at screening, unless medically contraindicated. The sponsor will collect and store all tumour measurement images on all patients throughout the study. A review of the scans may be performed by the sponsor for an independent analysis of anti-tumour activity.

6 TREATMENT OF PATIENTS

6.1 Investigational Medicinal Product Preparation and Accountability

6.1.1 Investigational Medicinal Product Preparation

The investigator or an approved representative (for example pharmacist), will ensure that all IMP and any other study related material is stored in a secured area, under recommended temperature monitored storage conditions, in accordance with applicable regulatory requirements.

IPN60090 capsules do not require any special storage conditions but should not be refrigerated or frozen.

6.1.2 Investigational Medicinal Product Accountability

All IMP and any other study related material are to be accounted for on the IMP accountability log provided by the sponsor. It is essential that all used and unused supplies are retained for verification (by the sponsor or sponsor's representative). The investigator should ensure adequate records are maintained in the IMP accountability log.

6.2 Study Drugs Administered

6.2.1 IPN60090

The sponsor will provide the site with adequate supplies of IPN60090, which will be supplied as 10 mg, 60 mg and 240 mg capsules.

Patients in Part D will receive IPN60090 as a single dose in the morning on Day -7 and Day -3 as described in Section 3.1.3. Patients in all parts (Parts A, B, C and D [from Day 1]) should take IPN60090 BID (every 12 hours), during or after a meal. IPN60090 will be administered in the clinic on the first treatment day so that each patient can be observed for initial tolerability. Subsequent doses will be self-administered at home by taking IPN60090 BID at the same time each day until the next visit. Patients will be given a medication diary to record the day and time of administration, missed administration, if any, with related reasons, if available, or retake medication in case of rejection, if applicable. Any unused study treatment must be returned to the study site for drug accountability and disposal.

The assigned dose of IPN60090 will vary from cohort to cohort and will be defined by each SRC meeting, except for the starting dose for each part that is defined in the protocol. Patients should maintain their assigned dose in the absence of treatment-emergent toxicity.

If patients experience emesis, they should be instructed not to take additional doses of study medication and to maintain the planned dosing schedule. Patients should not make up for missed doses if more than 6 hours have elapsed after the time the patient would usually take IPN60090. In the event of missed doses, patients should not take 2 doses to make up for the one the patient missed.

During the Part A dose escalation, doses of IPN60090 will range from 20 mg BID (40 mg total daily dose) (starting dose) to 720 mg BID (1440 mg daily dose) (maximum dose).

During the Part B dose escalation, the starting dose of IPN60090 will be a dose showing pharmacological activity (at least 50% inhibition of Glu:Gln ratio in PBMC at C_{trough} (12 hours postdose) on Day 14 in 66% of patients at this dose level) and good tolerability as identified in Part A. Details of the dose of pembrolizumab are provided in Section 6.2.2.

During the Part C dose escalation, the starting dose of IPN60090 will be a dose showing pharmacological activity (at least 50% inhibition of Glu:Gln ratio in PBMC at C_{trough} (12 hours postdose) on Day 14 in 66% of patients at this dose level) and good tolerability as identified in Part A. Details of the dose of paclitaxel are provided in Section 6.2.2. When

H2 blockers are administered for paclitaxel premedication, they must be administered at least 30 minutes prior to paclitaxel infusion. IPN60090 intake should be performed at least 2.5 hours before the start of the paclitaxel infusion and at least 2 hours prior to H2 blocker administration.

The administration date and time of IPN60090 and pembrolizumab or paclitaxel should be recorded in the eCRF for days with PK/PD and ADA sampling. Administered doses, date and time of other concomitant medications (H2 blockers, or any other drugs) should be recorded in the eCRF for days when PK sampling is performed.

During Part D, the administered dose during the run-in period (Day -7 and Day -3) will be the RD (morning dose only) as defined by the SRC at the end of the Part A dose escalation. Then, starting from Day 1, IPN60090 will be administered at the RD BID during or after a meal.

The highest dose is also unknown. The proposed dose levels may be further modified and additional doses may be considered based on the safety, tolerability and efficacy observed during dose escalation. An intermediate, not predefined, previously evaluated or not previously evaluated dose or a less frequent dosing schedule that will not exceed the MTD level may be considered, if evaluation of toxicity at such a dose or schedule is desired.

6.2.1.1 Dose Expansion

In the expansion phases, the dose tested will be the RD determined in the dose escalation part.

6.2.2 Other Study Drugs

The sponsor will also provide the other study drugs to site (although locally supplied study drug may be used if needed or if required per local regulations and upon sponsor approval). Patients will be dosed with IPN60090 before being dosed with pembrolizumab or paclitaxel.

6.2.2.1 Part B: Pembrolizumab

Pembrolizumab will be supplied as a 100 mg/4 mL (25 mg/mL) solution in single-use vials to be diluted for infusion. It is a sterile, preservative-free, clear to slightly opalescent, colourless to slightly yellow solution that requires dilution for i.v. infusion. Each vial contains 100 mg of pembrolizumab in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg) and water for injection, USP.

(a) Dosage and administration:

IPN60090 capsules should be taken at least 1 hour before the pembrolizumab infusion. The predose, 30-minute (±5 minutes) and 1-hour (±5 minutes) blood samples for PK analysis should be drawn before initiating the pembrolizumab infusion.

The pembrolizumab dose will be fixed at 200 mg (or according to the approved local label for particular tumour types) administered as an i.v. infusion over 30 minutes every 21 days (±1 day in Cycle 1 and ±3 days in all other cycles) (Day 1 of every cycle) through an i.v. line containing a sterile, non-pyrogenic, low-protein binding 0.2 µm to 5 µm in-line or add-on filter. Premedication with antipyretic and antihistamine may be considered. Reconstitution and preparation of pembrolizumab solution for infusion should be done as per the locally-approved product information. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (i.e. infusion time is 30 minutes (-5 minutes/+10 minutes).

(b) Storage (per pembrolizumab prescribing information):

Unopened vials must be stored under refrigeration between 2°C and 8°C.

At room temperature for no more than 6 hours from the time of dilution. This includes room temperature storage of the infusion solution in the i.v. bag, and the duration of infusion.

Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration. Pembrolizumab should not be frozen.

6.2.2.2 Part C: Paclitaxel

For reconstitution and preparation of paclitaxel, please refer to the local label.

(a) Dosage and administration:

When H2 blockers are administered for paclitaxel premedication, they must be administered at least 30 minutes prior to paclitaxel infusion. IPN60090 intake should be performed at least 2.5 hours before the start of the paclitaxel infusion and at least 2 hours prior to H2 blocker administration.

The dose of paclitaxel will be fixed at 175 mg/m² or 135 mg/m² (or according to the local approved label for particular tumour types) administered as an i.v. infusion every 21 days (±1 day in Cycle 1 and ±3 days in all other cycles).

All patients should be premedicated prior to paclitaxel administration in order to prevent severe hypersensitivity reactions. Such premedication may consist of dexamethasone 20 mg administered approximately 12 and 6 hours before paclitaxel, diphenhydramine (or its equivalent) 50 mg i.v. 30 to 60 minutes prior to paclitaxel, and cimetidine (300 mg) or ranitidine (50 mg) i.v. 30 to 60 minutes before paclitaxel.

Paclitaxel infusion must be diluted prior to infusion. Paclitaxel should be diluted in 0.9% sodium chloride injection, USP; 5% dextrose injection, USP; 5% reference ID: 2939751 47 dextrose and 0.9% sodium chloride injection, USP; or 5% dextrose in Ringer's injection to a final concentration of 0.3 mg/mL to 1.2 mg/mL. The solutions are physically and chemically stable for up to 27 hours at ambient temperature (approximately 25°C) and room lighting conditions. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

(b) Storage (per paclitaxel prescribing information):

Unopened vials of paclitaxel infusion are stable until the date indicated on the package when stored between 20°C and 25°C (68°F to 77°F), in the original package. Neither freezing nor refrigeration adversely affects the stability of the product. Upon refrigeration, components in the paclitaxel vial may precipitate, but will redissolve upon reaching room temperature with little or no agitation. There is no impact on product quality under these circumstances [19].

6.3 Concomitant Medication/Therapy

Any prior or concomitant therapy or medication given to a patient within 28 days before, during, and up to 30 days after IMP administration will be indicated on the eCRF. The dose and generic name or trade name will be indicated.

6.3.1 List of Prohibited Medications During Study Drug Treatment

In general, the use of any concomitant medication deemed necessary for the care of the patient is permitted in this study, except as specifically prohibited. Concomitant administration of study drug could result in drug-drug interactions (DDI) that could potentially lead to reduced activity or enhanced toxicity of the concomitant medication and/or of IPN60090. Before any intake of a new concomitant treatment during the study treatment period, the investigator should assess the potential DDIs with IPN60090 using the Summary of Product Characteristics (SmPC) of the new concomitant treatment. The sponsor should be contacted in case of any doubt.

The prohibited drugs are reported in the exclusion criteria. In-vitro CYP mediated metabolism of IPN60090 might be catalysed by CYP3A4 and CYP2D6; for Parts A, B and C, drugs which are strong CYP3A4 and CYP2D6 inhibitors and strong CYP3A4 inducers are prohibited. In addition, since paclitaxel is a CYP2C8 substrate, for Part C only, drugs that are strong CYP2C8 inhibitors and inducers are prohibited.

The lists of strong inhibitors and inducers of CYP3A4, of strong inhibitors of CYP2D6 and of strong inhibitors and inducers of CYP2C8 are provided in Appendix 2, Appendix 3, Appendix 4 and Appendix 5.

Grapefruit (listed in Appendix 2), star fruit and Seville oranges may also increase plasma concentrations of IPN60090 by inhibition of CYP3A4 and therefore are prohibited.

St John's Wort (listed in Appendix 2) may decrease plasma concentrations of IPN60090 by induction of CYP3A4 and therefore is prohibited.

H2 blockers, proton pump inhibitors and antacids are prohibited during the run-in period (Day -7 to Day -3) of Part D.

In-vitro data show that IPN60090 does not induce CYP3A4, CYP2B6 and CYP1A2 and that IPN60090 does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 (Report P18-142-73, Report PK-15 and Report PK-17). Therefore, no DDI is anticipated in clinical settings regarding the induction of the CYP3A4, CYP2B6 and CYP1A2 by IPN60090. Similarly, no DDI is anticipated in clinical settings regarding the inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 by IPN60090.

6.3.2 List of Medications to be Used with Caution during Study Drug Treatment

Concomitant administration of study drug could result in DDIs that could potentially lead to reduced activity or enhanced toxicity of the concomitant medication and/or IPN60090.

Before any intake of a new concomitant treatment during the study treatment period, the investigator should assess the potential DDIs with IPN60090 using the SmPC of the new concomitant treatment. The sponsor should be contacted in case of any doubt.

Caution should be exercised when administering IPN60090 concomitantly with medicines known to be moderate inhibitors of CYP3A4 or CYP2D6. Administering IPN60090 concomitantly with medicines known to be moderate inducers of CYP3A4 is not recommended. Moreover, moderate inhibitors/inducers of CYP2C8 should also be used with caution for Part C as well as immunosuppressive agents for Part B.

The lists of moderate inhibitors of CYP3A4 and of CYP2D6 are provided in Appendix 3 and Appendix 4, respectively. The list of moderate inducers of CYP3A4 is provided in Appendix 3. The lists of moderate inhibitors/inducers of CYP2C8 are provided in Appendix 6. The list of immunosuppressive agents is provided in Appendix 7.

In-vitro data show that IPN60090 is an inhibitor of the human OATP1B3, OCT1, OCT2, MATE2-K, MATE1 and OATP1B1 uptake transporters. Based on the % of maximal inhibition in vitro, caution should be exercised when administering IPN60090 concomitantly with medicines known to be substrates of OATP1B3, OCT1 and OCT2 transporters (Report MD Anderson-05-08Nov2017).

The lists of drugs known to be substrates of OATP1B3, OCT1 and OCT2 transporters are provided in Appendix 8.

6.3.3 Permitted Concomitant Medications

The following concomitant medications are permitted during this study but they must be monitored closely and every effort should be made to keep their dose and dose regimen constant throughout the course of the study:

- Antiemetics and antidiarrheal medications are allowed prophylactically according to standard clinical practice if clinically indicated.
- Granulocyte colony-stimulating factors are allowed if used per clinical guidelines (for example American Society of Clinical Oncology (ASCO) or European Society for Medical Oncology guidelines).
- Drugs used to control bone loss (e.g. bisphosphonates and denosumab) are allowed if started prior to screening. If indicated to be initiated or exchanged during the course of the study, sponsor's approval is required.
- Antacids, H2 blockers. Specific attention should be paid to these medications as they may have an impact on IPN60090 absorption. IPN60090 should be taken at least 2 hours before an antacid or H2 blocker intake.
- Any medication required for the safety of the patient.
- In Part B, premedication with antipyretic and antihistamine may be considered before pembrolizumab infusion.
- In Part C, the following premedications are allowed to prevent severe hypersensitivity reactions to paclitaxel: dexamethasone, diphenhydramine (or its equivalent) and cimetidine or ranitidine (see Section 6.2.2.2 for more details on dosage and administration).

The name, posology, date and time of any concomitant medication intake will be recorded in the eCRF.

6.4 Dose Modifications

6.4.1 Reduction of IPN60090 Monotherapy

Management of severe or intolerable adverse reactions requires dose reduction, temporary interruption, and/or discontinuation of IPN60090 therapy. Each patient is allowed a maximum of two dose reductions for IPN60090. After this, the patient will be discontinued from the study treatment.

If a dose reduction is required, reduce the current dose by one dose level from the current dose.

Table 18 Dose Adjustment for IPN60090

	DL1	DL2	DL3	DL4	DL5	DL6	DL7
Starting dose level	20 mg BID	40 mg BID	80 mg BID	180 mg BID	320 mg BID	480 mg BID	720 mg BID
First dose reduction	N/A	20 mg BID	40 mg BID	80 mg BID	180 mg BID	320 mg BID	480 mg BID
Second dose reduction	N/A	N/A	20 mg BID	40 mg BID	80 mg BID	180 mg BID	320 mg BID

BID=bis in die (twice daily); DL=dose level; N/A=not applicable

6.4.2 Reduction of IPN60090 + Pembrolizumab

Management of severe or intolerable adverse reactions requires dose reduction, temporary interruption, and/or discontinuation of IPN60090 therapy. Each patient is allowed a maximum of two dose reductions for IPN60090. Pembrolizumab will be at a fixed dose and the dose cannot be reduced; however, treatment with pembrolizumab can be delayed >6 weeks (2 cycles) for any reason. In this case, the patient must be permanently discontinued from study therapy, except in cases where permission to resume treatment is granted by the Ipsen Medical Monitor or designee. If a patient discontinues IPN60090, they may remain on study on pembrolizumab monotherapy.

If a dose reduction is required, the current dose should be reduced by one dose level from the current dose. This can be done up to two times before a patient must discontinue study treatment.

Table 19 Dose Adjustment for IPN60090 + Pembrolizumab

	DL1		DL2		DL3	
	IPN60090	**Pembrolizumab**	**IPN60090**	**Pembrolizumab**	**IPN60090**	**Pembrolizumab**
Starting dose level	180 mg BID	In accordance with approved label	320 mg BID	In accordance with approved label	480 mg BID	In accordance with approved label
First dose reduction	80 mg BID		180 mg BID		320 mg BID	
Second dose reduction	40 mg BID		80 mg BID		180 mg BID	

BID=bis in die (twice daily); DL=dose level

6.4.3 Reduction of IPN60090 + Paclitaxel

Management of severe or intolerable adverse reactions requires dose reduction, temporary interruption, and/or discontinuation of IPN60090 therapy. Each patient is allowed a maximum of two dose reductions for IPN60090; paclitaxel is a fixed dose and the dose cannot be reduced. If treatment with paclitaxel is delayed >6 weeks (2 cycles) for any reason, the patient must be permanently discontinued from study therapy, except in cases where permission to resume treatment is granted by the Ipsen Medical Monitor or designee. If a patient discontinues IPN60090 they may remain on study on paclitaxel monotherapy.

If a dose reduction is required, reduce the current dose by one dose level from the current dose. This can be done up to two times before a patient must discontinue study treatment.

Table 20 Dose Adjustment for IPN60090 + Paclitaxel

	DL1		DL2		DL3	
	IPN60090	**Paclitaxel**	**IPN60090**	**Paclitaxel**	**IPN60090**	**Paclitaxel**
Starting dose level	180 mg BID	In accordance with approved label	320 mg BID	In accordance with approved label	480 mg BID	In accordance with approved label
First dose reduction	80 mg BID		180 mg BID		320 mg BID	
Second dose reduction	40 mg BID		80 mg BID		180 mg BID	

BID=bis in die (twice daily); DL=dose level

6.4.4 Dose Adjustments and Modifications

The management of all study drugs, and any dose adjustments should be in line with the best clinical practice for individual patients and is ultimately left to the discretion of the investigator or treating physician.

Dose management of pembrolizumab and paclitaxel should be done according to the approved product information.

The following tables are recommended adjustments and modifications of IPN60090 in case of haematologic toxicity (Table 21), hepatotoxicity (Table 22), cardiac toxicity (Table 23), immune-related reactions: non-infectious pneumonitis (Table 24) and other toxicities (Table 26).

6.4.4.1 Dose Adjustments and Modifications for Nonimmune Related Adverse Events

Table 21 Dose Adjustment and Management Recommendations for IPN60090 in Case of Haematologic Toxicity

Toxicity/grade	Dose adjustment and management recommendations for IPN60090
Thrombocytopenia	
Grade 1(≥75x10^9/L)	No dose adjustment required.
Grade 2 (≥50x10^9/L to <75x10^9/L)	-Dose interruption until recovery to Grade ≤1. -Re-initiate at the same dose.
Grade 3 (≥25x10^9/L to <50x10^9/L)	-Dose interruption until recovery to Grade ≤1. -Re-initiate at the same dose level. -If toxicity recurs at Grade 3: temporary dose interruption until recovery to Grade ≤1 and reduce to the next lower dose level.
Grade 4 (<25x10^9/L)	-Dose interruption until recovery to Grade ≤1. -Re-initiate at the next lower dose level. -If toxicity recurs at Grade 4: discontinue IPN60090
Absolute neutrophil count (ANC)	
Grade 1 (≥1.5x10^9/L)	No dose adjustment required.
Grade 2 (≥1.0 to <1.5x10^9/L)	No dose adjustment required.
Grade 3 (≥0.5 to <1.0x10^9/L)	-Dose interruption of IPN60090 until recovery to ≥1.0x10^9/L. -Re-initiate IPN60090 at the same dose level. -If toxicity recurs at Grade 3: temporary dose interruption until recovery to ≥1.0x10^9/L. -If resolved in ≤7 days, then maintain dose level. -If resolved in >7 days, then reduce IPN60090 dose to the next lower dose level.
Grade 4 (<0.5x10^9/L)	-Dose interruption of IPN60090 and pembrolizumab (if applicable) until recovery to ≥1.0x10^9/L. -Re-initiate IPN60090 at the next lower dose level. -If toxicity recurs at Grade 4: discontinue IPN60090.
Febrile neutropenia	
Grade 3 ANC <1.0x10^9/L with a single temperature of >38.3ºC (101 ºF) or a sustained temperature of ≥38ºC (100.4ºF) for more than one hour	-Dose interruption of IPN60090 and pembrolizumab (if applicable) until improvement of ANC ≥1.0x10^9/L and no fever. Restart at the next lower dose level. -If febrile neutropenia recurs, discontinue IPN60090.
Grade 4 Life threatening consequences; urgent intervention indicated	-Discontinue IPN60090.
Anaemia (haemoglobin)	
Grade 1 (≥10.0 to LLN g/dL)	No dose adjustment required.
Grade 2 (≥8.0 to <10.0 g/dL)	No dose adjustment required.
Grade 3 (<8.0 g/dL)	-Dose interruption until recovery to Grade ≤2. -Re-initiate IPN60090 at the same dose.
Grade 4 Life threatening consequences; urgent intervention indicated	-Discontinue IPN60090.

LLN=lower limit of normal

Table 22 Dose Adjustment and Management Recommendations for IPN60090 in Case of Hepatotoxicity

Toxicity/grade	Dose adjustment and management recommendations for IPN60090
Total bilirubin without ALT/AST increase above baseline value	
Grade 1 (>ULN to 1.5xULN) (confirmed 48 to 72 hours later)	Maintain dose level with LFTs monitored biweekly.
Grade 2 (>1.5 to 3.0xULN)	-Dose interruption of IPN60090. -If resolved to ≤Grade 1 in ≤14 days, then maintain dose level. -If resolved to ≤Grade 1 in >14 days or toxicity recurs, then reduce IPN60090 by one dose level. -Repeat liver enzymes and bilirubin tests weekly for 2 weeks after dose resumption. -If toxicity recurs after two dose reductions, discontinue study treatment.
Grade 3 (>3.0 to 10.0xULN)	-Dose interruption of IPN60090. -If resolved to ≤Grade 1 in ≤14 days, lower one dose level of IPN60090. -Repeat liver enzymes and bilirubin tests weekly for 2 weeks after dose resumption. -If resolved to ≤Grade 1 in >14 days or toxicity recurs, discontinue IPN60090.
Grade 4 (>10.0xULN)	Discontinue IPN60090
Confounding factors and/or alternative causes for increase of total bilirubin should be excluded before dose interruption/reduction. They include but are not limited to: evidence of obstruction, such as elevated ALP and GGT typical of gallbladder or bile duct disease, hyperbilirubinaemia due to the indirect component only (i.e. direct bilirubin component ≤1xULN) due to haemolysis or Gilbert's syndrome, pharmacologic treatment, viral hepatitis, alcoholic or autoimmune hepatitis, other hepatotoxic drugs. For patients with Gilbert's syndrome, these dose modifications apply to changes in direct bilirubin only. Bilirubin will be fractionated if elevated.	

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma glutamyl transferase; LFTs=liver function tests; ULN=upper limit of normal

Table 23 Dose Adjustment and Management Recommendations for IPN60090 in Case of Cardiac Toxicity

Adverse drug reaction	Severity	Dose adjustment and management recommendations
QTcF prolongation	For all grades	-Check the quality of the ECG and the QT value and repeat if needed. -Perform analysis of serum electrolytes (potassium, calcium, phosphate, magnesium). If outside of normal range, hold IPN60090, correct with supplements or appropriate therapy as soon as possible, and repeat electrolytes until documented as normal. -Review concomitant medication usage for the potential to prolong the QT interval. -Check compliance with correct dose and administration of IPN60090. -Consider collecting a time matched PK sample; record date and time of last study drug intake.
	Grade 1 QTc 450 to 480 ms	No dose adjustment required.
	Grade 2 QTc 481 to 500 ms	-Hold IPN60090. -Perform repeat triplicate ECGs one hour after the first QTcF of ≥481 ms. -If QTcF <481 ms, restart IPN60090 at the same dose. No dose adjustment required for first occurrence. If QTcF remains ≥481 ms, repeat ECG as clinically indicated until the QTcF returns to <481 ms. Restart IPN60090 and pembrolizumab (if applicable) at the same dose. No dose adjustment required for first occurrence. -If QTcF ≥481 ms recurs, IPN60090 should be reduced by one dose level -Repeat ECGs 7 days and 14 days after dose resumption (then as clinically indicated) for any patients who had therapy interrupted due to QTcF ≥481 ms.

Adverse drug reaction	Severity	Dose adjustment and management recommendations
	Grade 3 QTc ≥501 ms on at least two separate ECGs	-Hold IPN60090. -Perform repeat triplicate ECGs within one hour of the first QTcF of ≥501 ms. -If QTcF remains ≥501 ms, consult with a cardiologist (or qualified specialist) and repeat cardiac monitoring as indicated until the QTcF returns to <481 ms. -If QTcF returns to <481 ms, IPN60090 will be reduced by one dose level. -Repeat ECGs 7 days and 14 days after dose resumption (then as clinically indicated) for any patients who had therapy interrupted due to QTcF ≥501 ms. -If QTcF of ≥501 ms recurs, discontinue study treatment. -Hold IPN60090 and perform frequent ECGs until the QTcF is <500 ms. Address electrolyte, calcium and magnesium abnormalities. Restart IPN60090 at a lower dose. -If findings recur on the lower dose, hold study treatment until resolve to ≤Grade 1, and restart at the next lower dose level. If findings recur, discontinue IPN60090.
	Grade 4 QT/QTc ≥501 or >60 ms change from baseline and Torsades de pointes or polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia	-Discontinue IPN60090. -Obtain local cardiologist (or qualified specialist) consultation and repeat cardiac monitoring as indicated until the QTcF returns to <481 ms. -Stop study treatment, institute emergency care, address electrolyte, calcium and magnesium abnormalities and perform frequent ECGs until the QTcF is <500 ms. -Discontinue the patient from the study.
Cardiac - Left Ventricular Systolic Dysfunction	Asymptomatic, resting ejection fraction 40% to 50%; or 10% to 20% drop from baseline	-Maintain dose level and continue study treatment with caution. -Repeat LVEF within 4 weeks or as clinically appropriate.
	Symptomatic, responsive to intervention, ejection fraction 20% to 39% or >20% drop from baseline	-Hold study treatment until resolved, then reduce one dose level. -LVEF measurement to be repeated, if not resolved, within 28 days.
	Refractory or poorly controlled, ejection fraction <20%	Discontinue IPN60090.

ECG=electrocardiogram; LVEF=left ventricular ejection fraction; QTc=corrected QT interval; QTcF=Fridericia corrected QT interval

6.4.4.2 Dose Adjustments and Modifications for Immune-Related Adverse Events Associated with Pembrolizumab

Adverse events associated with pembrolizumab exposure may represent an immune-related response. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm aetiology or exclude other causes. Additional procedures or tests such as bronchoscopy,

endoscopy, skin biopsy may be included as part of the evaluation. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 24.

Table 24 Dose Modification and Toxicity Management Guidelines for Immune-Related AEs Associated with Pembrolizumab

irAEs	Toxicity grade (CTCAE v5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhoea/colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (i.e. diarrhoea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e. peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhoea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhoea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via i.v. infusion
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity grade (CTCAE v5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
AST or ALT elevation or increased bilirubin	Grade 2[a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3[b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or hyperglycaemia	New onset T1DM or Grade 3 or 4 hyperglycaemia associated with evidence of β-cell failure	Withhold[d]	• Initiate insulin replacement therapy for participants with T1DM • Administer antihyperglycaemic in participants with hyperglycaemia	• Monitor participants for hyperglycaemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (e.g. propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3, 4	Continue	• Initiate thyroid replacement hormones (e.g. levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm aetiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		

irAEs	Toxicity grade (CTCAE v5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
All other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm aetiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event[e]		
	Recurrent Grade 3 or 4	Permanently discontinue		

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; GI=gastrointestinal; irAE=immune-related adverse event; i.v.=intravenous; T1DM=Type 1 diabetes mellitus; ULN=upper limit of normal

[a] AST/ALT: >3.0 to 5.0 × ULN if baseline normal; >3.0 to 5.0 × baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 × ULN if baseline normal; >1.5 to 3.0 × baseline, if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 × ULN if baseline normal; >5.0 to 20.0 × baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 × ULN if baseline normal; >3.0 to 10.0 × baseline, if baseline abnormal

[c] AST/ALT: >20.0 × ULN if baseline normal; >20.0 × baseline, if baseline abnormal; bilirubin: >10.0 × ULN if baseline normal; >10.0 × baseline, if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include but are not limited to: Guillain-Barre Syndrome, encephalitis, Stevens-Johnson Syndrome and toxic epidermal necrolysis.

General instructions:

(1) Severe and life-threatening irAEs should be treated with i.v. corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.

(2) Pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab treatment.

(3) The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue for at least 4 weeks.

(4) If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤ Grade 1 after the corticosteroid taper.

Table 25 Dose Adjustment and Management Recommendations for IPN60090 in Case of Immune-Related Reactions: Noninfectious Pneumonitis

Worst grade pneumonitis	Required investigations	Management of pneumonitis	Dose adjustment
Grade 1 Asymptomatic, radiographic findings only	CT scans with lung windows. Repeat at least every 12 weeks until return to within normal limits.	No specific therapy is required.	-Administer 100% of study treatment. -Consider patient referral to pulmonary specialist. -for recurrent pneumonitis, treat as Grade 3 or 4 event.
Grade 2 Symptomatic, not interfering with ADL	CT scan with lung windows. Consider pulmonary function testing includes: spirometry, DLCO, and room air O_2 saturation at rest. Repeat at least every 12 weeks until return to within normal limits. Consider a bronchoscopy with biopsy and/or BAL.	Symptomatic only. Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper.	-Hold pembrolizumab (if applicable) until recovery to ≤Grade 1. -Resume pembrolizumab if event resolves to Grade 1 or better within 12 weeks. -Permanently discontinue pembrolizumab and contact the sponsor if event does not resolve to Grade 1 or better within 12 weeks. -Reduce IPN60090 dose by one dose level until recovery to ≤Grade 1. Study treatment may also be interrupted if symptoms are troublesome. -Patients will discontinue IPN60090 and pembrolizumab (if applicable) if they fail to recover to ≤Grade 1 within 12 weeks. -If Grade 2 recurs discontinue study treatment.
Grade 3 Symptomatic, interfering with ADL; O_2 indicated	CT scan with lung windows and pulmonary function testing includes: spirometry, DLCO, and room air O_2 saturation at rest. Repeat at least every 6 weeks until return to within normal limits. Bronchoscopy with biopsy and/or BAL is recommended.	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper.	Discontinue IPN60090 and pembrolizumab (if applicable).
Grade 4 Life threatening; ventilatory support indicated	CT scan with lung windows and required pulmonary function testing, if possible, includes: spirometry, DLCO, and room air O_2 saturation at rest. Repeat at least every 6 weeks until return to within normal limits. Bronchoscopy with biopsy and / or BAL is recommended if possible.	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper.	Discontinue IPN60090 and pembrolizumab (if applicable).

ADL=activity of daily living; BAL=bronchoalveolar lavage; CT=computed tomography; DLCO=diffusing capacity of the lungs for carbon monoxide; O_2=oxygen

Table 26 Dose Adjustment and Management Recommendations for IPN60090 in Case of Other Toxicities

Toxicity	Action
Hyperlipidaemia and/or hypertriglyceridaemia	Any grade: Treat according to best clinical practice. No specific dose reductions are needed.
Hyperglycaemia	Any grade: Treat according to best clinical practice. No specific dose reductions are needed.
All other toxicities	Any grade: Treat according to best clinical practice. No specific dose reductions are needed.

6.4.5 Transition to Recommended Dose or Other Regimen

In Parts A, B and C, when the RD is defined, if a patient is still in the study at a different dose, this patient can be moved to the RD, at the discretion of the investigator.

In Part A, biomarker-positive patients who are enrolled and receive study treatment at initial dose levels below the pharmacologically active range for at least two cycles with good tolerability, and achieve and maintain at least SD, may be escalated to a higher dose level that has been tested and proven to be well tolerated at the recommendation of the SRC. These patients will be treated outside of the BOIN design.

Patients enrolled in monotherapy Part A and Part D may receive combination treatment with either pembrolizumab or with paclitaxel upon progression on IPN60090 monotherapy, at the discretion of the investigator, and with the approval of the sponsor, once the safe dose level for the combination is determined. These patients will need to satisfy the eligibility criteria for combination therapy prior to initiating treatment, and will be followed for safety and efficacy in a separate cohort.

6.5 Procedures for Monitoring Patient Compliance

The investigator will be responsible for monitoring patient compliance. Patients may be withdrawn from the study at any time if the investigator or the sponsor determines that the patient is not in compliance with the study protocol.

Administration compliance will be assessed by a capsule count at each visit. Deviations of >25% of the scheduled amount of IMP intake will be regarded as a major protocol deviation unless the dose is reduced due to toxicity.

If a patient is consistently noncompliant with IMP intake they should be discontinued from IMP/withdrawn from the study, at the discretion of the investigator. Please refer to Section 4.3 for the criteria for discontinuing the patient from IMP.

7 ASSESSMENT OF ANTI-TUMOUR ACTIVITY

For the timing of assessments in this study, refer to the schedule in Table 14.

7.1 Efficacy Endpoints and Evaluations

7.1.1 Dose Escalation (Part A - Monotherapy and Parts B and C - Combinations) and Food Effect Cohort (Part D)

Secondary tumour activity endpoints and evaluations planned during the dose escalation phase and food effect cohort are summarised in Table 27. All tumour endpoints will be assessed locally.

Table 27 Efficacy Endpoints and Evaluations During Dose Escalation and Food Effect Cohort

Measure	Timepoint	Variable	Endpoint
Tumour size (longest diameter)	Parts A, C and D: Baseline and every 6 weeks	Tumour response according to RECIST v1.1	CBR ORR PFS DCR OS
	Part B: Baseline and every 6 weeks	Tumour response according to iRECIST	CBR ORR DCR iPFS OS

CBR=clinical benefit rate; DCR=disease control rate; iPFS=immune progression-free survival; ORR=objective response rate; OS=overall survival; PFS=progression free survival

7.1.2 Dose Expansion Phases

Secondary tumour activity endpoints and evaluations planned in the dose expansions are summarised in Table 28. All tumour endpoints will be assessed centrally.

Table 28 Efficacy Endpoints and Evaluations During Dose Expansion

Measure	Timepoint	Variable	Endpoint
Tumour size (longest diameter)	Parts A and C: Baseline and every 6 weeks	Tumour response according to RECIST v1.1	CBR ORR PFS DCR OS
	Part B: Baseline and every 6 weeks	Tumour response according to iRECIST	CBR ORR DCR iPFS OS

CBR=clinical benefit rate; DCR=disease control rate; iPFS=immune progression-free survival; ORR=objective response rate; OS=overall survival; PFS=progression free survival

7.2 Methods and Timing of Assessing, Recording and Analysing Efficacy Data

The methods for assessing efficacy data are described below. The timing of efficacy assessments is discussed in Section 5. The procedures for recording efficacy data are discussed in Section 15.1 and the methods of analyses are discussed in Section 11.

Radiographic response and disease progression will be determined using RECIST v1.1 (CT/MRI) and iRECIST (Part B only).

7.2.1 Tumour Response Using RECIST v1.1

For this study, tumour response will be evaluated using the revised RECIST guideline v1.1.

All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline.

The tumour response of each patient will be graded as CR, PR, SD, progressive disease, or unevaluable according to RECIST v1.1. Based on this classification, the following endpoints will be calculated as defined by RECIST v1.1:

- ORR: proportion of patients with a BOR characterised as either CR or PR relative to the total number of evaluable patients.
- CBR: proportion of patients with BOR of CR, PR and SD lasting ≥12 weeks.
- DCR: proportion of patients with a BOR characterised as CR, PR or SD relative to the total number of evaluable patients.
- PFS: time from first dose of study medication to the first documented objective disease progression or death due to any cause, whichever occurs first.
- OS: time from the date of first dose of study drug to death due to any cause.

7.2.2 Tumour Response Using iRECIST (Part B Only)

For patients in Part B, tumour response will be evaluated using the iRECIST guideline (see [20]). Only patients who have received at least one dose of IPN60090 treatment will be considered evaluable for response.

All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline.

The tumour response of each patient will be graded as iCR, iPR, iSD, immune unconfirmed progressive disease (iUPD) or immune confirmed progressive disease (iCPD) and unevaluable according to iRECIST. Based on this classification, the following endpoints will be calculated:

- ORR: proportion of patients with a BOR characterised as either iCR or iPR relative to the total number of evaluable patients.
- CBR: proportion of patients with BOR of iCR, iPR and iSD lasting ≥12 weeks.
- DCR: proportion of patients with a BOR characterised as iCR, iPR or iSD relative to the total number of evaluable patients.
- immune PFS: time from first dose of study medication to the first documented objective disease progression (time of iUPD if followed by iCPD) or death due to any cause, whichever occurs first.
- OS: time from the date of first dose of study drug to death due to any cause.

iRECIST is adapted to account for the unique tumour response seen with immunotherapeutic drugs. When clinically stable, patients should not be discontinued until progression is confirmed by the investigator. Some patients can have initial radiographic progressive disease due to a transient tumour flare in the first few months after the start of immunotherapy, and then experience subsequent disease response.

Clinical stability is defined as the following:

- absence of symptoms and signs indicating clinically significant progression of disease
- no decline in ECOG performance status
- no requirements for intensified management, including increased analgesia, radiation or other palliative care

Any patient deemed clinically unstable should be discontinued from study treatment at first radiologic evidence of progressive disease and will not be required to have repeat tumour imaging for confirmation of progressive disease by iRECIST.

Patients who are clinically stable and exhibit initial radiographic progressive disease may continue to receive study treatment and the tumour assessment should be repeated 4 to 6 weeks later to confirm progressive disease by iRECIST, per investigator assessment. If repeated imaging does not confirm progressive disease per iRECIST, as assessed by the investigator, and the patient continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If progressive disease is confirmed, patients will be discontinued from study treatment.

If a patient has confirmed radiographic progression as defined in Appendix 9, study treatment should be discontinued; however, if the patient is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the sponsor. In this case, if study treatment is continued, tumour imaging should follow the 6-week tumour assessment schedule.

A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 29.

Table 29 Imaging and Treatment after First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST v1.1	Repeat imaging at 4 to 8 weeks to confirm PD	May continue study treatment at the investigator's discretion while awaiting confirmatory tumour imaging by site by iRECIST	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only	Discontinue treatment
Repeat tumour imaging confirms PD (iCPD) by iRECIST per investigator assessment	No additional imaging required	Discontinue treatment (exception is possible upon consultation with sponsor)	No additional imaging required	Not applicable
Repeat tumour imaging shows iUPD by iRECIST per investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study treatment at the investigator's discretion	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only	Discontinue treatment
Repeat tumour imaging shows iSD, iPR or iCR by iRECIST per investigator assessment.	Continue regularly scheduled imaging assessments	Continue study treatment at the investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion. Next tumour imaging should occur according to the regular imaging schedule.

BICR=Blinded Independent Central Review; iCPD=iRECIST confirmed progressive disease; iCR=iRECIST complete response; iRECIST=modified Response Evaluation Criteria in Solid Tumors for immune-based therapeutics; iSD=iRECIST stable disease; iUPD=iRECIST unconfirmed progressive disease; PD=progressive disease; RECIST=Response Evaluation Criteria in Solid Tumors; VOP=verification of progression

8 ASSESSMENT OF SAFETY

8.1 Adverse Events

Adverse events will be monitored from the time that the patient gives informed consent and throughout the study (see Section 3.6 for a definition of the study duration) and will be elicited by direct, nonleading questioning. Further details of AE reporting can be found in Section 8.1.2.

8.1.1 Definition of an Adverse Event

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (for example nausea, chest pain), signs (for example tachycardia, enlarged liver) or the abnormal results of an investigation (for example laboratory findings, ECG). In clinical studies an AE can include an undesirable medical condition occurring at any time, including run in or washout periods, even if no IMP has been administered.

This definition includes events occurring from the time of the patient giving informed consent until the end of the study (as defined in Section 3.6).

Natural progression or deterioration of the malignancy under study will be recorded as part of the efficacy evaluation and should not be recorded as an AE/SAE.

Death due to disease progression will be recorded as part of the efficacy evaluation and will not be regarded as an SAE.

Signs and symptoms should not be reported as AEs/SAEs if they are clearly related to a relapse or an expected change or progression of the baseline malignancy.

These signs and symptoms should only be reported as AEs/SAEs (depending on the investigator's judgement) if they are:

- Judged by the investigator to be unusually severe or an accelerated malignancy, or
- If the investigator considers the deterioration of malignancy signs and symptoms to be caused directly by the IMP.

If there is any uncertainty about an AE being due solely to the malignancy under study, it should be reported as an AE/SAE as appropriate.

The following events must be reported to the sponsor within 24 hours of the site's awareness, irrespective of causality: serum aminotransferases ALT/AST >3×ULN, with increase in total serum bilirubin >2×ULN.

8.1.2 Categorisation of Adverse Events

8.1.2.1 Intensity Classification

Adverse events will be recorded and graded according to the current version of the NCI-CTCAE v5.0. In view of meta-analyses and for conversion purposes, the following conversion mapping will apply if the NCI-CTCAE scale is not available for a given AE:

- NCI-CTCAE Grade 1 corresponds to mild,
- NCI-CTCAE Grade 2 corresponds to moderate,
- NCI-CTCAE Grade 3 corresponds to severe,
- NCI-CTCAE Grade 4 corresponds to life threatening/disabling,
- NCI-CTCAE Grade 5 corresponds to death (related to AE).

Where:

- **Mild**: symptoms do not alter the patient's normal functioning
- **Moderate**: symptoms produce some degree of impairment to function, but are not hazardous, uncomfortable or embarrassing to the patient
- **Severe**: symptoms definitely hazardous to wellbeing or causing significant impairment of function or incapacitation.
- **Life threatening**: any event that places the patient at immediate risk of death from the event as it occurred, i.e. it does not include a reaction that, had it occurred in a more severe form, might have caused death (also see Section 8.1.4).

8.1.2.2 Causality Classification

The relationship of an AE to IMP administration will be classified according to the following:

- **Related**: reports including good reasons and sufficient information (for example plausible time sequence, dose response relationship, pharmacology, positive dechallenge and/or rechallenge) to assume a causal relationship with IMP administration in the sense that it is plausible, conceivable or likely. Since attribution of an observed toxicity to a new drug can be uncertain, related events should include any toxicities considered related, probably related or possibly related to the drug.
- **Not related**: reports including good reasons and sufficient information (for example implausible time sequence and/or attributable to concurrent disease or other drugs) to rule out a causal relationship with IMP administration.

8.1.2.3 Assessment of Expectedness

The reference document for assessing expectedness of AEs/event in this study will be the current Investigator's Brochure (IB) for IPN60090, the EU SmPC (for EU centres) or US Prescribing Information (for US centres).

8.1.2.4 Laboratory Test Abnormalities

Abnormalities in laboratory test values should only be reported as AEs if any of the following apply:

- They result in a change in IMP schedule of administration (change in dosage, delay in administration, IMP discontinuation),
- They require intervention or a diagnosis evaluation to assess the risk to the patient,
- They are considered as clinically significant by the investigator.

8.1.2.5 Abnormal Physical Examination Findings

Clinically significant changes, in the judgement of the investigator, in physical examination findings (abnormalities) will be recorded as AEs.

8.1.2.6 Other Investigation Abnormal Findings

Abnormal test findings judged by the investigator as clinically significant (for example ECG changes, thyroid function disturbances) that result in a change in study drug dosage or administration schedule, or in discontinuation of the study drug, or require intervention or diagnostic evaluation to assess the risk to the patient, should be recorded as AEs.

8.1.3 Recording and Follow-up of Adverse Events

At each visit, the patient should be asked a nonleading question such as: "How have you felt since starting the last assessment?"

All observed or volunteered AEs, regardless of treatment group or suspected causal relationship to IMP, will be recorded on the AE page(s) of the eCRF. Events involving drug reactions, accidents, illnesses with onset during the treatment phase of the study, or exacerbations of pre-existing illnesses should be recorded according to the National Cancer Institute terminology if applicable.

Any AEs already recorded and designated as 'continuing' should be reviewed at each subsequent assessment.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to the sponsor or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE (i.e. IMP or other illness). The investigator is required to assess causality and record that assessment on the eCRF. Follow-up of the AE, after the date of IMP discontinuation, is required if the AE or its sequelae persist. Follow-up is required until the event or its sequelae resolve or stabilise at a level acceptable to the investigator and the sponsor's clinical monitor or his/her designated representative.

All SAEs that are ongoing 30 days after the last dose of study treatment, and AEs assessed Grade 3 or 4 that led to study treatment discontinuation that are ongoing 30 days after the date of the decision to discontinue study treatment, are to be followed until either:

- the AE has resolved
- the AE has improved to CTCAE Grade 2 or lower
- the investigator determines that the event has become stable or irreversible.

This follow-up requirement also applies to related SAEs that occur >30 days after the date of the decision to discontinue study treatment.

The status of all other AEs that are ongoing 30 days after the date of the decision to discontinue study treatment will be documented as of the Post-Treatment Follow-Up Visit.

8.1.4 Reporting of Serious Adverse Events

All SAEs (as defined below), regardless of treatment group or suspected relationship to IMP, must be reported immediately (within 24 hours of the investigator's knowledge of the event) using the electronic data capture (EDC) system. In instances where the EDC system is not available, the SAE form must be completed and sent to the email address or fax number (if not possible to email) specified at the beginning of this protocol. If the immediate report is submitted by telephone, or if the EDC was not available at initial reporting, this must be followed by the reporting of this SAE using the EDC system as soon as it becomes available.

An SAE is any AE that:

(1) Results in death;

(2) Is life threatening, that is any event that places the patient at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death;

(3) Results in in-patient hospitalisation or prolongation of existing hospitalisation, excluding admission for social or administrative reasons (see below);

(4) Results in a persistent or significant disability/incapacity, where disability is a substantial disruption of a person's ability to conduct normal life functions;

(5) Results in congenital anomaly/birth defect in the offspring of a patient who received the IMP;

(6) Is an important medical event that may not result in death, be life threatening, or require hospitalisation when, based upon appropriate medical judgement, it may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalisation, or the development of drug dependency or drug abuse.

In addition to the above criteria, the following events must be reported to the sponsor within 24 hours of the site's awareness, irrespective of causality: serum aminotransferases ALT/AST >3×ULN, with increase in total serum bilirubin >2×ULN.

- **Hospitalisation** is defined as any in-patient admission (even if less than 24 hours). For chronic or long-term in-patients, in-patient admission also includes transfer within the hospital to an acute/intensive care in-patient unit.
- **Prolongation of hospitalisation** is defined as any extension of an in-patient hospitalisation beyond the stay anticipated/required in relation to the original reason for the initial admission, **as determined by the investigator or treating physician**. For protocol-specified hospitalisation in clinical studies, prolongation is defined as any extension beyond the length of stay described in the protocol. Prolongation in the absence of a precipitating, treatment-emergent, clinical AE (i.e. not associated with the development of a new AE or worsening of a pre-existing condition) may meet the criteria for "seriousness" but is not an adverse experience and thus is not subject to immediate reporting to the sponsor.
- Preplanned or elective treatments/surgical procedures should be noted in the patient's screening documentation. Hospitalisation for a preplanned or elective treatment/surgical procedure should not be reported as an SAE unless there are complications or sequelae that meet the criteria for seriousness described above.

Any SAE must be reported immediately (within 24 hours) using the EDC system or email address or fax number (if not possible to email) specified at the beginning of this protocol in case the EDC system is not available, independent of the circumstances or suspected cause, if it occurs or comes to the attention of the investigator at any time during the study period.

Any AE/SAE with a suspected causal relationship to IMP administration occurring at any other time after completion of the study must be reported promptly, within 24 hours.

The following information is the minimum that must be provided to the sponsor within 24 hours for each SAE:

- study number
- centre number
- patient number
- AE
- investigator's name and contact details.

The additional information included in the SAE form must be collected on the eCRF as soon as it is available. The investigator should always provide an assessment of causality for each event reported to the sponsor. Upon receipt of the initial report, the sponsor will ask for the investigator's causality assessment if it was not provided initially.

The investigator should report a diagnosis or a syndrome rather than individual signs or symptoms. The investigator should also try to separate a primary AE considered as the foremost untoward medical occurrence from secondary AEs that occurred as complications.

All AEs meeting serious criteria, from the time of treatment/allocation through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever occurs first, must be reported by the investigator.

Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to the sponsor if the event is considered to be drug-related.

8.1.5 Pregnancy

If pregnancy occurs during the study, the study treatments (IPN60090, pembrolizumab and paclitaxel) should be discontinued immediately. The outcome of the pregnancy will be collected following completion of the study.

Information regarding pregnancies must be collected on the AE/SAE page of the eCRF and reported to the sponsor as an SAE via the EDC system. The sponsor will request further information from the investigator as to the course and outcome of the pregnancy using the standard Pregnancy Outcome Report Form.

The investigator must instruct all female patients to inform them immediately should they become pregnant during the study. The investigator should counsel the patient, discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the patient should continue until conclusion of the pregnancy, which may involve follow-up after the patient's involvement in the study has ended.

All pregnancies, from the time of treatment/allocation through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, must be reported by the investigator.

If the investigator becomes aware of a pregnancy occurring in the partner of a patient participating in the study, this should be reported to the sponsor. After the partner has given written consent, she should be counselled and followed as described above. Monitoring of the partner should continue until conclusion of the pregnancy

8.1.6 Deaths

For AEs leading to death, NCI-CTCAE Grade 5 is the only appropriate grade (see Section 8.1.2.1). Deaths that cannot be attributed to an NCI-CTCAE term associated with Grade 5 or that cannot be reported within an NCI-CTCAE category as 'Other' have to be reported as one of these four AE options:

- death not otherwise specified (NOS)
- disease progression NOS
- multi-organ failure
- sudden death.

8.1.7 Discontinuation/Withdrawal due to Adverse Events/Serious Adverse Events

Discontinuation/withdrawal due to AEs should be distinguished from discontinuation/withdrawal due to insufficient response to the IMP (see Section 4.3).

If the IMP is discontinued due to an SAE, it must be reported immediately to the sponsor's designated representative (see Section 8.1.4).

In all cases, the investigator must ensure that the patient receives appropriate medical follow-up (see Section 8.1.3).

8.1.8 Reporting to Competent Authorities/IECs/IRBs/Other Investigators

The sponsor will ensure that processes are in place for the submission of reports of suspected unexpected serious adverse reactions occurring during the study to the CAs, IECs and other investigators concerned by the IMP. Reporting will be in accordance with the applicable regulatory requirements.

For study centres in the USA, investigational new drug application safety reports will be submitted directly to the investigators. It is the investigators' responsibility to notify their IRB in a timely manner.

8.2 Clinical Laboratory Tests

During the dose escalation part, all clinical safety laboratory tests listed below will be performed at local laboratories (except anti-pembrolizumab antibodies). A list of laboratory normal ranges should be provided to the sponsor. Any change in laboratory normal ranges during the study will be forwarded to the sponsor. During the dose expansion part, safety blood samples will also be analysed centrally.

Blood and urine samples will be collected as per the visit evaluation schedule in Table 14 for the evaluation of haematology, serum chemistry and urinalysis.

The investigator will review the safety laboratory test results, document the review and record any clinically relevant changes occurring or observed during the study in the AE section of the eCRF (see Section 8.1.2.4 for abnormal laboratory tests that should be recorded as AEs).

All clinically relevant abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until they return to baseline or to a level deemed acceptable by the investigator and the sponsor's clinical monitor (or his/her designated representative) or until the abnormality is explained by an appropriate diagnosis.

8.2.1 Haematology

Blood samples (2 mL) (Table 16) will be collected to assess the following variables: red blood cell count, haemoglobin, haematocrit, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, white blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils and others) and platelet count.

8.2.2 Blood Biochemistry

Blood samples (5 mL) (Table 16) will be collected to assess the following parameters:

- urea, creatinine, total bilirubin, conjugated bilirubin
- chloride, bicarbonate, sodium, potassium, calcium, phosphate
- ALP, AST, ALT, GGT
- albumin, total protein, total cholesterol, triglycerides, fasting glucose.

Creatine clearance will be calculated using the Cockcroft-Gault equation and eGFR will be calculated based on serum creatinine levels using the modification of diet in renal disease formula as follows:

eGFR (mL/min/1.73 m^2) = 175 (serum creatinine in µmol/L×0.011312)−1.154×(age)−0.203×(0.742 if female) × (1.212 if African American/black)

Blood (2mL) (Table 16) will be collected to assess the following coagulation parameters: activated partial thromboplastin time, prothrombin time and its derived measures of prothrombin ratio and international normalised ratio.

At screening, patients will have tests for thyroid stimulating hormone. Thyroid stimulating hormone assessment will be repeated on Day 1 every three cycles.

8.2.3 Urinalysis

Fresh urine samples (at least 10 mL) will be collected to assess the following variables: pH, protein, ketones, bilirubin, blood, urobilinogen, nitrites, leukocytes, glucose and specific gravity by dipstick.

Microscopy will be performed, if indicated, but results will not be collected on the eCRF. If, in the opinion of the investigator, there are any clinically significant abnormalities in microscopy, they will be recorded as an AE on the eCRF.

8.2.4 Pregnancy Test

A beta human chorionic gonadotrophin (HCG) serum test will be performed for all female patients of childbearing potential at screening (Visit 1). Then an HCG urine test will be conducted on Day 1 every three cycles. Any patient becoming pregnant during the study will be withdrawn. All pregnancies that occur during the study are to be reported as described in Section 8.1.5.

8.2.5 Antipembrolizumab Antibody Testing (Part B Only)

Blood samples (6 mL) should be collected at each time point (Table 14) with serum clot activator for the determination of putative binding/neutralising antibodies against pembrolizumab. The tubes should be inverted eight times and left for 30 minutes (for a maximum of 60 minutes) at ambient temperature and then centrifuged for 10 minutes at 1300*g* at 4°C. The resulting serum will be transferred into three aliquots into 2.0 mL cryovials: 1 mL for binding antibody samples, 1 mL for neutralising antibody samples, and <1 mL for backup samples. Samples should be stored at ≤-20°C.

Full details regarding required the processing, labelling and shipment processes for these samples are provided in the study manual.

The determination of putative antibodies against pembrolizumab will be evaluated using validated methods: ElectroChemiLuminiscence Assay (ECLA) electrochemiluminescent bridging assay for binding antibodies and cell-based assay for neutralising antibodies.

8.3 Physical Examination

Physical examinations consisting of: general appearance, dermatological, head/neck, pulmonary, cardiovascular, gastrointestinal, genitourinary, lymphatic, musculoskeletal system, extremities, eyes, nose, throat, and neurologic status, including body weight, will be conducted at baseline (Visit 2), Cycle 1, Day 1, Cycle 1, Day 3, Cycle 1, Day 5, Cycle 1, Day 8, Cycle 1, Day 15, then Day 1 of every cycle, and at the End of Study/Early Withdrawal visit. Height will be measured at screening.

Any clinically significant physical examination findings (abnormalities) observed during the study will be reported as AEs. Any physical examination findings (abnormalities) persisting at the end of the study will be followed by the investigator until resolution or until reaching a clinically stable endpoint.

8.4 Infusion Reactions and Local Tolerance

For Parts B and C, local tolerance of pembrolizumab or paclitaxel infusions will be checked. The infusion site will be examined by a physician or Medical Research Associate and assessed for characteristics such as tenderness, erythema, swelling, rash, pain, itching, induration, haematoma, ulceration or necrosis. If present, the extent of erythema, haematoma, rash, ulceration or necrosis will be described and assessed quantitatively; this will at least include measurement of maximum length and maximum width.

Infusion related reactions such as hypersensitivity reactions or cytokine release syndromes with symptoms including flushing, alternation in heart rate and blood pressure, dyspnoea,

bronchospasm, back pain, fever, urticaria, oedema, nausea and all types of rashes must be recorded as AEs on the eCRF. Transient infusion related reactions that can be controlled by medication should not be recorded as a DLT if occurring during the DLT observation period.

8.5 Vital Signs

Blood pressure and heart rate will be assessed with an automated device so that measurements are independent of the observer. Blood pressure and heart rate will be recorded after 5 minutes' rest in a sitting position. Absolute values and change from baseline will be analysed.

Respiratory rate and temperature will be recorded.

8.6 Electrocardiography

At screening and during the study, triplicate ECG assessments will be performed with standard 12-lead ECG equipment according to standard procedures to determine the QTcF. For eligibility, a QTcF ≤470 ms for females, and ≤450 ms for males within 28 days before the first dose of study treatment is required. ECGs should be performed approximately 2 minutes apart when in triplicate, and should always be done just before any blood draw.

ECGs will be performed at the time points indicated in Table 14 and as clinically indicated. A more detailed ECG assessment schedule is listed in Table 30.

Table 30 Electrocardiogram Timepoints

Visit	Timepoint	Method
Screening	Day (D) -28 to D -1 (Parts A to C) and D -28 to D -8 (Part D)	Triplicate
Run-in, Day -7 and Day -3 (Part D only)	1 hours postdose	Triplicate
	2 hours postdose	Triplicate
	4 hours postdose	Triplicate
Cycle 1, Day 1	30 minutes postdose	Triplicate
	1 hours postdose	Triplicate
	2 hours postdose	Triplicate
	4 hours postdose	Triplicate
	8 hours postdose	Triplicate
	12 hours postdose	Triplicate
Cycle 2, Day 1	Predose	Triplicate
	30 minutes postdose	Triplicate
	1 hours postdose	Triplicate
	2 hours postdose	Triplicate
	4 hours postdose	Triplicate
	8 hours postdose	Triplicate
	12 hours postdose	Triplicate
Cycle 3, Day 1	Predose	Triplicate
Cycle 4, Day 1	Predose	Triplicate
End of treatment	30 days after last dose	Triplicate

Abnormalities in the ECG that lead to a change in patient management (such as dose reduction or interruption, discontinuation of treatment, or requirement for additional medication or monitoring) or results in clinical signs and symptoms that are considered clinically significant for the purposes of this study, will be deemed AEs. If the values meet the criteria defining them as serious, they must be reported as SAEs.

The Fridericia formula is depicted below for calculation of QTcF.

$$QTcF = \frac{QT}{RR^{1/3}}$$

QT=measured QT interval in milliseconds; RR=measured R to R interval (which can be derived from the heart rate as 60/heart rate).

8.7 Echocardiogram/multigated acquisition

Echocardiogram or multigated acquisition assessment will be performed at screening and at the end of study (EOS), or at any point if clinically indicated. For eligibility, LVEF of >50% at screening is required.

9 ASSESSMENTS OF PHARMACOKINETICS/PHARMACODYNAMICS

9.1 Pharmacokinetics

9.1.1 Sample Collection

9.1.1.1 Assessment of IPN60090 Plasma Concentrations

Blood samples for the determination of IPN60090 are described in Table 31.

Table 31 Timepoints for IPN60090 PK Blood Sample Determination

Visit	Timepoint	Volume
Run-in phase Day -7 (Part D only)	Predose	2.0 mL
	30 minutes postdose	2.0 mL
	1 hour postdose	2.0 mL
	2 hours postdose	2.0 mL
	4 hours postdose	2.0 mL
	8 hours postdose	2.0 mL
	12 hours postdose	2.0 mL
	24 hours postdose	2.0 mL
	48 hours postdose	2.0 mL
	72 hours postdose	2.0 mL
Run-in phase Day -3 (Part D only)	Predose	2.0 mL
	30 minutes postdose	2.0 mL
	1 hour postdose	2.0 mL
	2 hours postdose	2.0 mL
	4 hours postdose	2.0 mL
	8 hours postdose	2.0 mL
	12 hours postdose	2.0 mL
	24 hours postdose	2.0 mL
	48 hours postdose	2.0 mL
	72 hours postdose	2.0 mL
Cycle 1, Day 1	Predose	2.0 mL
	30 minutes postdose	2.0 mL
	1 hour postdose	2.0 mL
	2 hours postdose	2.0 mL
	4 hours postdose	2.0 mL
	8 hours postdose	2.0 mL
	12 hours postdose	2.0 mL
Cycle 1, Day 2	Predose	2.0 mL
Cycle 1, Day 14	Predose	2.0 mL
	30 minutes postdose	2.0 mL
	1 hour postdose	2.0 mL
	2 hours postdose	2.0 mL
	4 hours postdose	2.0 mL
	8 hours postdose	2.0 mL
	12 hours postdose	2.0 mL
Cycle 1, Day 15	Predose	2.0 mL
	2 to 4 hours postdose	2.0 mL
Cycle 2, Day 1	Predose	2.0 mL
	2 hours postdose	2.0 mL
Cycle 3, Day 1	Predose	2.0 mL
	2 hours postdose	2.0 mL
Cycle 4, Day 1	Predose	2.0 mL
	2 hours postdose	2.0 mL
All cycles after Cycle 4	Predose	2.0 mL
	2 hours postdose	2.0 mL
End of study		2.0 mL

During the study, the nominal sample collection times may be changed, but the total number of samples will not increase. The exact dates and times of blood sample collection, study drug administration and vomiting events within 2 hours of administration must be recorded on the eCRF.

Blood samples (2.0 mL) should be collected in a K2-ethylenediaminetetraacetic acid (EDTA) tube at each time point and gently inverted eight times. The tubes will be centrifuged at 4ºC for 10 minutes. The resulting plasma will be stored at -80°C ±10°C in polypropylene tubes, as two 500 µL aliquots, prior to shipment to the analysis laboratory: MD Anderson Cancer Centre, USA for IPN60090 during the dose escalation and Kymos Pharma Services, Spain for IPN60090 during the dose expansion. Each tube should be labelled in accordance with the sponsor's requirements. Aliquots will be shipped on dry ice.

9.1.1.2 Assessment of IPN60090 Urine Concentrations

Assessment of IPN60090 urine concentrations are part of the exploratory endpoint and will be performed for the Part A dose escalation only. Assessment of IPN60090 urine concentrations will be performed at the MD Anderson Cancer Centre, USA.

The urine collection intervals are indicated in the study schedule of assessments (Table 14). Urine collection will start after a request to the patient to empty his or her bladder following the morning dose. All urine voided during the collection interval will be retained.

9.1.1.3 Assessment of Pembrolizumab Serum Concentrations

The time points for blood sampling for pembrolizumab determination are indicated in Table 14 and Table 32. Blood samples (2.0 mL) should be collected at each time point with serum clot activator for the determination of serum pembrolizumab levels. Blood samples should be collected from the contralateral arm used for the study drug infusion, or from another anatomical site. After blood collection, the tubes should be inverted eight times and left for 30 minutes (for a maximum of 60 minutes) at ambient temperature and then centrifuged for 10 minutes at 1300*g* at 4°C. The resulting serum should be transferred into two aliquots in 2.0 mL cryovials (0.5 mL for the determination of the PK of pembrolizumab and <0.5 mL for backup samples). Samples should be stored at ≤ -20°C prior to shipment to the analysis laboratory for pembrolizumab level determination.

Table 32 Additional Timepoints for PK Pembrolizumab Blood Sampling of Patients in Part B

Visit	Timepoint	Volume
Cycle 1, Day 1	Pre-pembrolizumab infusion	2.0 mL
Cycle 2, Day 1	Pre-pembrolizumab infusion	2.0 mL
Cycle 3, Day 1	Pre-pembrolizumab infusion	2.0 mL
Cycle 4, Day 1	Pre-pembrolizumab infusion	2.0 mL

Full details regarding processing, labelling and shipment processes for these samples are provided in the study manual.

Pembrolizumab blood levels will be determined using a validated, specific and sensitive solid phase enzyme-linked immunosorbent assay (ELISA) based on the sandwich principle.

9.1.1.4 Assessment of Paclitaxel Plasma Concentrations

Blood samples for the determination of paclitaxel are described in Table 33.

Table 33 Additional Timepoints for PK Paclitaxel Blood Sampling of Patients in Part C

Visit	Timepoint	Volume
Cycle 1, Day 1	Pre-paclitaxel infusion	2.0 mL
	Post-paclitaxel infusion[a]	2.0 mL
Cycle 2, Day 1	Pre-paclitaxel infusion	2.0 mL
	Post-paclitaxel infusion[a]	2.0 mL
Cycle 3, Day 1	Pre-paclitaxel infusion	2.0 mL
	Post-paclitaxel infusion[a]	2.0 mL

a i.e. 3 hours after the start of the infusion

Blood samples (2.0 mL) should be collected from the uninfused arm, in a K2-EDTA tube at each time point and gently inverted eight times. The samples should be centrifuged at 2000*g* at 4°C for 10 minutes. The resulting plasma will be stored at -80°C ±10°C in polypropylene tubes as two 500 µL aliquots (primary and back-up) prior to shipment to the analysis laboratory for paclitaxel level determination.

9.1.2 Analytical Procedures

Plasma samples will be analysed to determine concentrations of IPN60090 during dose escalation using a validated, specific and sensitive liquid chromatography (LC)-mass spectrometry (MS)/MS method at MD Anderson Cancer Centre, USA.

Plasma samples will be analysed to determine concentrations of IPN60090 (dose expansion) and paclitaxel (dose escalation and dose expansion) using a validated, specific and sensitive LC-MS/MS method.

Urine samples will be analysed to determine urine IPN60090 concentrations. Assessment of IPN60090 urine concentrations will be performed at MD Anderson Cancer Centre, USA.

Serum samples will be analysed to determine concentrations of pembrolizumab using a validated, specific and sensitive solid phase ELISA based on the sandwich principle.

An analytical method for the determination of the presence of binding antibodies to pembrolizumab in human serum by ECLA in a bridging format will be developed and validated.

For neutralising anti-pembrolizumab antibodies, a cell-based assay consisting in coculture of PD-1 effector cells and PD-L1 expressing cells and induction of T-cell receptor-mediated luminescence by blockade of PD-1/PD-L1 interaction with pembrolizumab will be developed and validated.

9.1.3 Data Analysis

Individual plasma concentrations of IPN60090 will be listed and summarised by timepoint and dose level using descriptive statistics for continuous variables (number of available observations, mean, median, standard deviation, minimum, maximum, geometric mean and geometric coefficient of variation assuming log-normally distributed data). Linear and semilogarithmic plots of individual and mean plasma concentration-time profiles as well as spaghetti plots will be reported.

The PK of IPN600900 plasma concentrations will be performed using noncompartmental analysis. The following PK parameters will be calculated:

- C_{max}
- T_{max}
- C_{trough}
- AUC
- $t_{1/2}$

- CL/F
- V/F

Additional PK parameters may be calculated. Dose proportionality of IPN60090 will be assessed over the dose ranges tested.

Descriptive statistics of PK parameters will be provided.

Urine IPN60090 concentrations are part of the exploratory endpoints. The amount excreted in urine and the renal clearance will be calculated if feasible.

The noncompartmental analysis plan will be detailed in a separate Data Analysis Plan and reported as a stand-alone report.

Population PK modelling will be performed to describe the PK profile of IPN60090 in patients by quantifying the degree of interpatient variability on the PK parameters of IPN60090 and the residual unexplained variability in the data and identifying the individual patient characteristics (covariates) that can have an impact on the PK parameters explaining part of their interpatient variability.

The population PK plan will be detailed in a separate Data Analysis Plan and reported as a stand-alone report.

For pembrolizumab and paclitaxel, C_{min} concentrations and descriptive statistics will be reported. For paclitaxel, C_{max} and C_{min} concentrations and descriptive statistics will be reported.

In Part B, the percentage of patients developing antibodies against pembrolizumab will be calculated at each time point. The potential impact of the antibodies against pembrolizumab on the concentrations of pembrolizumab will be explored.

9.2 Pharmacodynamic Biomarkers

Pharmacodynamic endpoints with the evaluation of Glu:Gln ratio will be assessed in PBMC at the timepoints shown in Table 34.

Table 34 Collection Time Points for PD evaluation in PBMC

Visit	Timepoint	Volume
Cycle 1, Day 1	Predose	4 tubes x 6 mL for PBMC isolation
	2 hours postdose	2 tubes x 6 mL for PBMC isolation
	12 hours postdose	2 tubes x 6 mL for PBMC isolation
Cycle 1, Day 14	Predose	2 tubes x 6 mL for PBMC isolation
	2 hours postdose	2 tubes x 6 mL for PBMC isolation
	12 hours postdose	2 tubes x 6 mL for PBMC isolation
Cycle 1, Day 15	Predose	2 tubes x 6 mL for PBMC isolation
	2 to 4 hours postdose	2 tubes x 6 mL for PBMC isolation

Two tubes of 6 mL collections per timepoint are needed to ensure the possibility of running the assay by purifying a sufficient number of PBMCs for analysis and procuring a back-up pellet for biobanking. At Cycle 1, Day 1 predose only, two additional tubes of 6 mL blood are needed to be used as quality control samples. In this case, a total of four tubes of 6 mL of blood are required at Cycle 1, Day 1 predose. At Cycle 1, Day 14 and Cycle 1, Day 15, two tubes of 6 mL will be collected at each time point.

9.3 Pharmacokinetics/Pharmacodynamics Interactions

Pharmacokinetic/PD modelling will be performed, if feasible, to describe the relationship between relevant selected biomarkers and/or efficacy parameters and/or adverse effects and PK descriptors. A PK/PD modelling plan will be described in a separate Data Analysis Plan and results will be reported in a standalone report.

10 BIOMARKER EVALUATION AND BIOBANKING

10.1 Biomarker Evaluation

10.1.1 Collection of Biopsies for Biomarker Analysis

Fresh and/or archival tumour tissue from the biopsy obtained between the completion of the most recent line of treatment until study entry must be available for mutation and biomarker analysis unless KEAP1/NRF2 mutations were present in any previous biopsy, in which case, no further biopsy is required. For ovarian cancer patients, both archival biopsies obtained between the completion of the most recent line of treatment until study entry and fresh biopsies must be available to evaluate the evolution of ASNS levels over time. A fresh tumour biopsy is performed at the screening visit, Cycle 1, Day 15, and the EOS/early withdrawal (EOS/EW [separate consent is required]). The EOS fresh biopsy is optional and requires an additional informed consent for collection. If available, a biopsy at initial diagnosis will be also collected for biomarker analysis.

10.1.2 Collection of cfDNA for Biomarker Analysis

Blood samples (10 mL) will be collected in cfDNA (Streck tubes) for plasma isolation and will be used for biomarker analysis. Sampling is done at screening, on Cycle 1, Day 15 (predose), Cycle 3, Day 1 (predose), then on Day 1 of every other cycle after Cycle 3 (predose) and at EOS/EW.

10.1.3 Biomarkers of Patient Stratification

KEAP1/NRF2 mutations and ASNS levels will be evaluated in fresh and/or archival biopsies and will be correlated with clinical outcome.

10.1.4 Biomarkers of Disease Evolution Under Treatment

In HGSOC patients, blood samples (2 mL) will also be collected for serum Ca-125 assessment at baseline, on Day 1 of Cycle 3 and then on Day 1 of every other cycle.

10.2 Exploratory Biomarkers

Biomarkers of tumour biology evolution under treatment (e.g. immune profiling, PD-L1 expression, Ki67, phosphorylation of histone variant H2AX (γH2AX), LKB1, etc) may be evaluated and correlated with clinical outcome.

10.3 Biobanking

Instructions for collection, processing, handling and shipment of the biobanking samples will be outlined in the laboratory manual.

Samples to be used for biobanking storage will be taken for those individuals who have signed a specific consent for the biobank samples at a different visit depending on sampling type as described below.

10.3.1 Serum

Blood samples (2.5 mL) will be collected in specific dry tubes for serum isolation and frozen for storage.

Sampling is done on Cycle 1, Day 1 (predose and postdose), Cycle 1, Day 15, Day 1 of each following cycle and EOS/EW.

10.3.2 Plasma

Blood samples (2 mL) will be collected in specific EDTA tubes for plasma isolation and frozen for storage.

Sampling is done on Cycle 1, Day 1 (predose and postdose), Cycle 1, Day 15, Day 1 of each following cycle and EOS/EW.

10.3.3 Blood for RNA for Biobank

Blood samples (2.5 mL) will be collected in PAXgene RNA tubes and frozen for storage.

Sampling is done on Cycle 1, Day 1 (predose and postdose), Cycle 1, Day 15, Day 1 of each following cycle and EOS/EW.

10.3.4 Blood for DNA for Biobank

Blood samples (2.5 mL) will be collected in PAXgene DNA tubes and frozen for storage.

Sampling is done on Cycle 1, Day 1 (predose only).

10.3.5 Blood for CfDNA for Biobank

Blood samples (10 mL) will be collected in CfDNA (Streck tubes) for plasma isolation and frozen for storage.

Sampling is done on Cycle 1, Day 1, Cycle 1, Day 15, Cycle 3, Day 1, then on Day 1 of every other cycle after Cycle 3 and at EOS/EW.

10.3.6 Blood for PBMC

Remaining and not used PBMC for PD biomarker evaluation (see Section 9.2) should be biobanked.

Sampling is done on Cycle 1, Day 1 (predose, and 2 and 12 hours postdose), Cycle 1, Day 14 (predose, and 2 and 12 hours postdose) and Cycle 1, Day 15 (predose, and 2 to 4 hours postdose).

10.3.7 Stools

The sampling procedure will be outlined in a laboratory manual.

Sampling is done on Cycle 1, Day 1 (predose), Cycle 1, Day 15 (predose) and EOS/EW.

10.3.8 Leftover Tissue Material and Additional Biopsies for Biobanking

Leftover tissue material from mandatory biopsies used for biomarker analysis (e.g. remaining formalin-fixed paraffin-embedded blocks) and additional fresh biopsies (fine-needle aspiration and/or core biopsies) collected will be used for biobanking (if patient consent is on the check box for the biobanking in the ICF).

Samples will be biobanked for future analysis of intratumour or circulating biomarkers, including proteins, pharmacogenetic and pharmacogenomic biomarkers and will only be collected for those patients who have agreed to it by signing the specific ICF for the exploratory part of the study (see Section 14.2.1).

The biobanked samples will be stored for up to 15 years from the end of the study, to be made available for future research towards further understanding of (i) treatment response including, but not limited to, the safety profile, (ii) drug treatment mode of actions and (iii) disease understanding.

Samples will be archived in a central biorepository designated by the sponsor and according to local administration regulations and/or the European Medicines Agency and will not carry personal identification (for example social security number or name). Analysis of additional biomarkers (including potential genetic research) from the biobank samples will be performed outside the scope of the main study and reported separately.

Only people designated by the sponsor will be allowed access to the samples. All information collected will be kept strictly confidential and all clinical information will be de-identified. This means that no personally identifiable information will be retained with the results of the

exploratory analyses, so that no individual or collective results will be linked to the individual patient whose sample was taken in the study. No individual genetic results will be communicated to the investigator or patient unless required by local regulations.

The sponsor will comply with all local regulations related to the establishment, management and application of a human blood samples biobank.

11 STATISTICS

Statistical analyses will be performed by an external contract research organisation (CRO), managed by the sponsor's biometry department.

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a SAP. The SAP may modify the plans outlined in the protocol; however, any major modifications of the primary or secondary endpoints and/or their analysis will also be reflected in a protocol amendment.

Statistical evaluation will be performed using SAS® (version 9 or higher).

Data will be listed and summarised by dose level and part in the dose escalation phase; by cohort and part for safety and by cohort for efficacy in the dose expansion phase. Safety results will be presented for all the patients included in the study at the RD (dose escalation and dose expansion phases) by part and RD. Furthermore, all safety and efficacy results could be presented by group of patients depending on the interest there may be in these groups.

Categorical variables will be summarised by frequency distributions (number and percentages of patients). The 95% confidence interval (CI) will be calculated following the exact method. Continuous variables will be summarised by descriptive statistics (mean, standard deviation, median, minimum and maximum).

Time-to-event variables will be summarised using the Kaplan-Meier method and the 95% CI of the median will be given.

11.1 Analysis Populations

The following populations will be defined during statistical analyses:

- **Screened population**: All patients screened (i.e. who signed the informed consent).
- **Safety population**: All patients who are exposed to (or started receiving) IPN60090 and/or the combination agents.
- **DLT evaluable population for the escalation phase only:** All patients from the safety population who are evaluable for DLT (patients who have completed at least one cycle of treatment and have received ≥75% of the total planned dose of IPN60090 over the DLT assessment period). Patients with noncompliance (<75% of total planned dose) due to DLT will be included in this population).
- **Efficacy population**: All patients who receive at least one dose of IPN60090.
- **Pharmacokinetic population for noncompartmental analysis:** All patients who have no major protocol deviation affecting the PK variables and who have a sufficient number of IPN60090 plasma concentrations to estimate the main PK parameters (C_{max}, T_{max}, area under the plasma concentration time curve from time 0 to the last time point with quantifiable concentrations ($AUC_{0\text{-last}}$)).
- **Pharmacokinetic population for population PK modelling**: All patients who receive at least one IPN60090 dose and who have at least one plasma IPN60090 concentration and who have no major protocol deviation affecting the PK variables.
- **Food effect population**: All patients in Part D who have received IPN60090 under fasting and fed conditions (Day -7 and Day -3), have consumed ≥80% of the moderate fat meal in approximately 30 minutes on Day -3, and who have no major protocol deviation affecting the PK variables and who have a sufficient number of IPN60090 plasma concentrations to estimate the main PK parameters (C_{max}, T_{max} and $AUC_{0\text{-last}}$).
- **Pharmacodynamic population**: All patients who have at least one PD endpoint measurement. PD endpoints refer to target engagement levels (Glu:Gln ratio in PBMC).

11.1.1 Populations Analysed

The analyses of safety data will be performed on the safety population and DLT evaluable population when applicable.

The analyses of PK data will be performed on the PK population.

The analyses of anti-tumour activity will be performed on the efficacy population.

The analyses of PD parameters will be performed on the PD population.

The analyses of food effect PK parameters will be performed on the food effect population.

11.1.2 Reasons for Exclusion from the Analyses

Any major protocol deviation (see Section 13.1.2 for definition) will be described and its impact on inclusion in each analysis population (efficacy, PK and safety populations) for any patient will be specified. The final list of protocol deviations impacting the populations will be reviewed prior to database lock.

11.2 Statistical Methods for Dose Escalation Phase and Food Effect

11.2.1 Sample Size Determination

11.2.1.1 Monotherapy Dose Escalation – Part A

A BOIN design with target toxicity rate of 30% (with escalation and de-escalation thresholds of 23.6% and 35.9%, respectively) with maximum number of approximately 30 patients will be used to estimate the IPN60090 monotherapy MTD.

The design will proceed with accelerated titration up to DL3, i.e. cohorts of one will be enrolled until either the third dose level is evaluated, a Grade 2 AE that is at least possibly related to the study drug(s) occurs, or a DLT is observed (whichever occurs first). If a Grade 2 AE that is at least possibly related to the study drug(s) or a DLT is observed in a single patient cohort (i.e. in one of the first three dose levels), two additional patients will be added at this dose level with the same rules for escalation and de-escalation as the cohorts of three patients detailed below.

If the DLT rate within a cohort at a given dose level is less than the escalation boundary of 23.6% the rule is then to escalate, if the DLT rate is higher than the de-escalation boundary of 35.9% then the rule is either to de-escalate, or to retain the dose or to stop if the maximum sample size is reached. Following the requisite follow-up in a cohort, the dose level for the next cohort will be determined using the decision rules in Table 35, where ↑indicates the next cohort at one dose level higher, ↓ indicates the next dose level at one dose level lower and "Elim" indicates that the dose level (and all higher dose levels) is removed from further consideration.

Table 35 Dose Escalation Decision Rules

	Number of patients at current dose level							
Action	3	4	5	6	7	8	9	10
↑ if number of DLT ≤	0	0	1	1	1	1	2	2
Stay current dose if DLT	1	1	-	2	2	2	3	3
↓ if number of DLT ≥	2	2	2	3	3	3	4	4
Elim if number of DLT ≥	3	3	4	4	5	5	5	6

DLT=dose limiting toxicity; Elim=eliminate

In the event that operational/practical circumstances result in an over-enrolment (i.e. n>3) for a BOIN cohort, the next dose level decision would be based on the actual number of patients exposed in the cohort and the BOIN criteria.

If none of the actions is indicated, then the next cohort is enrolled at the same dose level as the current dose level. If the current dose level is the lowest dose level and the action

indicated is de-escalation, then the next cohort is enrolled at the same dose level (i.e. the lowest dose level). Similarly, if the current dose level is the highest dose level and the action indicated is escalation then the next cohort is treated at the same dose level. When a dose is eliminated, the next cohort is enrolled at the next lower dose level. If the lowest dose is eliminated, then the study is stopped and none of the dose levels is selected as the MTD.

The study will continue until one of the following occurs:

(a) the maximum number of patients has been reached (approximately 30)

(b) the decision indicated by the table would result in adding patients to a dose level where at least nine patients have already been treated

(c) the number of patients treated at the lowest dose level is ≥3 and the probability that the DLT rate at the lowest dose level exceeds the target is >0.90.

When (a) or (b) occurs, the MTD of IPN60090 will be estimated as the dose level at which the isotonic estimate of the DLT rate is closest to 30%. If there are ties, the MTD is selected as the higher dose level when the isotonic estimate is lower than the target toxicity rate and selected as the lower dose level when the isotonic estimate is greater than or equal to the target toxicity rate. The operating characteristics for the MTD dose selected for the planned design for seven true DLT rate scenarios were estimated by simulation of 2000 studies per scenario.

Table 36 Operating Characteristics for Monotherapy BOIN Dose Finding from Simulation

Scenario	True DLT rate for DL1 %MTD is DL1 (avg n)	True DLT rate for DL2 %MTD is DL2 (avg n)	True DLT rate for DL3 %MTD is DL3 (avg n)	True DLT rate for DL4 %MTD is DL4 (avg n)	True DLT rate for DL5 %MTD is DL5 (avg n)	True DLT rate for DL6 %MTD is DL6 (avg n)	True DLT rate for DL7 %MTD is DL7 (avg n)	Average number of patients to be enrolled	% early stop
1	0.025 <1 (1.1)	0.05 <1 (1.4)	0.075 1 (1.7)	0.10 4 (4.4)	0.15 13 (5.0)	0.20 20 (5.2)	0.25 61 (5.9)	24.7	<1
2	0.025 <1 (1.1)	0.05 <1 (1.4)	0.075 2 (1.9)	0.125 10 (4.9)	0.20 23 (5.6)	0.25 26 (5.0)	0.30 39 (4.1)	24.0	<1
3	0.025 <1 (1.1)	0.05 <1 (1.5)	0.10 4 (2.2)	0.15 17 (5.5)	0.25 33 (6.1)	0.30 32 (4.6)	0.45 14 (2.3)	23.3	<1
4	0.025 <1 (1.1)	0.05 <1 (1.5)	0.10 6 (2.7)	0.20 30 (6.3)	0.30 45 (6.3)	0.45 16 (3.4)	0.55 2 (0.7)	22.0	<1
5	0.05 <1 (1.4)	0.10 5 (2.6)	0.20 27 (4.9)	0.30 47 (6.8)	0.45 17 (3.9)	0.55 3 (0.9)	0.65 <1 (0.1)	20.5	<1
6	0.075 2 (1.8)	0.15 22 (4.8)	0.30 55 (7.4)	0.50 20 (4.9)	0.70 <1 (0.9)	0.80 0 (<0.1)	0.85 0 (<0.1)	19.8	1
7	0.15 20 (4.7)	0.30 58 (7.7)	0.50 17 (5.0)	0.70 1 (1.6)	0.80 0 (0.1)	0.85 0 (<0.1)	0.90 0 (0)	19.1	5
8	0.30 50 (7.0)	0.45 23 (5.5)	0.60 3 (2.3)	0.75 0 (0.6)	0.85 0 (<0.1)	0.90 0 (0)	0.95 0 (0)	10.4	24

avg n=the average number of patients treated at each dose level; BOIN=Bayesian Optimal Interval; DL=dose level; DLT=dose limiting toxicity; MTD=maximum tolerated dose
% early stop is the percentage of times the study would stop early due to case (c)
% MTD is DLx means selection percentage at dose level x

11.2.1.2 Combination Dose Escalation – Parts B and C

A BOIN design with target toxicity rate of 30% (with escalation and de-escalation thresholds of 23.6% and 35.9%, respectively) with maximum number of approximately 18 patients (for each combination dose finding) will be used to estimate the IPN60090 combination MTD. The design will enrol up to six cohorts of three patients. Patients in the first cohort will be treated at combination DL1. Because the escalation and de-escalation thresholds are the same as those used for the monotherapy, the escalation and de-escalation rules as a function of number of patients treated are the same as those presented for the monotherapy.

The study will continue until one of the following occurs:

(a) the maximum number of patients has been reached (approximately18)

(b) the decision indicated by the table would result in the number of patients at a dose level exceeding nine patients

(c) the number of patients treated at the lowest dose level is ≥3 and the probability that the DLT rate at the lowest dose level exceeds the target is greater than 0.90.

In the event that operational/practical circumstances result in an over-enrolment (i.e. n>3) for a BOIN cohort, the next dose level decision would be based on the actual number of patients exposed in the cohort and the BOIN criteria.

When (a) or (b) occurs, the MTD of IPN60090 will be estimated as the dose level at which the isotonic estimate of the DLT rate is closest to 30%. If there are ties, the MTD is selected as the higher dose level when the isotonic estimate is lower than the target toxicity rate and selected as the lower dose level when the isotonic estimate is greater than or equal to the target toxicity rate. The operating characteristics for the MTD dose selected for the planned design for the following true DLT rate scenarios were estimated by simulation (R package BOIN) of 2000 studies per scenario.

Table 37 Operating Characteristics for Combination BOIN Dose Finding from Simulation

Scenario	True DLT rate for DL1 %MTD is DL1 (avg n DL1)	True DLT rate for DL2 %MTD is DL2 (avg n DL2)	True DLT rate for DL3 %MTD is DL3 (avg n DL3)	Average/expected number of patients to be enrolled	% early stop
1	0.10 12 (4.3)	0.20 35 (5.4)	0.30 50 (5.2)	14.9	3
2	0.20 29 (5.3)	0.30 44 (5.6)	0.40 21 (2.9)	13.8	6
3	0.30 49 (6.4)	0.40 22 (3.4)	0.50 5 (1.0)	10.7	24

avg n=the average number of patients treated at each dose level; BOIN=Bayesian Optimal Interval; DL=dose level; DLT=dose limiting toxicity; MTD=maximum tolerated dose
% early stop is the percentage of times the study would stop early due to case (c)
% MTD is DLx means selection percentage at dose level x

11.2.1.3 Sample Size for Part D

The sample size (n=8) is not based on statistical calculation. A sample size of eight patients allows for a preliminary assessment of the potential effect of food on the PK of IPN60090.

11.2.2 Significance Testing and Estimations

As this is a descriptive safety and tolerability/efficacy dose escalation phase, no formal statistical testing will be carried out.

11.2.3 Statistical Methods

11.2.3.1 Demographic and Other Baseline Characteristics

Descriptive summary statistics (n, mean, standard deviation, median, minimum, maximum) and frequency counts of demographic and baseline data including disease characteristics at diagnosis, medical history, prior and concomitant medications, and tumour assessment at baseline will be presented for the safety population and per dose level.

Medical and surgical history findings will be summarised using Medical Dictionary for Regulatory Activities (MedDRA) terms.

Unless prohibited by local regulation, race and ethnicity will be collected to ensure data robustness for safety and efficacy evaluation and to prevent adverse reactions or improve benefits in the target population.

11.2.3.2 Patient Disposition and Withdrawals

The numbers and percentages of patients enrolled and included in each population will be tabulated by dose level and overall. The reasons for patient exclusions from each of the populations will also be tabulated. Primary reasons for discontinuation of study treatments (IPN60090, pembrolizumab or paclitaxel) will be tabulated

11.2.3.3 Pharmacokinetic Data

For methodology, please refer Section 9.1.3.

11.2.3.4 Anti-tumour Activity Evaluation

Tumour response will be assessed locally by investigators. Response and progression will be evaluated using the revised RECIST guideline v1.1 or iRECIST guideline (Part B only).

The analyses will be carried out on patients in the efficacy population by dose level and overall for each part of the dose escalation phase.

The efficacy proportions CBR, ORR and DCR will be summarised using descriptive statistics and will be graphically displayed, if appropriate. The corresponding exact binomial 95% CI will be provided.

Time-to-event variables (PFS and OS) will be analysed using survival methods (Kaplan-Meier). The results will be presented both in summary tables and graphically in Kaplan-Meier plots. In addition, the 95% CI for median duration will be provided.

11.2.3.5 Safety Evaluation

Unless otherwise specified, the safety analyses will be carried out on patients in the safety population by dose level and overall for each part.

Physical examination findings, vital signs, 12-lead ECG and clinical laboratory parameters will be summarised descriptively. Actual and change from baseline at each assessment will be calculated and summarised, where data are available. The investigator's interpretation of 12-lead ECGs will be listed. For laboratory data, abnormal values will be flagged in the data listings, and a list of clinically significant abnormal values will be presented. Haematological and biochemistry toxicities will be graded and presented according to the NCI-CTCAE criteria.

Concomitant medications will be coded using the latest version of the World Health Organization drug dictionary (WHO-DD) and will be summarised with the number and

percentage of patients receiving concomitant medication by drug class and preferred drug name.

All AEs will be coded according to the latest version of MedDRA and NCI-CTCAE version 5.0.

Study drug treatment-emergent AE (TEAE) summaries will include the overall incidence (by system organ class (SOC) and preferred term (PT)), events by maximum intensity, events by relationship to study drug, events leading to discontinuation of study treatments and SAEs.

Maximum grade or severity will be tabulated by patient for each MedDRA SOC and PT. Analyses of AEs and SAEs will be performed in two different ways: regardless of the relationship to the study drug and related to the study drug.

For haematological and biochemical toxicities, the worst NCI-CTCAE grade by patient and by cycle will be tabulated and listed. For white blood cells, neutrophils, platelets and haemoglobin with associated Grade 3 or 4 toxicities, nadir and day to nadir will be calculated.

A TEAE is defined as any AE that occurs during the study if:

- It was not present prior to receiving the first administration of study drugs; or
- It was present prior to receiving the first administration of study drugs but the intensity increased during the active phase of the study; or
- It was present prior to receiving the first administration of one of the study drugs, the intensity is the same but the drug relationship became related during the active phase of the study.

11.2.3.6 Food Effect Assessment

The assessment of food effect will be based upon the ratio of the population geometric means (fed versus fasted, i.e. Day -3 versus Day -7) for the PK parameters (C_{max} and AUC). The data will be transformed prior to analysis using a logarithmic transformation. T_{max} between fed and fasted states will be compared using a non-parametric test such as the Wilcoxon test. Descriptive statistics of other PK parameters will be presented both for fasting and fed conditions.

11.2.3.7 Interim Analyses/Safety Review Committees

Safety, in particular DLT occurrence, as well as PK and PD data will be reviewed on an ongoing basis during the dose escalation phases. An SRC will be set up at the end of each dose escalation cohort to review DLTs and overall safety data and judge the relevance of events to the dose escalation scheme. At the time of the SRC meeting, all cumulative available information will be reviewed. In case of emerging safety issues, the SRC will immediately be informed and an ad hoc SRC meeting may be organised. The composition of the SRC and its specific working procedures will be described in a separate SRC charter, which will be established prior to the screening of the first patient.

Bayesian optimal interval modelling of DLT rates will be performed before the planned review meetings in order to generate additional relevant information for the adaptive dose selection decisions. The SRC will review all available data and make the final decision as to dose escalation, de-escalation, or cohort expansion during the adaptive dose escalation. This group will also determine when to implement predefined stopping rules.

An interim analysis will be performed at the end of the dose escalation to characterise the safety and define the RD but also to investigate preliminary anti-tumour activity in biomarker selected and unselected patients.

Full analysis will be performed on the entire dataset at the EOS/EW and at the end of the follow-up.

11.3 Statistical Methods for the Expansion Phase

11.3.1 Sample Size Determination

Preliminary anti-tumour activity will be evaluated in each dose expansion cohort (each regimen and indication combination) according to a sequential two-stage design based on a fixed sample size with look at 10 and at 18. The first stage will enrol 10 patients and stop for futility if no patients or only one patient achieves the efficacy criterion defined by a BOR of CR, PR or SD lasting at least 12 weeks for Parts A and C cohorts (respectively iCR, iPR or iSD for 12 weeks for Part B cohorts). If an expansion cohort passes the first stage, then a total of 18 patients (eight additional patients) would be enrolled. Six or more patients achieving the efficacy criterion already defined would suggest promising anti-tumour activity in the corresponding expansion cohort. Table 38 shows the operating characteristics for a range of true CBRs.

Table 38 Operating Characteristics for True CBRs

True CBR rate	Pr(find encouraging)	Pr(stop at stage 1)
0.10	0.01	0.74
0.20	0.13	0.38
0.30	0.46	0.15
0.35	0.64	0.09
0.40	0.78	0.05
0.45	0.89	0.02
0.50	0.95	0.01

CBR=clinical benefit rate; Pr=probability

As this is a signal seeking study, no statistical adjustments are considered for the multiple comparisons.

The design and its characteristics (uninteresting and target CBRs, type I error, power and the sample size to have a sequential 2-stage design for example) may be updated in a protocol amendment based on results from the dose escalation phase.

11.3.2 Significance Testing and Estimation

As this is a descriptive expansion phase, no formal statistical testing will be done to compare the cohorts presented.

11.3.3 Statistical Methods

11.3.3.1 Demographics and Other Baseline Characteristics

The statistical methodology and data presentation will be the same as that for the dose escalation phase (presentation by cohort and by part (if applicable)). Please see Section 11.2.3.1.

11.3.3.2 Patient Disposition and Withdrawals

The statistical methodology and data presentation will be the same as that for the dose escalation phase. Please see Section 11.2.3.2.

11.3.3.3 Pharmacokinetic Data

Please refer to the PK sections (Section 9.1.3).

11.3.3.4 Anti-tumour Activity Evaluation

Tumour response in the expansion phase will be assessed centrally every 6 weeks.

Response and progression will be evaluated using the revised RECIST guideline v1.1 or iRECIST guideline (Part B cohorts only).

The planned 2-stage procedure has an unadjusted type 1 error rate of less than 0.15 within each dose expansion cohort for a null hypothesis that the true CBR is 20%.

The CBR will be analysed at the end of Stage 1 for each cohort separately after the inclusion of 10 patients by cohort. If no patients or only one patient is responding at the second scheduled tumour assessment i.e. with a BOR of CR, PR or SD lasting at least 12-weeks (iCR, iPR or iSD for 12 weeks for part B) the respective study cohort will be stopped for futility. Otherwise, eight additional patients will be treated to complete the planned enrolment. At the end of Stage 2, the null hypothesis will be rejected suggesting promising anti-tumour activity in the corresponding cohort if six patients or more are responding. The CBR will be calculated along with its CI for each cohort.

The other efficacy proportions, ORR and DCR, will be summarised using descriptive statistics by cohort and will be graphically displayed if appropriate at the end of the dose expansion phase for each cohort whenever it comes (after the first stage when the expansion phase is stopped for futility and after the second one otherwise). The corresponding exact binomial 95% CIs will be provided.

Time-to-event variables (PFS and OS) will be analysed using survival methods (Kaplan-Meier). The results will be presented both in summary tables and graphically in Kaplan-Meier plots. In addition, 95% CIs for median durations will be provided.

11.3.3.5 Safety Evaluation

The statistical methodology and data presentation will be the same as that for the dose escalation phase (presentation by cohort and by part (if applicable)). Please see Section 11.2.3.7.

11.3.3.6 Interim Analyses

Please see Section 11.3.3.4.

11.3.4 Independent Safety Assessment Committee

An ISAC will be established to monitor the safety and progress of the study on a regular basis. The committee will operate independently from the sponsor and the clinical investigators. To minimize the potential introduction of bias, these individuals will not have any direct contact with the study site personnel or patients. ISAC members will be selected for their expertise in oncology.

The ISAC will meet and evaluate all available data once all patients in Stage 1 (n=10) of each respective cohort have either been on treatment for 12 weeks or have discontinued study treatment for any reason. Evaluation may be done sooner if enough CBR events at 12 weeks have occurred (based on the SAP) to inform a decision on moving to Stage 2, prior to all patients being enrolled. Upon evaluation, the ISAC will make the recommendation to the sponsor based on the results of the analyses over continuation to Stage 2, or stoppage of the cohort. This decision will be made based on, but not limited to: safety events, any available results of PK, PD and tumour assessments (local and/or central).

The ISAC will meet and evaluate all available data again once all patients in Stage 2 (n=18) of each respective cohort have either been on treatment for 12 weeks or have discontinued study treatment for any reason. Upon evaluation, the ISAC will give a recommendation to further peruse the given drug combination and patient population in the clinical development plan, or to stop any further investigation. This decision will be made based on, but not limited

to: safety events, any available results of PK, PD and tumour assessments (local and/or central).

The ISAC will meet 1 year after the start of the study or at the end of the dose escalation, whichever occurs first.

The ISAC will also be responsible for any adhoc assessments of safety and futility for each cohort, and can meet as needed to recommend protocol modifications, or any other actions including but not limited to:

- Changing the eligibility criteria if the risks of the intervention seem to be higher in a subgroup;
- Altering the drug product dosage and/or schedule if the AEs observed appear likely to be reduced by such changes;
- Identifying information needed to inform current and future study patients of newly identified risks via changes in the ICF and, in some cases, obtaining reconsent of current patients for continued study participation.

Further details regarding the ISAC and their requirements will be outlined in the ISAC charter.

12 DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS

Authorised personnel from external CAs and sponsor authorised Quality Assurance personnel may carry out inspections and audits. The purpose of an audit is to ensure that ethical, regulatory and quality requirements are fulfilled in all studies performed by the sponsor.

Auditors and inspectors must have direct access to study documents and site facilities as specified in Section 13.4 and to any other locations used for the purpose of the study in question (for example laboratories).

In the event of the site being notified directly of a regulatory inspection, the investigator must notify the sponsor's representative as soon as possible, to assist with preparations for the inspection.

13 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Protocol Amendments and Protocol Deviations

13.1.1 Protocol Amendments

No changes from the final approved (signed) protocol will be initiated without the prior written approval or favourable opinion by the IEC/IRB, except when necessary to eliminate immediate safety concerns to the patients or when the change involves only logistics or administration.

In the event that an amendment to this protocol is required, it will be classified into one of the following three categories:

- ***Nonsubstantial amendments*** are those that are not considered 'substantial' (for example administrative changes) and as such only need to be notified to the IECs or regulatory authorities for information purposes.
- ***Substantial amendments*** are those considered 'substantial' to the conduct of the clinical study where they are likely to have a significant impact on:
  - the safety or physical or mental integrity of the patients;
  - the scientific value of the study;
  - the conduct or management of the study; or
  - the quality or safety of the study drug used in the study.

  Substantial amendments must be submitted to and approved by the IECs and relevant regulatory authorities, according to local regulations, prior to implementing changes.
- ***Urgent amendments*** are those that require urgent safety measures to protect the study patients from immediate hazard and as such may be implemented immediately by the sponsor with subsequent IECs and regulatory authority notification, forthwith.

The principal investigator and the sponsor will sign all protocol amendments.

13.1.2 Protocol Deviations and Exceptions

All protocol deviations will be identified and recorded by the sponsor or sponsor's representative.

A major protocol deviation is any significant divergence from the protocol, i.e. nonadherence on the part of the patient, the investigator, or the sponsor to protocol-specific inclusion/exclusion criteria, primary objective evaluation criteria and/or GCP guidelines. Generally, a protocol deviation qualifies as major if:

(1) the deviation has harmed or posed a significant or substantive risk of harm to the research patient;

(2) the deviation compromises the scientific integrity of the data collected for the study;

(3) the deviation is a wilful or knowing breach of human patient protection regulations, policies, or procedures on the part of the investigator(s);

(4) the deviation involves a serious or continuing noncompliance with any applicable human patient protection regulations, policies, or procedures;

(5) the deviation is inconsistent with the sponsor's research, medical and/or ethical principles.

See also Section 11.1.2 for details on the impact of major protocol deviations on the inclusion of patients in each analysis population.

A minor protocol deviation is any significant divergence from the protocol that does not impact the study results.

As a matter of policy, the sponsor will not grant exceptions to protocol-specific entry criteria to allow patients to enter a study. If under extraordinary circumstances such action is considered ethically, medically and scientifically justified for a particular patient, prior approval from the sponsor and the responsible IRB/IEC, in accordance with the Standard Operating Procedure (SOP), is required before the patient will be allowed to enter the study. If investigative centre personnel learn that a patient who did not meet protocol eligibility criteria was entered in a study (a protocol violation), they must immediately inform the sponsor. Such patients will be discontinued from the study, except in an exceptional instance following review and written approval by the sponsor and the responsible IRB/IEC, according to the applicable SOP. Retention of these patients in the study will be discussed between the sponsor and investigator, taking into account patient safety and data reliability. The IRB/IEC will be informed if patient safety/protection is ignorantly impacted.

13.2 Information to Study Personnel

To ensure accurate, complete and reliable data, the sponsor or its representatives will provide instructional material to the study sites, as appropriate. A study initiation visit will be conducted prior to screening start to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the eCRF and all study procedures. The investigator is responsible for giving information about the study to all staff members involved in the study or in any element of patient management, both before starting any study procedures and during the course of the study (for example when new staff become involved). The investigator must assure that all study staff members are qualified by education, experience and training to perform their specific responsibilities. These study staff members must be listed on the study centre authorisation form, which includes a clear description of each staff member's responsibilities. This list must be updated throughout the study, as necessary.

The study monitor is responsible for explaining the protocol to all study staff, including the investigator and for ensuring their compliance with the protocol. Additional information will be made available during the study when new staff become involved in the study and as otherwise agreed upon with either the investigator or the study monitor.

13.3 Study Monitoring

The investigator is responsible for the validity of all data collected at the site.

The sponsor or delegate is responsible for monitoring these data to verify that the rights and wellbeing of patients are protected, that study data are accurate (complete and verifiable to source data) and that the study is conducted in compliance with the protocol, GCP guidelines and regulatory requirements.

The sponsor or delegate assigned monitors will conduct regular site visits. The investigator will allow direct access to all relevant files (for all patients) and clinical study supplies (dispensing and storage areas) for the purpose of verifying entries made in the eCRF and will assist with the monitor's activities, if requested. Adequate time and space for monitoring visits should be made available by the investigator.

The site must complete the eCRFs on an ongoing basis to allow regular review by the study monitor, both remotely by the internet and during site visits. The central study monitor at the sponsor will use functions of the EDC system to address any queries raised while reviewing the data entered by the study site personnel in a timely manner.

Whenever a patient name is revealed on a document required by the sponsor (for example laboratory print outs), the name must be blacked out permanently by the site personnel and annotated with the patient number as identification.

An ISAC will be established to monitor the safety and progress of the study on a regular basis (see Section 11.3.4 for more details).

13.4 Investigator's Regulatory Obligations

All clinical work under this protocol will be conducted according to GCP guidelines. This includes that the study may be audited at any time by a quality assurance personnel designated by the sponsor, or inspected by regulatory bodies. The investigator must adhere to ICH GCP guidelines in addition to any applicable local regulations.

If requested, the investigator will provide the sponsor, applicable regulatory agencies and applicable IECs with direct access to any original source documents.

The investigator(s) should demonstrate due diligence in the recruitment and screening of potential study patients. The enrolment rate should be sufficient to complete the study as agreed with the sponsor. The sponsor should be notified of any projected delays, which may impact the completion of the study.

This clinical study will be conducted in compliance with all international laws and regulations and national laws and regulations of the country(ies) in which the clinical study is performed, as well as any applicable guidelines.

13.5 Audit and Inspection

Authorised personnel from external CAs and the sponsor's authorised Quality Assurance personnel may carry out inspections and audits (see Section 12).

13.6 Data Quality Assurance

Monitored eCRFs will be reviewed by the assigned data management group for completeness, consistency, legibility and protocol compliance.

Reasons should be given on the relevant eCRF for any missing data and other protocol deviations. Any electronic queries and items not adequately explained will require additional electronic manual queries to be raised to the investigator by the monitor for clarification/correction. The investigator must ensure that queries are dealt with promptly. All data changes and clarifications can be viewed in the audit trail function of the eCRF.

14 ETHICS

14.1 Compliance with Good Clinical Practice and Ethical Considerations

This study will be conducted in compliance with IECs/IRBs, informed consent regulations, the Declaration of Helsinki, FDA 21 CFR Part 11, Electronic Records, Electronic Signatures and FDA, Guidance for Industry: Computerized Systems Used in Clinical Trials and ICH GCP guidelines (Section 1.7).

In addition, this study will adhere to all local regulatory requirements.

Before initiating the study, the investigator/institution should have written and dated approval/favourable opinion from the IEC/IRB for the study protocol/amendment(s), written ICF, any ICF updates, patient emergency study contact cards, patient recruitment procedures (for example advertisements), any written information to be provided to patients and a statement from the IEC/IRB that they comply with GCP requirements. The IEC/IRB approval must identify the protocol version as well as the documents reviewed.

After IEC/IRB approval, changes will require a formal amendment. Once the study has started, amendments should be made only in exceptional circumstances. Changes that do not affect patient safety or data integrity are classified as administrative changes and generally do not require ethical approval. If ethically relevant aspects are concerned, the IEC/IRB must be informed and, if necessary, approval sought prior to implementation. Ethical approval on administrative changes will be obtained if required by local/site IEC/IRB.

14.2 Informed Consent for Participation in the Study

Prior to study entry, the investigator, or a person designated by the investigator, will explain the nature, purpose, benefits and risks of participation in the study to each patient, patient's legally acceptable representative or impartial witness. Written informed consent must be obtained prior to the patient entering the study (before initiation of any study-related procedure and administration of the IMP). Sufficient time will be allowed to discuss any questions raised by the patient.

The sponsor will provide a sample ICF. The final version-controlled form must be agreed to by the sponsor and the IEC/IRB and must contain all elements included in the sample form, in language readily understood by the patient. Each patient's original consent form, personally signed and dated by the patient or by the patient's legally acceptable representative and by the person who conducted the informed consent discussion, will be retained by the investigator. The investigator will supply patients with a copy of their signed ICF.

The ICF may need to be revised during the study should important new information become available that may be relevant to the safety of the patient or as a result of protocol amendments. In this instance, approval should always be given by the IEC/IRB. It is the investigator's responsibility to ensure that all patients subsequently entered into the study and those currently in the study sign the amended form. This is documented in the same way as described above. Patients who have completed the study should be informed of any new information that may impact on their welfare/wellbeing.

The investigator should, with the consent of the patient, inform the patient's primary physician about their participation in the clinical study.

14.2.1 Optional Informed Consent for Biobanking

This study has the option for patients to consent to the collection of samples for biobanking for future exploratory analysis and storage for up to 15 years (where local regulations allow). A specific informed consent is required for the collection of these samples and will be explained after the patient has given written informed consent for the main study.

Patients must receive an explanation that they are completely free to refuse to enter the exploratory part of the study and may withdraw from it at any time and for any reason up to 15 years after the end of the study and will still be allowed to take part in the main study.

14.3 Health Authorities and Independent Ethics Committees/Institutional Review Boards

As required by local regulations, the sponsor's Regulatory Affairs and Clinical Operations groups (or their delegates) will ensure all legal regulatory aspects are covered and obtain approval of the appropriate regulatory bodies, prior to study initiation in regions where an approval is required.

The following documents should be submitted to the relevant IEC/IRB for review and approval to conduct the study (this list may not be exhaustive):

- protocol/amendment(s) approved by the sponsor;
- currently applicable IB or package labelling;
- relevant investigator's curriculum vitae;
- patient information and informed consent document(s) and form(s);
- patient emergency study contact cards;
- recruitment procedures/materials (advertisements), if any.

The IEC(s)/IRB(s) will review all submission documents as required and a written favourable opinion for the conduct of the study should be made available to the investigator before initiating the study. This document must be dated and clearly identify the version number(s) and date(s) of the documents submitted/reviewed and should include a statement from the IEC/IRB that they comply with GCP requirements.

The study may begin at the investigative site(s) only after receiving this dated and signed documentation of the IEC/IRB approval or favourable opinion.

During the study, any update to the following documents will be sent to the IEC/IRB, either for information, or for review and approval, depending on how substantial the modifications are: (1) IB; (2) reports of SAEs; (3) all protocol amendments and revised informed consent(s), if any.

At the end of the study, the IEC/IRB will be notified about the study completion.

14.4 Confidentiality Regarding Study Patients

The investigator must assure that the privacy of the patients, including their personal identity and all personal medical information, will be maintained at all times. In eCRFs and other documents or image material submitted to the sponsor, patients will be identified not by their names, but by an identification code (for example initials and identification number).

Personal medical information may be reviewed for the purpose of verifying data recorded on the eCRF. This review may be conducted by the study monitor, properly authorised persons on behalf of the sponsor, the quality assurance unit, or regulatory authorities. Personal medical information will always be treated as confidential.

15 DATA HANDLING AND RECORD KEEPING

15.1 Recording of Study Data

In compliance with GCP guidelines, the medical records/medical notes, etc., should be clearly marked and permit easy identification of a patient's participation in the specified clinical study.

The investigator must record all data relating to protocol procedures, IMP administration, laboratory data, safety data and efficacy ratings on the eCRFs provided for the study. The investigator, by completing the signature log, may formally designate authority to complete eCRFs to appropriately qualified staff having certified user access to the eCRF.

The investigator (or authorised subinvestigator) must, as a minimum, provide an electronic signature (e-signature) to each eCRF to attest to the accuracy and completeness of all the data. If any changes are made to the eCRF after a form has been locked and electronically signed, the investigator (or authorised subinvestigator) will be required to perform an additional e-signature authorising agreement with any new information or changes to the eCRF.

All corrections on the eCRF will be automatically tracked and a reason for the change is always required. In the eCRF, the audit trail function will allow the changes made to be viewed on each item entered.

15.2 Data Management

Electronic data capture will be utilised for collecting patient data. Each site is required to have a computer and internet connection available for site entry of clinical data. All entries in the eCRF will be made under the e-signature of the person performing the action. This electronic signature consists of an individual and confidential username and password combination. It is declared to be the legally binding equivalent of the handwritten signature. Only sponsor authorised users will have access to the eCRF as appropriate to their study responsibilities. Users must have successfully undergone software application training prior to entering data into the eCRF.

Data management will be conducted by a CRO, directed by the sponsor's data management department. All data management procedures will be completed in accordance with the sponsor and the contracted CRO SOPs. Electronic CRF data will be monitored at the investigator site, (for further details see Section 13.3). The study data documentation removed from the investigator site(s) will be tracked by the CRO and the monitor.

The sponsor or delegate will ensure that an appropriate eCRF is developed to capture the data accurately and suitable queries are raised to resolve any missing or inconsistent data. The investigator will receive their data, from the clinical study, in an electronic format (PDF files) which will be an exact copy of the eCRF and will include the full audit trail, for archiving purposes and future reference.

Any queries generated during the data management process will also be tracked by the contracted data management CRO/will be raised within the EDC system. It is the central study monitor's responsibility to ensure that all queries are resolved by the relevant parties.

The sponsor will also ensure that SAE data collected in the eCRF are consistent with information provided to the sponsor's pharmacovigilance department (and vice versa).

The coding of an AE, medical history, surgical procedures and concomitant medication terms will be performed by the contracted CRO/a coding CRO, directed by the sponsor's Biometry department and reviewed and approved by the sponsor. Concomitant medications will be coded using WHO-DD and AEs/medical history terms will be coded using MedDRA.

Only data from patients who give informed consent will be reported in the eCRFs and collected in the sponsor's database.

For screening failure patients, the Unique Patient Identifier, the date of informed consent signature, the reason why the patient failed screening and the potential AEs that occurred during the screening phase will be reported in the eCRFs at a minimum and collected in the sponsor's database.

15.3 Record Archiving and Retention

During the prestudy and initiation visits, the monitor must ensure the archiving facilities are adequate and archiving/retention responsibilities of the investigator have been discussed.

Study documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or planned marketing applications in an ICH region (that is at least 15 years) or at least 2 years have elapsed since the formal discontinuation of clinical development of the product. However, these documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. The investigator should take measures to prevent accidental or premature destruction of these documents. The final archiving arrangements will be confirmed by the monitor when closing out the site. The sponsor will inform the investigator, in writing, as to when these documents no longer need to be retained.

If the principal investigator relocates or retires, or otherwise withdraws his/her responsibility for maintenance and retention of study documents, the sponsor must be notified (preferably in writing) so that adequate provision can be made for their future maintenance and retention.

16 FINANCING AND INSURANCE

16.1 Contractual and Financial Details

The investigator (and/or, as appropriate, the hospital administrative representative) and the sponsor will sign a clinical study agreement prior to the start of the study, outlining overall sponsor and investigator responsibilities in relation to the study. Financial remuneration will cover the cost per included patient, based on the calculated costs of performing the study assessments in accordance with the protocol and the specified terms of payment will be described in the contract. The contract should describe whether costs for pharmacy, laboratory and other protocol required services are being paid directly or indirectly.

Financial disclosure statements will need to be completed, as requested by FDA 21 CFR Part 54.

16.2 Insurance, Indemnity and Compensation

The sponsor will provide product liability insurance for all patients included in the clinical study. Where required, a hospital specific indemnity agreement will be used.

17 REPORTING AND PUBLICATION OF RESULTS

17.1 Publication Policy

The sponsor is committed to disclosing information about the clinical studies it sponsors. Results will be communicated at scientific meetings and all reasonable efforts must be made to seek publication in a peer-reviewed scientific journal. Specific publication concepts, including data to be covered, target congress/journal and proposed authors, should be discussed with the appropriate Global Publications Manager and incorporated in the relevant publication plan before initiation. A dedicated Publications Committee, involving interested members of the study Steering Committee as well as the Global Publications Manager, may be established to plan specific publications. As a minimum, summary results of this study should be posted on the relevant clinical study registry. When the study has been conducted by a large multicentre group, the principal investigator, the study steering committee (if applicable) and the sponsor's responsible physician should discuss and agree the selection of authors for planned publications in advance. They may decide to use a group name and nominate authors on behalf of the study group. All contributing investigators will be listed in the acknowledgements together with any others who may have contributed but not sufficiently to qualify for authorship.

Selection of authors for scientific publications will follow the International Committee of Medical Journal Editors guidelines [http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html]. In particular, those named as authors, whether employed by a sponsor's affiliate or the sponsor, or external investigators, 'should have participated sufficiently in the work to take public responsibility for the content'.

Authorship should be based on:

- substantial contributions to the conception and design, or acquisition of data, or analysis and interpretation of data; AND
- drafting the article or revising it critically for important intellectual content; AND
- final approval of the version to be published; AND
- agreement to be accountable for all aspects for the work, thereby ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

All authors of a publication should meet all four criteria. Each author must agree to their inclusion in the list of authors. Use of professional medical writing support may be employed.

Resolution of scientific differences in the presentation or interpretation of study findings will be conducted along principles of honest scientific debate. The sponsor shall be promptly notified of any amendments subsequently requested by referees or journal editors.

All publications arising from this study will be reviewed by relevant functions at the sponsor, coordinated by the Global Publications team. Requests and suggestions for changes will be discussed with all authors (and the medical writer, if applicable). Resolution of scientific differences in the presentation or interpretation of study findings will be conducted along principles of honest scientific debate. The sponsor's review comments must be answered before a final version for submission can be approved by the author team.

If patentability would be adversely affected by publication, this will be delayed until (i) a patent application is filed for the content of the publication in accordance with applicable provisions of the clinical study agreement concerned, (ii) the sponsor consents to the publication, or (iii) the time period as may be agreed in the contractual arrangements,

including clinical study agreements, governing the relationship between the sponsor and authors (or authors' institution) after receipt of the proposed publication by the sponsor, whichever of (i), (ii) or (iii) occurs first.

17.2 Clinical Study Report

A final clinical study report (CSR) will be prepared according to the ICH E3 guideline on the structure and contents of CSRs. A final CSR will be prepared where any patient has signed informed consent, regardless of whether the study is completed or prematurely terminated. Where appropriate, an abbreviated report may be prepared. The CSR will comply with any applicable regulatory requirements and national laws in force, and will be in English.

As indicated in Section 11, an analysis will be performed on the final response data after the last patient has completed the treatment period. This analysis will be included in the final CSR. An addendum to the CSR, including the analysis of data from the follow-up period, will be prepared after the last patient completes the follow-up period.

Analysis of biobank samples will be performed outside the scope of the main study and reported separately.

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19 LIST OF APPENDICES

Appendix 1 TREATMENT PLAN AND DOSE MODIFICATION GUIDELINES

Treatment Plan and Dose Modification Guidelines

Reduction for IPN60090 monotherapy

Management of severe or intolerable adverse reactions requires dose reduction, temporary interruption, and/or discontinuation of IPN60090 therapy. Each patient is allowed a maximum of two dose reductions for IPN60090. After this, the patient will be discontinued from the study treatment.

If a dose reduction is required, reduce the current dose by one dose level from the current dose.

Dose Adjustment for IPN60090

	DL1	DL2	DL3	DL4	DL5	DL6	DL7
Starting dose level	20 mg BID	40 mg BID	80 mg BID	180 mg BID	320 mg BID	480 mg BID	720 mg BID
First dose reduction	N/A	20 mg BID	40 mg BID	80 mg BID	180 mg BID	320 mg BID	480 mg BID
Second dose reduction	N/A	N/A	20 mg BID	40 mg BID	80 mg BID	180 mg BID	320 mg BID

BID=bis in die (twice daily); DL=dose level; N/A=not applicable

Reduction of IPN60090 + Pembrolizumab

Management of severe or intolerable adverse reactions requires dose reduction, temporary interruption, and/or discontinuation of IPN60090 therapy. Each patient is allowed a maximum of two dose reductions for IPN60090. Pembrolizumab will be a fixed dose and cannot be dose reduced, however treatment of pembrolizumab can be delayed >6 weeks (2 cycles) for any reason. In this case, the patient must be permanently discontinued from study therapy, except in cases where permission to resume treatment is granted by the Ipsen Medical Monitor or designee. If a patient discontinues IPN60090, they may remain on study on pembrolizumab monotherapy.

If a dose reduction is required, reduce the current dose by one dose level from the current dose. This can be done up to two times before a patient must discontinue study treatment.

Dose Adjustment for IPN60090 + Pembrolizumab

	DL1		DL2		DL3	
	IPN60090	Pembrolizumab	IPN60090	Pembrolizumab	IPN60090	Pembrolizumab
Starting dose level	180 mg BID	In accordance with approved label	320 mg BID	In accordance with approved label	480 mg BID	In accordance with approved label
First dose reduction	80 mg BID		180 mg BID		320 mg BID	
Second dose reduction	40 mg BID		80 mg BID		180 mg BID	

BID=bis in die (twice daily); DL=dose level

Reduction of IPN60090 + Paclitaxel

Management of severe or intolerable adverse reactions requires dose reduction, temporary interruption, and/or discontinuation of IPN60090 therapy. Each patient is allowed a maximum of two dose reductions for IPN60090, paclitaxel is a fixed dose and cannot be dose reduced. If treatment of paclitaxel is delayed >6 weeks (2 cycles) for any reason, the patient must be permanently discontinued from study therapy, except in cases where permission to resume treatment is granted by the Ipsen Medical Monitor or designee. If a patient discontinues IPN60090 they may remain on study on paclitaxel monotherapy.

If a dose reduction is required, reduce the current dose by one dose level from the current dose. This can be done up to two times before a patient must discontinue study treatment.

Dose Adjustment for IPN60090 + Paclitaxel

	DL1		DL2		DL3	
	IPN60090	**Paclitaxel**	**IPN60090**	**Paclitaxel**	**IPN60090**	**Paclitaxel**
Starting dose level	180 mg BID	In accordance with approved label	320 mg BID	In accordance with approved label	480 mg BID	In accordance with approved label
First dose reduction	80 mg BID		180 mg BID		320 mg BID	
Second dose reduction	40 mg BID		80 mg BID		180 mg BID	

BID=bis in die (twice daily); DL=dose level

Dose Adjustment/Modification Recommendation for Haematological Adverse Reactions

Dose adjustments and modifications of pembrolizumab and paclitaxel therapy should be done according to the approved product information. For IPN60090 the instructions in the below tables are recommended for dose adjustment and management.

The management of all study drugs, and any dose adjustments should be in line with the best clinical practice for individual patients and is ultimately left to the discretion of the investigator or treating physician.

Toxicity/grade	Dose adjustment and management recommendations
	IPN60090
Thrombocytopenia	
Grade 1 (≥75×10^9/L)	No dose adjustment required.
Grade 2 (≥50×10^9/L to <75×10^9/L)	-Dose interruption until recovery to Grade ≤1. -Re-initiate at the same dose.
Grade 3 (≥25×10^9/L to <50×10^9/L)	-Dose interruption until recovery to Grade ≤1. -Re-initiate at the same dose level. -If toxicity recurs at Grade 3: temporary dose interruption until recovery to Grade ≤1 and reduce to the next lower dose level.
Grade 4 (<25×10^9/L)	-Dose interruption until recovery to Grade ≤1. -Re-initiate at the next lower dose level. -If toxicity recurs at Grade 4: discontinue IPN60090.
Absolute neutrophil count (ANC)	
Grade 1 (≥1.5×10^9/L)	No dose adjustment required.
Grade 2 (≥1.0 to <1.5×10^9/L)	No dose adjustment required.
Grade 3 (≥0.5 to <1.0×10^9/L)	-Dose interruption of IPN60090 until recovery to Grade 2 or 1 ≥1.0×10^9/L. -Re-initiate IPN60090 at the same dose level. -If toxicity recurs at Grade 3: temporary dose interruption until recovery to ≥1.0×10^9/L. -If resolved in ≤7 days, then maintain dose level. -If resolved in >7 days, then reduce IPN60090 dose to the next lower dose level.
Grade 4 (<0.5×10^9/L)	-Dose interruption of IPN60090 and pembrolizumab (if applicable) until recovery to Grade 2 or 1 ≥1.0×10^9/L. -Re-initiate IPN60090 at the next lower dose level. -If toxicity recurs at Grade 4: discontinue IPN60090.
Febrile neutropenia	
Grade 3 ANC <1.0×10^9/L with a single temperature of >38.3ºC (101 ºF) or a sustained temperature of ≥38ºC (100.4ºF) for more than one hour	-Dose interruption of IPN60090 and pembrolizumab (if applicable) until improvement of ANC ≥1.0×10^9/L and no fever. -Restart at the next lower dose level. -If febrile neutropenia recurs, discontinue IPN60090.
Grade 4 Life threatening consequences; urgent intervention indicated	-Discontinue IPN60090.
Anaemia (Haemoglobin)	
Grade 1 (≥10.0 to LLN g/dL)	No dose adjustment required.
Grade 2 (≥8.0 to <10.0 g/dL)	No dose adjustment required.
Grade 3 (<8.0 g/dL)	-Dose interruption until recovery to Grade ≤2. -Re-initiate IPN60090 at the same dose.
Grade 4 Life threatening consequences; urgent intervention indicated	-Discontinue IPN60090.

ANC=absolute neutrophil count

Recommendations for Dose Modification in Case of Hepatotoxicity

Hepatotoxicity (bilirubin, SGPT/ALT, SGOT/AST)	
Total bilirubin without ALT/AST increase above baseline value	
Grade 1 (>ULN to 1.5×ULN) (confirmed 48 to 72 hrs later)	Maintain dose level with LFTs monitored biweekly.
Grade 2 (>1.5 to 3.0×ULN)	-Dose interruption of IPN60090. -If resolved to ≤Grade 1 in ≤14 days, then maintain dose level. -If resolved to ≤Grade 1 in >14 days or toxicity recurs, then reduce IPN60090 by one dose level. -Repeat liver enzymes and bilirubin tests weekly for 2 weeks after dose resumption. -If toxicity recurs after two dose reductions, discontinue study treatment.
Grade 3 (>3.0 to 10.0×ULN)	-Dose interruption of IPN60090. -If resolved to ≤Grade 1 in ≤14 days, lower one dose level of IPN60090 -Repeat liver enzymes and bilirubin tests weekly for 2 weeks after dose resumption. -If resolved to ≤Grade 1 in >14 days or toxicity recurs, discontinue IPN60090.
Grade 4 (>10.0×ULN)	Discontinue IPN60090.

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase

Confounding factors and/or alternative causes for increase of total bilirubin should be excluded before dose interruption/reduction. They include but are not limited to: evidence of obstruction, such as elevated ALP and GGT typical of gallbladder or bile duct disease, hyperbilirubinaemia due to the indirect component only (i.e. direct bilirubin component ≤1×ULN) due to haemolysis or Gilbert's syndrome, pharmacologic treatment, viral hepatitis, alcoholic or autoimmune hepatitis, other hepatotoxic drugs. For patients with Gilbert's syndrome, these dose modifications apply to changes in direct bilirubin only. Bilirubin will be fractionated if elevated.

Recommendations for IPN60090 Dose Modification in Case of Cardiac Toxicities

Adverse drug reaction	Severity	Dose adjustment and management recommendations
QTcF prolongation	For all grades	-Check the quality of the ECG and the QT value and repeat if needed. -Perform analysis of serum electrolytes (K+, Ca++, Phos, Mg++). If outside of normal range, hold IPN60090, correct with supplements or appropriate therapy as soon as possible, and repeat electrolytes until documented as normal. -Review concomitant medication usage for the potential to prolong the QT interval. -Check compliance with correct dose and administration of IPN60090. -Consider collecting a time matched PK sample; record date and time of last study drug intake.
	Grade 1 QTc 450 to 480 ms	No dose adjustment required.
	Grade 2 QTc 481 to 500 ms	-Hold IPN60090. -Perform repeat triplicate ECGs one hour after the first QTcF of ≥481 ms. -If QTcF <481 ms, restart IPN60090 at the same dose. No dose adjustment required for first occurrence. If QTcF remains ≥481 ms, repeat ECG as clinically indicated until the QTcF returns to <481 ms. Restart IPN60090 and pembrolizumab (if applicable) at the same dose. -No dose adjustment required for first occurrence. -If QTcF ≥481 ms recurs, IPN60090 should be reduced by one dose level. -Repeat ECGs 7 days and 14 days after dose reduction (then as clinically indicated) for any patients who had therapy interrupted due to QTcF ≥481 ms.
	Grade 3 QTc ≥501 ms on at least two separate ECGs	-Hold IPN60090 -Perform repeat triplicate ECGs within one hour of the first QTcF of ≥501 ms. -If QTcF remains ≥501ms, consult with a cardiologist (or qualified specialist) and repeat cardiac monitoring as indicated until the QTcF returns to <481 ms. -If QTcF returns to <481 ms, IPN60090 will be reduced by one dose level. -Repeat ECGs 7 days and 14 days after dose reduction (then as clinically indicated) for any patients who had therapy interrupted due to QTcF ≥501 ms. -If QTcF of ≥501 ms recurs, discontinue study treatment. -Hold IPN60090 and perform frequent ECGs until the QTcF is <500 ms. Address electrolyte, calcium and magnesium abnormalities. Restart IPN60090 at a lower dose. -If findings recur on the lower dose, hold study treatment until resolve to ≤Grade 1, and restart at the next lower dose level. -If findings recur, discontinue IPN60090.
	Grade 4 QT/QTc ≥501 or >60 ms change from baseline and Torsades de pointes or polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia	-Discontinue IPN60090 -Obtain local cardiologist (or qualified specialist) consultation and repeat cardiac monitoring as indicated until the QTcF returns to <481 ms. -Stop study treatment, institute emergency care, address electrolyte, calcium and magnesium abnormalities and perform frequent ECGs until the QTcF is <500 ms. -Discontinue the patient from the study.

Adverse drug reaction	Severity	Dose adjustment and management recommendations
Cardiac - Left Ventricular Systolic Dysfunction	Asymptomatic, resting ejection fraction 40% to 50%; or 10% to 20% drop from baseline	-Maintain dose level, and continue study treatment with caution. -Repeat LVEF within 4 weeks or as clinically appropriate.
	Symptomatic, responsive to intervention, ejection fraction 20% to 39% or >20% drop from baseline	-Hold study treatment until resolved, then reduce one dose level. -LVEF measurement to be repeated, if not resolved, within 28 days.
	Refractory or poorly controlled, ejection fraction <20%	Discontinue IPN60090.

ECG=electrocardiogram; LVEF=left ventricular ejection fraction; QTc=corrected QT interval; QTcF=Fridericia corrected QT interval

Dose Adjustment and Management Recommendations for IPN60090 in Case of Other Toxicities

Toxicity	Action
Hyperlipidaemia and/or hypertriglyceridaemia	Any grade: Treat according to best clinical practice. No specific dose reductions are needed.
Hyperglycaemia	Any grade: Treat according to best clinical practice. No specific dose reductions are needed.
All other toxicities	Any grade: Treat according to best clinical practice. No specific dose reductions are needed.

Management of IPN60090 and Pembrolizumab for Noninfectious Pneumonitis

Worst grade pneumonitis	Required investigations	Management of pneumonitis	Dose adjustment
Grade 1 Asymptomatic, radiographic findings only	CT scans with lung windows. Repeat at least every 12 weeks until return to within normal limits.	No specific therapy is required.	-Administer 100% of study treatment. -Consider patient referral to pulmonary specialist. -For recurrent pneumonitis, treat as Grade 3 or 4 event.
Grade 2 Symptomatic, not interfering with ADL	CT scan with lung windows. Consider pulmonary function testing includes: spirometry, DLCO, and room air O_2 saturation at rest. Repeat at least every 12 weeks until return to within normal limits. Consider a bronchoscopy with biopsy and / or BAL.	Symptomatic only. Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper.	-Hold pembrolizumab (if applicable) until recovery to ≤Grade 1. -Resume pembrolizumab if event resolves to Grade 1 or better within 12 weeks. -Permanently discontinue pembrolizumab and contact the sponsor if event does not resolve to Grade 1 or better within 12 weeks. -Reduce IPN60090 dose by one dose level until recovery to ≤Grade 1. -Study treatment may also be interrupted if symptoms are troublesome. -Patients will discontinue IPN60090 and pembrolizumab (if applicable) if they fail to recover to ≤Grade 1 within 12 weeks. -If Grade 2 recurs discontinue study treatment.
Grade 3 Symptomatic, interfering with ADL; O_2 indicated	CT scan with lung windows and pulmonary function testing includes: spirometry, DLCO, and room air O_2 saturation at rest. Repeat at least every 6 weeks until return to within normal limits. Bronchoscopy with biopsy and / or BAL is recommended.	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper.	-Discontinue IPN60090 and pembrolizumab (if applicable).
Grade 4 Life threatening; ventilatory support indicated	CT scan with lung windows and required pulmonary function testing, if possible, includes: spirometry, DLCO, and room air O_2 saturation at rest. Repeat at least every 6 weeks until return to within normal limits. Bronchoscopy with biopsy and / or BAL is recommended if possible.	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper.	-Discontinue IPN60090 and pembrolizumab (if applicable).

ADL=activities of daily living; BAL=bronchoalveolar lavage; CT=computed tomography; DLCO=diffusing capacity of the lungs for carbon monoxide

Appendix 2 LIST OF STRONG INDUCERS AND INHIBITORS OF CYP3A4

Based on the in-vitro results, CYP3A4 may be involved in the metabolism of IPN60090.

A strong inhibitor for a specific CYP450 enzymes is defined as an inhibitor which increases the AUC of a sensitive substrate 'victim drug' for that CYP450 enzymes by 5-fold or greater.

A strong inducer: decreases the AUC of a victim drug by ≥80%.

Strong inhibitors of CYP3A4	**Strong inducers of CYP3A4**
Antivirals	Carbamazepine
Boceprevir	Enzalutamide
Cobicistat	Mitotane
Conivaptan	Phenytoin
Danoprevir	Rifampin
Dasabuvir	Rifabutin
Elvitegravir	Phenobarbital
Indinavir	Avasimib
Lopinavir	St. John's Wort
Nelfinavir	
Ombitasvir	
Paritaprevir	
Ritonavir	
Saquinavir	
Telaprevir	
Tipranavir	
Antifungals	
Itraconazole	
Ketoconazole	
Posaconazole	
Voriconazole	
Antibiotics	
Clarithromycin	
Telithromycin	
Troleandomycin	
Other	
Mibefradil	
LCL161	
Grapefruit juice	
Idelalisib	
Nefazodone	

This above table is not all inclusive.

The above lists were compiled from the Indiana University School of Medicine's "P450 Drug Interaction Table – Clinically Relevant Table" [21], supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (October 2017) and the University of Washington's Drug Interaction Database (January 2017). These lists are not comprehensive and are only meant to be used as a guide.

The sponsor should be contacted in case of any doubt. If a medication appears on both the list of prohibited and the list of medications to be used with caution, the medication is prohibited.

Appendix 3 LIST OF MODERATE INDUCERS AND INHIBITORS OF CYP3A4

A moderate inhibitor for a specific CYP450 enzymes is defined as an inhibitor which increases the AUC of a sensitive substrate for that CYP450 enzymes by 2-fold or greater, but less than 5-fold.

A moderate inducer: decreases the AUC of a victim drug between 50% to 80%.

Moderate inhibitors of CYP3A4	**Moderate inducers of CYP3A4**
Antivirals	Bosentan
Amprenavir	Efavirenz
Atazanavir	Etravirine
Darunavir	Genistein
Faldaprevir	Lersivirine
Antifungals	Lopinavir
Fluconazole	Modafinil
Isavuconazole	Nafcillin
Antibiotics	Ritonavir and St. John's Wort
Ciprofloxacin	Semagacestat
Erythromicin	Talviraline
Other	Thioridazine
ACT-178882	Tipranavir
Aprepitant	
Casopitant	
Cimetidine	
Crizotinib	
Cyclosporine	
Diltiazem	
Dronedarone	
FK1706	
GSK2647544	
Grapefruit juice	
Imatinib	
Nilotinib	
Netupitant	
Schisandra sphenanthera (herbal medications)	
Tofisopam	
Verapamil	

This above table is not all inclusive.

The above lists were compiled from the Indiana University School of Medicine's "P450 Drug Interaction Table – Clinically Relevant Table" [21], supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (October 2017) and the University of Washington's Drug Interaction Database (January 2017). These lists are not comprehensive and are only meant to be used as a guide.

The sponsor should be contacted in case of any doubt. If a medication appears on both the list of prohibited and the list of medications to be used with caution, the medication is prohibited.

Appendix 4 LIST OF STRONG AND MODERATE INHIBITORS OF CYP2D6

Based on the in-vitro results, CYP2D6 may be involved in the metabolism of IPN60090.

Strong inhibitors of CYP2D6	Moderate inhibitors of CYP2D6
Bupropion	AMD070
Dacomitinib	Cinacalcet
Fluoxetine	Dronedarone
3,4-Methyl-enedioxy-methamphetamine (Ecstasy)	Duloxetine
Paroxetine	Eliglustat
Quinidine	Mirabegron
Terbinafine	Moclobemide
	Rolapitant
	Terbinafine
	Tipranavir/Ritonavir
	Zuojin pill (herbal medications)

This above table is not all inclusive.

The above lists were compiled from the Indiana University School of Medicine's "P450 Drug Interaction Table – Clinically Relevant Table" [21], supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (October 2017) and the University of Washington's Drug Interaction Database (January 2017). These lists are not comprehensive and are only meant to be used as a guide.

The sponsor should be contacted in case of any doubt. If a medication appears on both the list of prohibited and the list of medications to be used with caution, the medication is prohibited.

Appendix 5 LIST OF STRONG INHIBITORS OF CYP2C8

Paclitaxel is mainly metabolised by CYP2C8. Therefore, inhibitors of CYP2C8 may have an impact on the AUC of paclitaxel.

A strong inhibitor for a specific CYP450 enzyme is defined as an inhibitor which increases the AUC of a sensitive substrate for that CYP450 enzymes by 5-fold or greater.

Strong inhibitors of CYP2C8
Clopidogrel
Gemfibrozil

This above table is not all inclusive.

The above lists were compiled from the Indiana University School of Medicine's "P450 Drug Interaction Table – Clinically Relevant Table" [21], supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (October 2017) and the University of Washington's Drug Interaction Database (January 2017). These lists are not comprehensive and are only meant to be used as a guide.

The sponsor should be contacted in case of any doubt. If a medication appears on both the list of prohibited and the list of medications to be used with caution, the medication is prohibited.

Appendix 6 LIST OF MODERATE INHIBITORS AND INDUCERS OF CYP2C8

Paclitaxel is mainly metabolised by CYP2C8. Therefore, inhibitors and inducers of CYP2C8 may have an impact on the AUC of paclitaxel.

A moderate inhibitor for a specific CYP450 enzymes is defined as an inhibitor which increases the AUC of a sensitive substrate for that CYP450 enzymes by 2-fold or greater, but less than 5-fold.

A moderate inducer: decreases the AUC of a victim drug between 50% to 80%.

Moderate Inhibitors of CYP2C8
Letermovir Teriflunomide Deferasirox
Moderate Inducers of CYP2C8
Rifampin Carbamazepin Ivosidenib Hormonal contraceptives

This above table is not all inclusive.

The above lists were compiled from the Indiana University School of Medicine's "P450 Drug Interaction Table – Clinically Relevant Table" [21], supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (October 2017) and the University of Washington's Drug Interaction Database (January 2017). These lists are not comprehensive and are only meant to be used as a guide.

The sponsor should be contacted in case of any doubt. If a medication appears on both the list of prohibited and the list of medications to be used with caution, the medication is prohibited.

Appendix 7 LIST OF IMMUNOSUPPRESSIVE AGENTS

Immunosuppressants	Azathioprine Betamethasone Dexamethasone Hydrocortisone Hydroxychloroquine Leflunamide Methotrexate Methylprednisolone Prednisolone Triamcinolone Tenflunomide
Anti-rejection agents	Ciclosporin Everolimus Mycophenolic acid Tacrolimus Sirolimus
Biological agents	Abatacept Adalimumab Alemtuzumab Anakinra Apremilast Basiliximab Bevacizumab Canakinumab Certolizumab Daclizumab Eculizumab Erlotinid Etanercept Golimumab Infliximab Imatinib Ixekizumab Natalizumab Nilotinib Perfenidone Pomalidomide Rituximab Secukinumab Siltuximab Sortatinib Thalidomide Tocilizumab Ustenkinumab Vedolizumab Fingolimod Lenalidomide

Cytotoxic chemotherapy agents	Paclitaxel Capecitabine Fludarabine Etoposide Bendamustine Busulfan Carmustine Chlorambucil Dacarbazine Ifosfamide Melphalan Temozolamide Thiotepa Treosulfan Daunorubicin Doxorubicin Epirubicin Idarubicin Mitoxanthrone Azacitidine Cladribine Clofarabine Cytarabine Decitabine Fluorouracil Gemcitabine Mercaptopurine Nelarabine Pemetrexed Tioguanine Crisantaspase Eribulin Hydroxycarbamide (previously hydroxyurea) Mitotane Raltitrexed Bleomycin Mitomycin Pentostatin Carboplatin Cisplatin Trabectedin Oxaliplatin Cabazitaxel Docetaxel Irinotecan Topotecan Vinblastine Vincristine Vinorelbine Vinflunine
Others	Carbimazole Clozapine Deferiprone Olanzapine Phenytoin Phenobarbital Propylthiouracil

The above list can be found on:
https://www.hse.ie/eng/services/publications/clinical-strategy-and-programmes/list-of-immunosuppressant-medication.pdf

Appendix 8 LIST OF SUBSTRATES OF OATP1B3, OCT1 AND OCT2

IPN60090 is an inhibitor of the human OATP1B3, OCT1 and OCT2 transporters.

OATP1B3 substrates
Ambrisentan
Atorvastatin
Caspofungin
Cholecystokinin
Cholic acid
Cobimetinib
Conjugated oestrogens
Digoxin
Docetaxel
Gadoxetic acid
Glecaprevir
Grazoprevir
Letermovir
Levosalbutamol
Levomenthol
Liothyronine
Liotrix
Methotrexate
Mycophelate mofetil
Ouabain
Olmesartan
Paclitaxel
Parachlorophenol
Paritaprevir
Pravastatin
Pitavastatin
Rifampicine
Romidepsin
Selexipag
Simeprevir
Technetium mebrofenin
Valsartan
Voxilaprevir

OCT1 substrates
Acyclovir
Amantadine
Bamet-UD2
Bleomycin
Cimetidine
Ciprofloxacin
Furamidine
^{123}I or ^{131}I m-iodobenzylguanidine
Imatinib
Irinotecan
Levodopa
Lamivudine
Lamotrigine
Metformin
Mitoxantrone
O-desmethyltramadol
Ondansetron
Oxaliplatin
Pancuronium
Pentamidine
Pramipexole
Quinidine
Rocuronium
Sorafenib
Sulpiride
Tropisetron
YM155

OCT2 substrates
Amantadine
Amiloride
Cimetidine
Creatinine
Dofetilide
Dopamine
Famotidine
Memantine
Metformin
Oxaliplatin
Pindolol
Procainamide
Ranitidine
Trimethoprim
Varenicline

The above tables are not all inclusive.

The above lists were compiled from the following sources:

- OATP1B3: DrugBank https://www.drugbank.ca/biodb/bio_entities/BE0003659
- OCT1: Lozano E, Herraez E, Briz O, et al. Role of the plasma membrane transporter of organic cations OCT1 and its genetic variants in modern liver pharmacology. Biomed Res Int 2013(1):692071 [22].
- OCT2: https://www.straighthealthcare.com/organic-cation-transporter-2.html

Appendix 9 DESCRIPTION OF THE iRECIST PROCESS FOR ASSESSMENT OF DISEASE PROGRESSION

Assessment at Screening and Prior to RECIST 1.1 Progression

Until radiographic disease progression based on RECIST 1.1, there is no distinct iRECIST assessment.

Assessment and Decision at RECIST 1.1 Progression

For patients who show evidence of radiological progressive disease by RECIST v1.1 as determined by the investigator, the investigator will decide whether to continue a patient on study treatment until repeat imaging is obtained (using iRECIST for patient management). This decision by the investigator should be based on the patient's overall clinical condition.

Clinical stability is defined as the following:

- absence of symptoms and signs indicating clinically significant progression of disease
- no decline in ECOG performance status
- no requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any patient deemed **clinically unstable** should be discontinued from study treatment at site-assessed first radiologic evidence of progressive disease, and is not required to have repeat tumour imaging for confirmation of progressive disease by iRECIST.

If the investigator decides to continue treatment, the participant may continue to receive study treatment and the tumour assessment should be repeated 4 to 8 weeks later to confirm progressive disease by iRECIST, per investigator assessment. Images should continue to be sent in to the central imaging vendor for potential retrospective Blinded Independent Central Review.

Tumour flare may manifest as any factor causing radiographic progression per RECIST v1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥20% and ≥5 mm from nadir
  - Note: the iRECIST publication uses the terminology "sum of measurements", but "sum of diameters" will be used in this protocol, consistent with the original RECIST v1.1 terminology.
- Unequivocal progression of non-target lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including unconfirmed progressive disease (iUPD) and confirmed progressive disease (iCPD). For the purposes of iRECIST assessment, the first visit showing progression according to RECIST v1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and nontarget lesions identified at baseline by RECIST v1.1 will be assessed as usual.

New lesions will be classified as measurable or nonmeasurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST v1.1. From measurable new lesions, up to five lesions total (up to two per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated, and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Nontarget.

Assessment at the Confirmatory Imaging

On the confirmatory imaging, the patient will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening
  - For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm, compared to any prior iUPD timepoint
  - For nontarget lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD timepoint; this does not have to meet the "unequivocal" standard of RECIST v1.1
  - For new lesions, worsening is any of these:
    - An increase in the new lesion sum of diameters by ≥5 mm from a prior iUPD timepoint
    - Visible growth of new nontarget lesions
    - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST v1.1

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) remains above the initial progressive disease threshold (by RECIST v1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the imaging on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation imaging proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial progressive disease threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudoprogression, and the level of suspicion for progression is "reset". This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management Following the Confirmatory Imaging

If repeat imaging does not confirm progressive disease per iRECIST, as assessed by the investigator, and the patient continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, patients will be discontinued from study treatment.

NOTE: If a patient has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the sponsor. In this case, if study treatment is continued, tumour imaging should continue to be performed following the intervals previously outlined and submitted to the central imaging vendor.

Detection of Progression at Visits After Pseudoprogression Resolves

After resolution of pseudoprogression (i.e. achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
  - Sum of diameters reaches the progressive disease threshold (≥20% and ≥5 mm increase from nadir) either for the first time, or after resolution of previous pseudoprogression. The nadir is always the smallest sum of diameters seen during the entire study, either before or after an instance of pseudoprogression.
- Nontarget lesions
  - If nontarget lesions have never shown unequivocal progression, their doing so for the first-time results in iUPD.
  - If nontarget lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of nontarget lesions, taken as a whole.
- New lesions
  - New lesions appear for the first time
  - Additional new lesions appear
  - Previously identified new target lesions show an increase of ≥5 mm in the new lesion sum of diameters, from the nadir value of that sum
  - Previously identified nontarget lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, with one exception: if new lesions occurred at a prior instance of iUPD, and at the confirmatory imaging the burden of new lesions has increased from its smallest value (for new target lesions, the sum of diameters is ≥5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

Additional details about iRECIST are provided in the iRECIST publication.

Appendix 10 PROTOCOL AMENDMENT FORMS

STUDY NUMBER:	D-US-60090-001
PROTOCOL TITLE:	PHASE I OPEN LABEL, DOSE ESCALATION AND DOSE EXPANSION STUDY TO INVESTIGATE THE SAFETY, PHARMACOKINETICS, PHARMACODYNAMICS AND ANTI TUMOUR ACTIVITY OF IPN60090 AS SINGLE AGENT AND IN COMBINATION IN PATIENTS WITH ADVANCED SOLID TUMOURS
AMENDED PROTOCOL VERSION NUMBER & DATE	Version 1.2, 21 December 2018
REASON(S) FOR CHANGES	Changes were made to address the FDA's comments received during the review of the initial IND.

THE FOLLOWING CHANGE(S) IS/ARE PROPOSED: Minor formatting, typos and rephrasing of text to enhance clarity have not been recorded. Any new or amended text added to the protocol is indicated in italic. Removed text is shown as stricken out.

Version Date	VERSION 1.0 29 OCT 2018	VERSION 1.2 21 DEC 2018
Section	**WAS**	**IS**
Synopsis 3.1 3.1.3	- Dose Expansion Cohort 6: KEAP1 or NRF2 wild-type tumours - Dose Expansion Cohort 9: KEAP1 or NRF2 wild-type tumours	- Dose Expansion Cohort 6: KEAP1 or NRF2 wild-type tumours *with any level of ASNS expression* - Dose Expansion Cohort 9: KEAP1 or NRF2 wild-type tumours *with any level of ASNS expression*
Synopsis 3.1.2.1	Part A monotherapy dose-escalation will enrol single-patient cohorts for the first three dose levels (if no Grade 2 adverse event (AE) ~~clearly not due to underlying disease~~ or DLT is observed) and then cohorts of three patients each at the predefined dose levels. If a Grade 2 AE ~~clearly not due to underlying disease~~ or a DLT is observed in a single patient cohort (first three dose levels), two additional patients will be added at this dose level with the same rules for escalation and de-escalation as the cohorts of three patients.	Part A monotherapy dose-escalation will enrol single-patient cohorts for the first three dose levels (if no Grade 2 adverse event (AE) *that is at least possibly related to the study drug(s)* or DLT is observed) and then cohorts of three patients each at the predefined dose levels. If a Grade 2 AE *that is at least possibly related to the study drug(s)* or a DLT is observed in a single patient cohort (first three dose levels), two additional patients will be added at this dose level with the same rules for escalation and de-escalation as the cohorts of three patients.
Synopsis 3.1.2.1 3.1.2.2 3.1.2.3	**DLT Criteria** The DLTs for Part … are defined for the investigational medicinal product (IMP)-related related AEs according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) …	**DLT Criteria** The DLTs for Part … are defined for the investigational medicinal product (IMP)-*related, probably related or possibly* related AEs according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) …

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Section	**WAS**	**IS**
3.1.2.1 3.1.2.2 3.1.2.3	• ~~Grade 3 or 4~~ Febrile neutropenia (absolute neutrophil count (ANC) <1000/mm^3 with a single temperature episode of 38.3°C or a sustained temperature of 38°C for >1 hour). • Grade 3 or higher nonhaematological toxicity ~~lasting more than 72 hours despite adequate supportive care~~ excluding: - Grade 3 nausea, vomiting or diarrhoea for ~~more~~ than 72 hours with adequate supportive care. - Grade 3 fatigue lasting ~~more~~ than a week. - Grade 3 or higher electrolyte abnormality that lasts for ~~more~~ than 72 hours that is not clinically complicated and resolves spontaneously or with conventional medical interventions. - Grade 3 or higher amylase or lipase not associated with ~~symptoms or~~ clinical manifestations of pancreatitis.	• Febrile neutropenia *of any grade* (absolute neutrophil count (ANC) <1000/mm^3 with a single temperature episode of 38.3°C or a sustained temperature of 38°C for >1 hour). • *ALT/AST ≥3×ULN with total bilirubin ≥2×ULN without elevation of alkaline phosphatase and no other reasonable explanation for the abnormality (Hy's law criteria).* • Grade 3 or higher nonhaematological toxicity excluding: - Grade 3 nausea, vomiting or diarrhoea for *less* than 72 hours with adequate supportive care. - Grade 3 fatigue lasting *less* than a week. - Grade 3 or higher electrolyte abnormality that lasts for *less* than 72 hours that is not clinically complicated and resolves spontaneously or with conventional medical interventions. - Grade 3 or higher amylase or lipase lasting *less than 72 hours and* not associated with clinical manifestations of pancreatitis.
Synopsis 3.1.2.1 3.1.2.2 3.1.2.3 3.6	Patients who experience a DLT (or other study treatment ~~related toxicity~~) will be permitted to continue to receive study treatment at a lower dose level than the dose at which the DLT was observed, at the discretion of the investigator (see Section 6.4.4) and will be followed for safety.	Patients who experience a DLT (or other *toxicities considered related, probably related or possibly related to* the study treatment) will be permitted to continue to receive study treatment at a lower dose level than the dose at which the DLT was observed, at the discretion of the investigator (see Section 6.4.4) and will be followed for safety.

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3.6	All patients will then be followed post end of treatment at 30 days ±3 days for the end of treatment visit, at 180 days ±14 days for the safety follow-up visit and then every 3 months +/-14 days for survival until the end of the study.	All patients will then be followed post end of treatment at 30 days ±3 days *(for Parts A and C) and 90±3 days (for Part B)* for the end of treatment visit, at 180 days ±14 days for the safety follow-up visit and then every 3 months +/-14 days for survival until the end of the study.
Synopsis 4.1.1	(3) Histologically or cytologically confirmed advanced solid tumours including tumours known to harbour KEAP1 and NRF2 mutations or have low ASNS expression levels (immunohistochemistry (IHC) Grade 0 or 1). (6) Fresh or archival tumour tissue is available for mutation and biomarker analysis. In addition archival tumour tissue from time of initial diagnosis will be collected if available.	(3) Histologically or cytologically confirmed advanced solid tumours including tumours known to harbour KEAP1 and NRF2 mutations or have low ASNS expression levels (immunohistochemistry (IHC) Grade 0 or 1). - *In dose escalations of all Parts, patients may be KEAP1/NRF2 wild-type or mutated and have tumours with any level of ASNS expression. For dose expansions, see specific inclusion criteria per Part below.* (6) Fresh or archival tumour tissue *must be* available for mutation and biomarker analysis. *Patients should not be put at undue risk to obtain fresh tumour biopsy. Procedures more invasive than core biopsy should not be used. Procedures to obtain biopsy should only be performed if the risk is minimal (no greater than 2% risk of serious or severe complications). If available,* archival tumour tissue from time of initial diagnosis will be collected *in addition to the most recent biopsy (archival or fresh).*
Synopsis 4.1.3	(B2) Patients with following tumour types will be recruited during dose expansion only: (c) KEAP1 or NRF2 wild-type tumours	(B2) Patients with following tumour types will be recruited during dose expansion only: (c) KEAP1 or NRF2 wild-type tumours *with any level of ASNS expression* Note: Section 4.1.3. B1 should read B2
Synopsis 4.1.4	(C2) Patients with following tumour types will be recruited during dose expansion only: (c) KEAP1 or NRF2 wild-type tumours	(C2) Patients with following tumour types will be recruited during dose expansion only: (c) KEAP1 or NRF2 wild-type tumours *with any level of ASNS expression*

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Section	**WAS**	**IS**
4.3.3	Determining an AE to be a potential DLT is independent of the investigator's causality assessment, but the event must be related to IMP administration (i.e. after IMP administration through the follow-up visit), clinically significant in the opinion of the investigator and of at least moderate severity.	Determining an AE to be a potential DLT is independent of the investigator's causality assessment, but the event must be *at least possibly* related to IMP administration (i.e. after IMP administration through the follow-up visit), clinically significant in the opinion of the investigator and of at least moderate severity.
Table 12		Header updated to reflect changes in Section 3.6. Footnote o: *added text:* *Fresh tumour biopsy should only be performed if the risk of the procedure is minimal (no greater than 2% risk of serious or severe complications).*
8.1.2.2	• **Related**: reports including good reasons and sufficient information (for example plausible time sequence, dose response relationship, pharmacology, positive dechallenge and/or rechallenge) to assume a causal relationship with IMP administration in the sense that it is plausible, conceivable or likely.	• **Related**: reports including good reasons and sufficient information (for example plausible time sequence, dose response relationship, pharmacology, positive dechallenge and/or rechallenge) to assume a causal relationship with IMP administration in the sense that it is plausible, conceivable or likely. *Since attribution of an observed toxicity to a new drug can be uncertain, related events should include any toxicities considered related, probably related or possibly related to the drug.*
10.2.8	Fresh tumour biopsy is performed at the screening visit, Cycle 1 Day 15, and EOS/EW (separate consent is required). Archival tumour tissue post the most recent line of treatment is acceptable in lieu of fresh biopsy at screening.	*Fresh or archival tumour tissue must be available for mutation and biomarker analysis.* Fresh tumour biopsy is performed at the screening visit, Cycle 1 Day 15, and EOS/EW (separate consent is required). Archival tumour tissue post the most recent line of treatment is acceptable in lieu of fresh biopsy at screening. *In case no archival tumour tissue is available in a patient, fresh biopsy should be performed only if the procedure to obtain biopsy has a serious/severe complication risk no greater than 2%. Procedures more invasive than core biopsy should not be used.*

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Section	**WAS**	**IS**
Synopsis 11.2.1.1	The design will proceed with accelerated titration up to DL3, i.e. cohorts of one will be enrolled until either the third dose level is evaluated, a Grade 2 AE ~~clearly not related to the underlying disease~~ occurs, or a DLT is observed (whichever occurs first). If a Grade 2 AE ~~clearly not due to underlying disease~~ or a DLT is observed in a single patient cohort (i.e. in one of the first three dose levels), two additional patients will be added at this dose level with the same rules for escalation and de-escalation as the cohorts of three patients detailed below.	The design will proceed with accelerated titration up to DL3, i.e. cohorts of one will be enrolled until either the third dose level is evaluated, a Grade 2 AE *that is at least possibly related to the study drug(s)* occurs, or a DLT is observed (whichever occurs first). If a Grade 2 AE *that is at least possibly related to the study drug(s)* or a DLT is observed in a single patient cohort (i.e. in one of the first three dose levels), two additional patients will be added at this dose level with the same rules for escalation and de-escalation as the cohorts of three patients detailed below.

STUDY NUMBER:	D-US-60090-001
PROTOCOL TITLE:	A PHASE I OPEN LABEL, DOSE ESCALATION AND DOSE EXPANSION STUDY TO INVESTIGATE THE SAFETY, PHARMACOKINETICS, PHARMACODYNAMICS AND ANTI-TUMOUR ACTIVITY OF IPN60090 AS SINGLE AGENT AND IN COMBINATION IN PATIENTS WITH ADVANCED SOLID TUMOURS
AMENDED PROTOCOL VERSION NUMBER & DATE	Amendment 1.0, Version 2.0, 24 May 2019

The Following Amendment(S) Is/Are Proposed:

Version Date		**VERSION 1.2 21 DEC 2018**	**VERSION 2.0 24 MAY 2019**
Page	**Section**	**WAS**	**IS**
1	Title Page	PHASE I OPEN LABEL, DOSE ESCALATION AND DOSE EXPANSION STUDY TO INVESTIGATE THE SAFETY, PHARMACOKINETICS, PHARMACODYNAMICS AND ANTI-TUMOUR ACTIVITY OF IPN60090 AS SINGLE AGENT AND IN COMBINATION IN PATIENTS WITH ADVANCED SOLID TUMOURS	**A** PHASE I OPEN LABEL, DOSE ESCALATION AND DOSE EXPANSION STUDY TO INVESTIGATE THE SAFETY, PHARMACOKINETICS, PHARMACODYNAMICS AND ANTI-TUMOUR ACTIVITY OF IPN60090 AS SINGLE AGENT AND IN COMBINATION IN PATIENTS WITH ADVANCED SOLID TUMOURS
1	Title Page	ClinicalTrials.gov number: Not yet available	ClinicalTrials.gov number: ~~Not yet available~~ **NCT03894540**
5	Synopsis	This study will evaluate the safety, the pharmacokinetics (PK), pharmacodynamics (PD) and anti-tumour activity of IPN60090 as a single agent (Part A) and in combination with pembrolizumab (Part B) or paclitaxel (Part C) in patients with advanced solid tumours. Specific objectives and corresponding endpoints for the study are outlined below.	This study will evaluate the safety, the pharmacokinetics (PK), pharmacodynamics (PD) and anti-tumour activity of IPN60090 as a single agent (Part A) and in combination with pembrolizumab (Part B) or paclitaxel (Part C) in patients with advanced solid tumours. **Part D will evaluate the safety of IPN60090 as a single agent and explore the effect of food on IPN60090 PK profile.** Specific objectives and corresponding endpoints for the study are outlined below.
5	Synopsis	• To assess the safety and tolerability of oral IPN60090 as a single agent (Part A) and in combination therapy with pembrolizumab (Part B) or paclitaxel (Part C).	• To assess the safety and tolerability of oral IPN60090 as a single agent (Part A **and Part D**) and in combination therapy with pembrolizumab (Part B) or paclitaxel (Part C).

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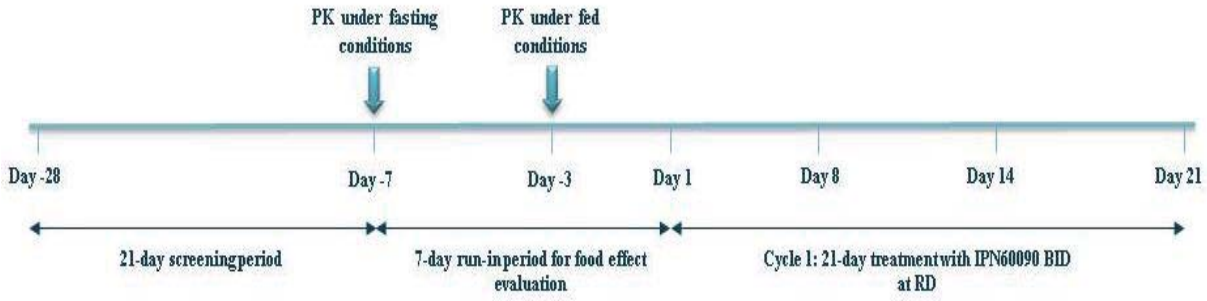
5	Synopsis	• To assess the preliminary anti-tumour activity of IPN60090 as a single agent (Part A) and in combination with pembrolizumab (Part B) or paclitaxel (Part C) in patients with or without biomarker selected specific tumour types.	• To assess the preliminary anti-tumour activity of IPN60090 as a single agent (Part A **and Part D**) and in combination with pembrolizumab (Part B) or paclitaxel (Part C) in patients with or without biomarker selected specific tumour types.
5	Synopsis	• To characterise the PK and PD profile of IPN60090 as a single agent (Part A) and in combination with pembrolizumab (Part B) or paclitaxel (Part C).	• To characterise the PK and PD profile of IPN60090 as a single agent (Part A **and Part D**) and in combination with pembrolizumab (Part B) or paclitaxel (Part C).
5	Synopsis	New text	• **To assess the effect of food on the PK profile of a single administration of IPN60090 (Part D).**
6	Synopsis	As summarised in Figure 1, the study will be divided into three parts.	As summarised in Figure 1, the study will be divided into ~~three~~ **four** parts.
6	Synopsis	Figure 1 IPN60090: Summary of Early Clinical Development	Figure 1 IPN60090: Summary of Early Clinical Development Amended as follows to include Part D:

PART D



ASNS=asparagine synthetase; **BID=bis in die (twice daily);** BOIN= Bayesian optimal interval; HGSOC= high-grade serous ovarian cancer; KEAP1=Kelch-like ECH-associated protein 1; NRF2=nuclear factor erythroid 2–related factor 2; NSCLC=non-small cell lung carcinoma; Ph.=pharmacologically; RD=recommended dose

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7	Synopsis	New text	**Part D: This cohort will evaluate the safety of IPN60090 administered as a single agent and explore the effect of a moderate fat meal on the PK profile of IPN60090 administered as a single dose under fasting and fed conditions at the RD as defined by the Safety Review Committee (SRC).**

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8	Synopsis	New text	**At the end of each part, up to two dose levels may be repeated in order to reach a total of 18 patients at each dose level to collect more PD/PK information to better define the RD. Decision to repeat a dose level will be made by the SRC. Safety data from these additional patients will not be included in the BOIN design to determine MTD but will be evaluated by the SRC and ultimately be taken into consideration for RD selection.**
9	Synopsis	At all dose levels, IPN60090 will be administered orally BID starting from Day 1 of each 21-day cycle and pembrolizumab will be administered as one intravenous (i.v.) infusion every 21 days starting from Day 1 of each cycle. The predefined dose-escalation plan is described in Table 2.	At all dose levels, IPN60090 will be administered orally BID starting from Day 1 of each 21-day cycle and pembrolizumab will be administered as one intravenous (i.v.) infusion every 21 days **(±1 day in Cycle 1 and ±3 days in all other cycles)** starting from Day 1 of each cycle. The predefined dose-escalation plan is described in Table ~~2~~ **3**.
10	Synopsis	New text	**At the end of each part, up to two dose levels may be repeated in order to reach a total of 18 patients at each dose level to collect more PD/PK information to better define the RD. Decision to repeat a dose level will be made by the SRC. Safety data from these additional patients will not be included in the BOIN design to determine MTD but will be evaluated by the SRC and ultimately be taken into consideration for RD selection.**
11	Synopsis	At all dose levels, IPN60090 will be administered orally BID starting from Day 1 of each 21-day cycle and paclitaxel will be administered as one i.v. infusion every 21 days starting from Day 1 of each cycle. The predefined dose-escalation plan is described in Table 3.	At all dose levels, IPN60090 will be administered orally BID starting from Day 1 of each 21-day cycle and paclitaxel will be administered as one i.v. infusion every 21 days **(±1 day in Cycle 1 and ±3 days in all other cycles)** starting from Day 1 of each cycle. The predefined dose-escalation plan is described in Table ~~3~~ **4**.

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Page	**Section**	**WAS**	**IS**
11	Synopsis	New text	**At the end of each part, up to two dose levels may be repeated in order to reach a total of 18 patients at each dose level to collect more PD/PK information to better define the RD. Decision to repeat a dose level will be made by the SRC. Safety data from these additional patients will not be included in the BOIN design to determine MTD but will be evaluated by the SRC and ultimately be taken into consideration for RD selection.**
13	Synopsis	New text	***Part D – Food Effect Assessment*** **Part D will start at the end of Part A dose escalation. Patients in Part D will not be part of the dose escalation and MTD assessment.** **Food effect evaluation will be conducted in patients with biomarker-positive and biomarker-negative advanced solid tumours.** **These patients will not be selected for KEAP1/NRF2 mutation status and may be wild-type or mutated.** **Patients may have tumours with any level of ASNS expression. Eligibility criteria for Part D will be the same as the criteria for Part A dose escalation.** **After screening, eight patients will enter a run-in period of 7 days.** **Full PK profiles will be obtained on Day -7 under fasting conditions and Day -3 after a moderate fat meal to assess the food effect on IPN60090 PK profile.** **In Part D, the moderate fat meal is defined as the following: total calories of 500 to 750 kCal including 30 to 35% fat.** **After the run-in period, patients will receive IPN60090 as a single agent administered orally BID (every 12 hours), during or after a meal, starting from Day 1 at the single agent RD. Patients in Part D will follow the same schedule of assessments as described for Part A (with the exception of the urine sampling for PK).**

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14	Synopsis	Patients enrolled in monotherapy Part A may receive combination treatment with either pembrolizumab or with paclitaxel upon progression on IPN60090 monotherapy at the discretion of the investigator and with the approval of the sponsor. These patients will need to satisfy eligibility criteria for combination therapy prior to initiating treatment, and will be followed for safety and efficacy in a separate cohort.	Patients enrolled in monotherapy Part A **or Part D** may receive combination treatment with either pembrolizumab or with paclitaxel upon progression on IPN60090 monotherapy at the discretion of the investigator and with the approval of the sponsor. These patients will need to satisfy eligibility criteria for combination therapy prior to initiating treatment, and will be followed for safety and efficacy in a separate cohort.
14	Synopsis	New text	***Food Effect Assessment*** **Part D (single agent): Eight patients for preliminary food effect assessment.**
15	Synopsis	(6) Fresh or archival tumour tissue must be available for mutation and biomarker analysis. Patients should not be put at undue risk to obtain fresh tumour biopsy. Procedures more invasive than core biopsy should not be used. Procedures to obtain biopsy should only be performed if the risk is minimal (no greater than 2% risk of serious or severe complications). If available, archival tumour tissue from time of initial diagnosis will be collected in addition to the most recent biopsy (archival or fresh).	(6**a**) Fresh **and**/or archival tumour tissue **from the biopsy obtained between the completion of the most recent line of treatment until study entry** must be available for mutation and biomarker analysis **unless KEAP1/NRF2 mutations were present in any previous biopsy, in which case, no further biopsy is required. For ovarian cancer patients, both archival biopsies obtained between the completion of the most recent line of treatment until study entry and fresh biopsies must be available to evaluate the evolution of ASNS levels over time**. Patients should not be put at undue risk to obtain fresh tumour biopsy. Procedures more invasive than core biopsy should not be used. Procedures to obtain biopsy should only be performed if the risk is minimal (no greater than 2% risk of serious or severe complications). If available, archival tumour tissue from time of initial diagnosis will be collected in addition to the most recent biopsy (archival **and**/or fresh).

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Page	**Section**	**WAS**	**IS**
15	Synopsis	(8) Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) ≤1.	(8a) Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) ≤1 **and a Royal Marsden Hospital (RMH) score of 0 or 1**.
17	Synopsis	New text	***Part D Specific Inclusion Criteria*** **(D1) Patients must be able to consume a moderate fat meal.**
18	Synopsis	New text	**(16) Patients unwilling to comply with protocol requirements related to the assigned part.**
18	Synopsis	Treatment with strong cytochrome P450 subtype 2C8 (CYP2C8) inhibitors and inducers within the 7 days of the paclitaxel infusion.	**(C1)** Treatment with strong cytochrome P450 subtype 2C8 (CYP2C8) inhibitors and inducers within the 7 days of the paclitaxel infusion.
18	Synopsis	New text	***Part D Specific Exclusion Criteria*** **(D1) Treatment with drugs that can alter the absorption of IPN60090 by affecting gastrointestinal motility or by changing the gastric pH during the run-in period (Day -7 to Day -3) of Part D.** **(D2) Patients suffering from conditions which are likely to adversely affect gastrointestinal motility and/or transit (for example, diarrhoea, vomiting or nausea, gastroparesis, irritable bowel syndrome and malabsorption) or patients with gastrointestinal resection (e.g. partial or total gastrectomy) likely to interfere with absorption of study treatment. Patients with Type 1 diabetes and hypercholesterolaemia are excluded.** **(D3) Patients unable to fast for up to 14 hours.**

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18	Synopsis	**Part B dose escalation**: the starting dose of IPN60090 will be a dose showing pharmacological activity (at least 50% inhibition of Glu:Gln ratio in PBMC at C_{trough} (12 hrs postdose) on Day 14 in 66% of patients at this dose level) and good tolerability as identified in Part A. IPN60090 intake should be performed at least 2 hours before the start of pembrolizumab infusion. The dose of pembrolizumab will be fixed at 200 mg Q3W (or according to the local approved label for specific tumour types) as an i.v. infusion.	**Part B dose escalation**: the starting dose of IPN60090 will be a dose showing pharmacological activity (at least 50% inhibition of Glu:Gln ratio in PBMC at C_{trough} (12 hrs postdose) on Day 14 in 66% of patients at this dose level) and good tolerability as identified in Part A. IPN60090 intake should be performed at least 2 hours before the start of pembrolizumab infusion. The dose of pembrolizumab will be fixed at 200 mg ~~Q3W~~ **every 21 days (±1 day in Cycle 1 and ±3 days in all other cycles)** (or according to the local approved label for specific tumour types) as an i.v. infusion.
19	Synopsis	The dose of paclitaxel will be fixed at 175 mg/m² or 135 mg/m^2 Q3W (or according to the local approved label for specific tumour types) administered as an i.v. infusion.	The dose of paclitaxel will be fixed at 175 mg/m² or 135 mg/m^2 ~~Q3W~~ **every 21 days (±1 day in Cycle 1 and ±3 days in all other cycles)** (or according to the local approved label for specific tumour types) administered as an i.v. infusion.

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19	Synopsis	New text	**Part D food effect assessment: single administration of IPN60090 at the RD (morning dose only), as defined by the SRC at the end of Part A dose escalation, will be performed during the run-in period at Day -7 and Day -3. On Day -7, IPN60090 will be administered following an overnight fast of at least 10 hours. On Day -3, IPN60090 will be administered 30 minutes after the start of a moderate fat meal. The moderate fat meal should be eaten in 30 minutes or less. On both days, the patients should not consume any food for at least 4 hours after the dose. IPN60090 should be taken with 240 mL (i.e. 8 fluid ounces) of water. Additional water is permitted ad libitum except for the period 1 hour before to 1 hour after administration of the drug product. Substitutions to the test meal can be made after discussion with the sponsor. It is understood that some patients may not be able to consume the entire meal. Study staff should record the percent of the test meal breakfast and the time it takes to be consumed. Then starting from Day 1, patients will receive IPN60090 BID (at the RD as defined by the SRC at the end of Part A) during or after a meal over 21 days (one cycle) as described in Part A.**

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20	Synopsis	• Define the safety and tolerability profile of oral IPN60090 as a single agent (Part A) and in combination therapy with pembrolizumab (Part B) or paclitaxel (Part C) as determined by the incidence and nature of AEs.	• ~~Define the~~ **The** safety and tolerability ~~profile~~ of ~~oral~~ IPN60090 as a single agent (Part A **and Part D**) and in combination ~~therapy~~ with pembrolizumab (Part B) or paclitaxel (Part C) ~~as determined by the incidence and nature~~ **will be assessed by continuous reporting** of AEs **and serious AEs (SAEs), clinical laboratory test results, the presence of anti-pembrolizumab antidrug antibodies (ADA; Part B only), vital signs measurements, ECG and physical examination results and concomitant medication usage**.

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20	Synopsis	• Anti-tumour activity parameters assessed locally (for dose escalation) and centrally (for dose expansion) using RECIST version 1.1 for Part A and C and iRECIST for Part B only, including: - Clinical benefit rate (CBR) is defined as the proportion of patients in whom the Best Overall Response (BOR) is equal to complete response (CR), partial response (PR) or stable disease (SD) lasting at least 12 weeks for Part A and C and equal to immune CR (iCR), immune PR (iPR) or immune SD (iSD) lasting at least 12 weeks for Part B - Objective response rate (ORR) is defined as the proportion of patients in whom the BOR is equal to CR and PR for Part A and C or iCR and iPR for Part B - Disease control rate (DCR) is defined as the proportion of patients in whom the BOR is equal to CR, PR or SD for Part A and C and equal to iCR, iPR or iSD for Part B	• Anti-tumour activity parameters assessed locally (for dose escalation) and centrally (for dose expansion) using RECIST version 1.1 for Part A**,** ~~and~~ C **and** D and iRECIST for Part B only, including: - Clinical benefit rate (CBR) is defined as the proportion of patients in whom the Best Overall Response (BOR) is equal to complete response (CR), partial response (PR) or stable disease (SD) lasting at least 12 weeks for Part A**,** ~~and~~ C **and D** and equal to immune CR (iCR), immune PR (iPR) or immune SD (iSD) lasting at least 12 weeks for Part B - Objective response rate (ORR) is defined as the proportion of patients in whom the BOR is equal to CR and PR for Part A**,** ~~and~~ C **and D** or iCR and iPR for Part B - Disease control rate (DCR) is defined as the proportion of patients in whom the BOR is equal to CR, PR or SD for Part A**,** ~~and~~ C **and D** and equal to iCR, iPR or iSD for Part B

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20	Synopsis	• Pharmacokinetic parameters of IPN60090, including but not limited to maximum observed plasma concentration (C_{max}), time to maximum observed plasma concentration (T_{max}), C_{trough}, area under the plasma concentration-time curve (AUC), elimination half-life ($t_{1/2}$), apparent total clearance from plasma (CL/F), apparent volume of distribution (V/F) of IPN60090 (Parts A to C).	• Pharmacokinetic parameters of IPN60090, including but not limited to maximum observed plasma concentration (C_{max}), time to maximum observed plasma concentration (T_{max}), C_{trough}, area under the plasma concentration-time curve (AUC), elimination half-life ($t_{1/2}$), apparent total clearance from plasma (CL/F), apparent volume of distribution (V/F) of IPN60090 (Parts A to ~~C~~ **D**).
20	Synopsis	New text	• **Describe the PK of a single dose of IPN60090 administered in fed state (Day -3) relative to fasted state (Day -7) using the following PK parameters: C_{max}, AUC, T_{max}, $t_{1/2}$, CL/F, V/F (Part D).**
21	Synopsis	New text	**Food effect population: All patients in Part D who have received IPN60090 under fasting and fed conditions (Day -7 and Day -3), have consumed ≥80% of the moderate fat meal on Day -3, and who have no major protocol deviation affecting the PK variables and who have a sufficient number of IPN60090 plasma concentrations to estimate the main PK parameters (C_{max}, T_{max} and $AUC_{0\text{-last}}$)** **Pharmacodynamic population: All patients who have at least one PD endpoints measurement. PD endpoints refer to target engagement levels (Glu:Gln ratio in PBMC).**

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22	Synopsis	New text	***Food effect assessment – Part D*** **The assessment of food effect will be based upon the ratio of the population geometric means (fed versus fasted, i.e. Day -3 versus Day -7) for the PK parameters (C_{max} and AUC). The data will be transformed prior to analysis using a logarithmic transformation. T_{max} between fed and fasted states will be compared using a non-parametric test such as the Wilcoxon test. Descriptive statistics of other PK parameters will be presented both in fasting and fed conditions.**
23	Synopsis	New text	***Food Effect Assessment - Part D*** **The sample size (n=8) is not based on statistical calculation. A sample size of eight patients allows for a preliminary assessment of the potential effect of food on the PK of IPN60090.**
36	List of abbreviations	New text	**RMH Royal Marsden Hospital**
48/49	1.5.5	New text	**1.5.5 Food Effect Assessment Rationale** **Part D will explore the effect of food on a single administration of IPN60090 (patients will receive the treatment under fed and fasted conditions). A moderate fat meal has been selected since patients with late stage cancer may have difficulties eating a high-fat meal as described in FDA Guidance for Industry *Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations.* For ethical reasons, after the run-in period designed to evaluate the effect of food on IPN60090 PK profile, patients will be allowed to receive IPN60090 BID as described in Part A.**

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49	1.6	• HGSOC with low expression levels of ASNS (approximatively 15% of HGSOC tumours). Tumours will be classified as ASNS low using a qualitative analysis of ASNS staining in tumour biopsies with a score of 0 or 1+ depending on the intensity (negative or weak) and pervasiveness of staining [18]. A quantitative method of ASNS staining using H SCORE will also be explored to evaluate the optimal range of H SCORE that would be associated with a clinical benefit.	• HGSOC with low expression levels of ASNS (approximatively 15% of HGSOC tumours). Tumours will be classified as ASNS low using a qualitative analysis of ASNS staining in tumour biopsies with a score of 0 or 1+ depending on the intensity (negative or weak) and pervasiveness of staining [18]. A quantitative method of ASNS staining using H SCORE ~~will~~ **may** also be explored to evaluate the optimal range of H SCORE that would be associated with a clinical benefit.
49	1.6	The dose escalation study will be performed in biomarker unselected patients with solid tumours to establish the RD of IPN60090. Patients will be actively screened for putative predictive biomarkers of response to IPN60090, for example KEAP1 and NRF2 mutations, and low ASNS expression levels for this trial. A retrospective analysis of the correlation between KEAP1/NRF2 mutations versus wild-type or $ASNS^{low}$ versus $ASNS^{high}$ tumours and the sensitivity to IPN60090 will be performed. Patients will be enrolled in three separate parts either: • Part A: IPN60090 monotherapy, or • Part B: IPN60090 + pembrolizumab, or • Part C: IPN60090 + paclitaxel	The dose escalation study **and the food assessment study** will be performed in biomarker unselected patients with solid tumours to establish the RD of IPN60090. Patients will be actively screened for putative predictive biomarkers of response to IPN60090, for example KEAP1 and NRF2 mutations, and low ASNS expression levels for this trial. A retrospective analysis of the correlation between KEAP1/NRF2 mutations versus wild-type or $ASNS^{low}$ versus $ASNS^{high}$ tumours and the sensitivity to IPN60090 will be performed. Patients will be enrolled in ~~three~~ **four** separate parts either: • Part A: IPN60090 monotherapy, or • Part B: IPN60090 + pembrolizumab, or • Part C: IPN60090 + paclitaxel**, or** • **Part D: IPN60090 monotherapy, food effect part**

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51	2.1	This is a phase I first in human dose escalation study with multiple expansion cohorts of IPN60090. The dose escalation part will investigate the safety and tolerability, and provide a better understanding of the mechanism of action of IPN60090 and of the potential of selected biomarkers to predict the clinical outcome in monotherapy as well as in combination with other cancer therapies. This study will also generate the first PK data in human and PK/PD correlation data that will support the choice of the RD. The dose expansion part will further define safety and tolerability of IPN60090 alone and in combination and investigate the preliminary anti-tumour activity.	This is a phase I first in human dose escalation study with multiple expansion cohorts of IPN60090. The dose escalation part will investigate the safety and tolerability, and provide a better understanding of the mechanism of action of IPN60090 and of the potential of selected biomarkers to predict the clinical outcome in monotherapy as well as in combination with other cancer therapies. This study will also generate the first PK data in human and PK/PD correlation data that will support the choice of the RD. **An additional cohort will explore the effect of food on IPN60090 PK profile.** The dose expansion part will further define safety and tolerability of IPN60090 alone and in combination and investigate the preliminary anti-tumour activity.
51	2.2	This study will evaluate the safety, PK, PD and anti-tumour activity of IPN60090 as a single agent (Part A) and in combination with pembrolizumab (Part B) or paclitaxel (Part C) in patients with advanced solid tumours. Specific objectives and corresponding endpoints for the study are outlined below.	This study will evaluate the safety, PK, PD and anti-tumour activity of IPN60090 as a single agent (Part A) and in combination with pembrolizumab (Part B) or paclitaxel (Part C) in patients with advanced solid tumours. **Part D will evaluate the safety of IPN60090 as a single agent and explore the effect of food on IPN60090 PK profile.** Specific objectives and corresponding endpoints for the study are outlined below.
51	2.2.1	• To assess the safety and tolerability of oral IPN60090 as a single agent (Part A) and in combination therapy with pembrolizumab (Part B) or paclitaxel (Part C).	• To assess the safety and tolerability of oral IPN60090 as a single agent (Part A **and Part D**) and in combination therapy with pembrolizumab (Part B) or paclitaxel (Part C).
51	2.2.2	• To assess the preliminary anti-tumour activity of IPN60090 as a single agent (Part A) and in combination with pembrolizumab (Part B) or paclitaxel (Part C) in patients with or without biomarker selected specific tumour types.	• To assess the preliminary anti-tumour activity of IPN60090 as a single agent (Part A **and Part D**) and in combination with pembrolizumab (Part B) or paclitaxel (Part C) in patients with or without biomarker selected specific tumour types.

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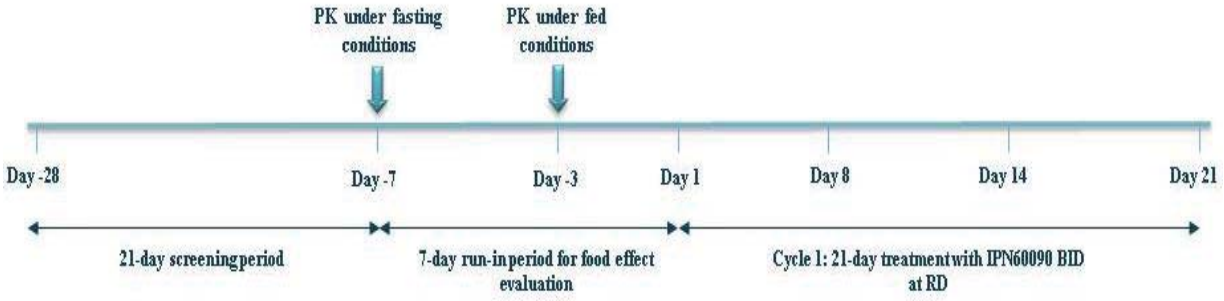
51	2.2.2	• To characterise the pharmacokinetic and pharmacodynamic profile of IPN60090 as a single agent (Part A) and in combination with pembrolizumab (Part B) or paclitaxel (Part C).	• To characterise the ~~pharmacokinetic~~ PK and ~~pharmacodynamic~~ PD profile of IPN60090 as a single agent (Part A **and Part D**) and in combination with pembrolizumab (Part B) or paclitaxel (Part C).
51	2.2.2	New text	• **To assess the effect of food on the PK profile of a single administration of IPN60090 (Part D).**
53	3.1	As summarised in Figure 5, the study will be divided into three parts.	As summarised in Figure 5, the study will be divided into ~~three~~ **four** parts.
53	3.1	Figure 5 IPN60090: Summary of Early Clinical Development	Figure 5 IPN60090: Summary of Early Clinical Development Amended as follows to include Part D:

PART D



ASNS=asparagine synthetase; BID=bis in die (twice daily); BOIN= Bayesian optimal interval; HGSOC= high-grade serous ovarian cancer; KEAP1=Kelch-like ECH-associated protein 1; NRF2=nuclear factor erythroid 2–related factor 2; NSCLC=non-small cell lung carcinoma; Ph.=pharmacologically; RD=recommended dose

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55	3.1	New text	**Part D: This cohort will evaluate the safety of IPN60090 administered as a single agent and explore the effect of a moderate fat meal on the PK profile of IPN60090 administered as a single dose under fasting and fed conditions at the RD as defined by the SRC**.
55	3.1.1	New text	***Food Effect Assessment*** **Part D: Eight patients for preliminary food effect assessment.**

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55	3.1.2.1	New text	**Dose levels provided are examples and after the starting dose, the dose level will be determined by the SRC. After each SRC meeting, the tested dose level can be escalated, de-escalated or extended as indicated per BOIN.**
56	3.1.2.1	New text	**At the end of each part, up to two dose levels may be repeated in order to reach a total of 18 patients at each dose level to collect more PD/PK information to better define the RD. Decision to repeat a dose level will be made by the SRC. Safety data from these additional patients will not be included in the BOIN design to determine MTD but will be evaluated by the SRC and ultimately be taken into consideration for RD selection.**
58/59	3.1.2.2	At all dose levels, IPN60090 will be administered orally BID starting from Day 1 of each 21-day cycle and pembrolizumab will be administered as one intravenous (i.v.) infusion every 21 days starting from Day 1 of each cycle. The predefined dose-escalation plan is described in Table 7.	At all dose levels, IPN60090 will be administered orally BID starting from Day 1 of each 21-day cycle and pembrolizumab will be administered as one intravenous (i.v.) infusion every 21 days **(±1 day in Cycle 1 and ±3 days in all other cycles)** starting from Day 1 of each cycle. The predefined dose-escalation plan is described in Table ~~7~~ **8**.
59	3.1.2.2	New text	**At the end of each part, up to two dose levels may be repeated in order to reach a total of 18 patients at each dose level to collect more PD/PK information to better define the RD. Decision to repeat a dose level will be made by the SRC. Safety data from these additional patients will not be included in the BOIN design to determine MTD but will be evaluated by the SRC and ultimately be taken into consideration for RD selection.**

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61	3.1.2.3	At all dose levels, IPN60090 will be administered orally BID starting from Day 1 of each 21-day cycle and paclitaxel will be administered as one i.v. infusion every 21 days starting from Day 1 of each cycle. The predefined dose-escalation plan is described in Table 8.	At all dose levels, IPN60090 will be administered orally BID starting from Day 1 of each 21-day cycle and paclitaxel will be administered as one i.v. infusion every 21 days **(±1 day in Cycle 1 and ±3 days in all other cycles)** starting from Day 1 of each cycle. The predefined dose-escalation plan is described in Table ~~8~~ **9**.
61/62	3.1.2.3	New text	**At the end of each part, up to two dose levels may be repeated in order to reach a total of 18 patients at each dose level to collect more PD/PK information to better define the RD. Decision to repeat a dose level will be made by the SRC. Safety data from these additional patients will not be included in the BOIN design to determine MTD but will be evaluated by the SRC and ultimately be taken into consideration for RD selection.**
63/64	3.1.3	New text	**3.1.3 Food Effect Assessment – Part D** **Part D will start at the end of Part A dose escalation. Patients in Part D will not be part of the dose escalation and MTD assessment. Food effect evaluation will be conducted in patients with biomarker-positive and biomarker-negative advanced solid tumours.** **These patients will not be selected for KEAP1/NRF2 mutation status and may be wild-type or mutated. Patients may have tumours with any level of ASNS expression. Eligibility criteria for Part D will be the same as the criteria for Part A dose escalation.** **After screening, eight patients will enter a run-in period of 7 days:** • **At Day -7, patients will receive a single administration of IPN60090 at the RD (as defined by the SRC at the end of Part A dose escalation) following an overnight fast of at least 10 hours. The patients should**

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			not consume any food for at least 4 hours after the dose. IPN60090 should be taken with 240 mL (i.e. 8 fluid ounces) of water. Additional water is permitted ad libitum except for the period 1 hour before to 1 hour after administration of the drug product. • At Day -3, patients will receive a single administration of IPN60090 at the RD (morning dose only, as defined by the SRC at the end of Part A dose escalation) 30 minutes after the start of a moderate fat meal. The moderate fat meal should be eaten in 30 minutes or less. The patients should not consume any food for at least 4 hours after the dose. IPN60090 should be taken with 240 mL (i.e. 8 fluid ounces) of water. Additional water is permitted ad libitum except for the period 1 hour before to 1 hour after administration of the drug product. Substitutions to the test meal can be made after discussion with the sponsor. It is understood that some patients may not be able to consume the entire meal. Study staff should record the percent of the test meal breakfast and the time it takes to be consumed. Full PK profiles will be obtained on Day -7 and Day -3 to assess the effect of a moderate fat meal on IPN60090 PK profile. Blood samples will be collected on Day -7 and Day -3 for the evaluation of haematology and serum chemistry, and AEs will be reported In Part D, the moderate fat meal is defined as the following: total calories of 500-750 kCal including 30

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			to 35% fat (see Table 13). **After the run-in period, patients will receive IPN60090 as a single agent administered orally BID (every 12 hours), during or after a meal, starting from Day 1 at the single agent RD. Patients in Part D will follow the same schedule of assessments as described for Part A (with the exception of the urine sampling for PK).** **Patients enrolled in monotherapy Part D may receive combination treatment with either pembrolizumab or with paclitaxel upon progression on IPN60090 monotherapy at the discretion of the investigator and with the approval of the sponsor, once the safe dose level for the combination is determined. These patients will need to satisfy eligibility criteria for combination therapy prior to initiating treatment (see Section 4.1), and will be followed for safety and efficacy in a separate cohort.**
65	3.2.1	• Define the safety and tolerability profile of oral IPN60090 as a single agent (Part A) and in combination therapy with pembrolizumab (Part B) or paclitaxel (Part C) as determined by the incidence and nature of AEs.	• ~~Define the~~ **The** safety and tolerability ~~profile~~ of ~~oral~~ IPN60090 as a single agent (Part A **and Part D**) and in combination ~~therapy~~ with pembrolizumab (Part B) or paclitaxel (Part C) ~~as determined by the incidence and nature~~ **will be assessed by continuous reporting** of AEs **and serious AEs (SAEs), clinical laboratory test results, the presence of anti-pembrolizumab antidrug antibodies (ADA; Part B only), vital signs measurements, ECG and physical examination results and concomitant medication usage**.

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66	3.2.2	• Anti-tumour activity parameters assessed locally (for dose escalation) and centrally (for dose expansion) using RECIST version 1.1 for Part A and C and iRECIST for Part B only, including: - Clinical benefit rate (CBR) is defined as the proportion of patients in whom the Best Overall Response (BOR) is equal to complete response (CR), PR or SD lasting at least 12 weeks for Part A and C and equal to immune complete response (iCR), immune partial response (iPR) or immune stable disease (iSD) lasting at least 12 weeks for Part B - ORR is defined as the proportion of patients in whom the BOR is equal to CR and PR for Part A and C or iCR and iPR for Part B - DCR is defined as the proportion of patients in whom the BOR is equal to CR, PR or SD for Part A and C and equal to iCR, iPR or iSD for Part B	• Anti-tumour activity parameters assessed locally (for dose escalation) and centrally (for dose expansion) using RECIST version 1.1 for Part A**,** ~~and~~ C **and** D and iRECIST for Part B only, including: - Clinical benefit rate (CBR) is defined as the proportion of patients in whom the Best Overall Response (BOR) is equal to complete response (CR), PR or SD lasting at least 12 weeks for Part A**,** ~~and~~ C **and D** and equal to immune complete response (iCR), immune partial response (iPR) or immune stable disease (iSD) lasting at least 12 weeks for Part B - ORR is defined as the proportion of patients in whom the BOR is equal to CR and PR for Part A**,** ~~and~~ C **and D** or iCR and iPR for Part B - DCR is defined as the proportion of patients in whom the BOR is equal to CR, PR or SD for Part A**,** ~~and~~ C **and D** and equal to iCR, iPR or iSD for Part B
66	3.2.2	• Pharmacokinetic parameters of IPN60090, including but not limited to maximum observed plasma concentration (C_{max}), time to maximum observed plasma concentration (T_{max}), C_{trough}, area under the plasma concentration-time curve (AUC), elimination half-life ($t_{1/2}$), apparent total clearance from plasma (CL/F), apparent volume of distribution (V/F) of IPN60090 (Parts A to C).	• Pharmacokinetic parameters of IPN60090, including but not limited to maximum observed plasma concentration (C_{max}), time to maximum observed plasma concentration (T_{max}), C_{trough}, area under the plasma concentration-time curve (AUC), elimination half-life ($t_{1/2}$), apparent total clearance from plasma (CL/F), apparent volume of distribution (V/F) of IPN60090 (Parts A to ~~C~~ **D**).

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66	3.2.2	New text	• **Describe the PK of a single dose of IPN60090 administered in fed state (Day -3) relative to fasted state (Day -7) using the following PK parameters: C_{max}, AUC, T_{max}, $t_{1/2}$, CL/F, V/F (Part D).**
67	3.2.5	For subjects participating in the optional research biobanking program, the samples listed below will be biobanked for potential future exploratory biomarkers evaluation:	For subjects participating in the optional research biobanking program, **whom consent to optional ICF procedures,** the samples listed below will be biobanked for potential future exploratory biomarkers evaluation:
68	3.5	**In Part B**, the dose of pembrolizumab will be fixed at 200 mg administered as an i.v. infusion over 30 minutes every 21 days (Day 1 of every cycle), consistent with pembrolizumab prescribing information. Premedication with antipyretic and antihistamine should be considered. The table below outlines the defined dose levels and the number of capsules in the dose escalation portion of the study. The RD for dose expansion, and number of capsules, will be determined at the completion of the dose escalation.	**In Part B**, the dose of pembrolizumab will be fixed at 200 mg administered as an i.v. infusion over 30 minutes every 21 days **(±1 day in Cycle 1 and ±3 days in all other cycles)** (Day 1 of every cycle), consistent with pembrolizumab prescribing information. Premedication with antipyretic and antihistamine should be considered. The table below outlines the defined dose levels and the number of capsules in the dose escalation portion of the study. The RD for dose expansion, and number of capsules, will be determined at the completion of the dose escalation.
68	3.5	**In Part C**, the dose of paclitaxel will be fixed at 175 or 135 mg/m² (or according to the local approved label for particular tumour types) administered as an i.v. infusion as per standard practice or at the approved recommended dose per indication every 21 days (Day 1 of each cycle), consistent with paclitaxel prescribing information. Premedication (e.g. dexamethasone, diphenhydramine, histamine H2 blockers) to prevent hypersensitivity reactions should be considered.	**In Part C**, the dose of paclitaxel will be fixed at 175 or 135 mg/m² (or according to the local approved label for particular tumour types) administered as an i.v. infusion as per standard practice or at the approved recommended dose per indication every 21 days **(±1 day in Cycle 1 and ±3 days in all other cycles)** (Day 1 of each cycle), consistent with paclitaxel prescribing information. Premedication (e.g. dexamethasone, diphenhydramine, histamine H2 blockers) to prevent hypersensitivity reactions should be considered.

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69	3.5	New text	**In Part D, single administration of IPN60090 at the RD (morning dose only) as defined by the SRC at the end of Part A dose escalation will be performed during the run-in period at Day -7 and Day -3. On Day -7, IPN60090 will be administered following an overnight fast of at least 10 hours. On Day -3, IPN60090 will be administered 30 minutes after the start of a moderate fat meal (see Table 13). The moderate fat meal should be eaten in 30 minutes or less. On both days, the patients should not consume any food for at least 4 hours after the dose. IPN60090 should be taken with 240 mL (i.e. 8 fluid ounces) of water. Additional water is permitted ad libitum except for the period 1 hour before to 1 hour after administration of the drug product. Substitutions to the test meal can be made after discussion with the sponsor. It is understood that some patients may not be able to consume the entire meal. Study staff should record the percent of the test meal breakfast eaten and the time it takes to be consumed.**
69	3.5	New text	**Table 13 Composition of the Moderate Fat Meal** Shown below:

Type of meal	**Total calories (Kcal)**	**Calories from fat (%)**	**Calories from carbohydrates (%)**	**Calories from proteins (%)**
Moderate fat	**500-750**	**30-35**	**≥55%**	**≥12-14**

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69	3.5	New text	**Then starting from Day 1, patients will receive IPN60090 BID (at the RD as defined by the SRC at the end of Part A) during or after a meal over 21 days (one cycle) as described in Part A.**

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70	3.6	During dose escalation, for each patient the study duration will consist of an up to 28-day screening period), followed by the DLT assessment period, which will consist of first 21 days of treatment (one cycle).	During dose escalation, for each patient the study duration will consist of an up to 28-day screening period **(up to 21 days in Part D)**, followed by the DLT assessment period, which will consist of first 21 days of treatment (one cycle).
70	3.6	All patients will then be followed post end of treatment at 30 days ±3 days (for Parts A and C) and 90±3 days (for Part B) for the end of treatment visit, at 180 days ±14 days for the safety follow-up visit and then every 3 months +/-14 days for survival until the end of the study.	All patients will then be followed post end of treatment at 30 days ±3 days (for Parts A**,** ~~and~~ C **and D**) and 90±3 days (for Part B) for the end of treatment visit, at 180 days ±14 days for the safety follow-up visit and then every 3 months ~~+/-~~ ±14 days for survival until the end of the study.
72	4.1	(6) Fresh or archival tumour tissue must be available for mutation and biomarker analysis. Patients should not be put at undue risk to obtain fresh tumour biopsy. Procedures more invasive than core biopsy should not be used. Procedures to obtain biopsy should only be performed if the risk is minimal (no greater than 2% risk of serious or severe complications). If available, archival tumour tissue from time of initial diagnosis will be collected in addition to the most recent biopsy (archival or fresh).	(6**a**) Fresh **and**/or archival tumour tissue **from the biopsy obtained between the completion of the most recent line of treatment until study entry** must be available for mutation and biomarker analysis **unless KEAP1/NRF2 mutations were present in any previous biopsy, in which case, no further biopsy is required. For ovarian cancer patients, both archival biopsies obtained between the completion of the most recent line of treatment until study entry and fresh biopsies must be available to evaluate the evolution of ASNS levels over time**. Patients should not be put at undue risk to obtain fresh tumour biopsy. Procedures more invasive than core biopsy should not be used. Procedures to obtain biopsy should only be performed if the risk is minimal (no greater than 2% risk of serious or severe complications). If available, archival tumour tissue from time of initial diagnosis will be collected in addition to the most recent biopsy (archival **and**/or fresh).

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Page	**Section**	**WAS**	**IS**
72	4.1	(8) Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) ≤1.	(8a) Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) ≤1 **and a Royal Marsden Hospital (RMH) score of 0 or 1 (Appendix 2)**.
74	4.1.5	New text	***4.1.5 Part D Specific Inclusion Criteria*** **(D1) Patients must be able to consume a moderate fat meal.**
75	4.2.1	New text	**(16) Patients unwilling to comply with protocol requirements related to the assigned part.**
75	4.2.5	New text	***4.2.5 Part D Specific Exclusion Criteria*** **(D1) Treatment with drugs that can alter the absorption of IPN60090 by affecting gastrointestinal motility or by changing the gastric pH during the run-in period (Day -7 to Day -3) of Part D.** **(D2) Patients suffering from conditions which are likely to adversely affect gastrointestinal motility and/or transit (for example, diarrhoea, vomiting or nausea, gastroparesis, irritable bowel syndrome and malabsorption) or patients with gastrointestinal resection (e.g. partial or total gastrectomy) likely to interfere with absorption of study treatment. Patients with Type 1 diabetes and hypercholesterolaemia are excluded.** **(D3) Patients unable to fast for up to 14 hours.**

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Page	**Section**	**WAS**	**IS**
76	4.3.1	Both safety and anti-tumour activity of IPN60090 in patients in dose expansion cohorts as well as of patients from dose escalation receiving additional cycles of IPN60090 treatment will continue to be monitored by the SRC, and by the ISAC on an ongoing basis. The decision to halt enrolment or to discontinue a patient or a cohort may be made by SRC and ISAC at any point if a safety signal or unacceptable toxicity are observed. Anti-tumour activity of IPN60090 will be accessed by SRC and ISAC after Stage I of the sequential two stage design, and if the study treatment does not demonstrate sufficient anti-tumour activity in any given cohort(s) as defined in Section 11.3.1 (CBR at 12 weeks in at least one patient out of 10), then the cohort(s) will be discontinued.	Both safety and anti-tumour activity of IPN60090 in patients in dose expansion cohorts as well as of patients from dose escalation receiving additional cycles of IPN60090 treatment will continue to be monitored by the SRC, and by the ISAC on an ongoing basis. **The ISAC will meet after 1 year of the start of the study or at the end of the dose escalation, whichever occurs first.** The decision to halt enrolment or to discontinue a patient or a cohort may be made by SRC and ISAC at any point if a safety signal or unacceptable toxicity are observed. Anti-tumour activity of IPN60090 will be accessed by SRC and ISAC after Stage I of the sequential two stage design, and if the study treatment does not demonstrate sufficient anti-tumour activity in any given cohort(s) as defined in Section 11.3.1 (CBR at 12 weeks in at least one patient out of 10), then the cohort(s) will be discontinued.
77	4.3.3	Patients who experience a DLT will be allowed to continue to receive study treatment at a lower dose level at the discretion of the investigator and will be closely monitored for safety. Criteria for DLTs are described in Section 3.1.2.1 for Part A, Section 3.1.2.2 for Part B, and Section 3.1.2.3 for Part C.	Patients who experience a DLT will be allowed to continue to receive study treatment at a lower dose level at the discretion of the investigator and will be closely monitored for safety. **The SRC may consider additional sparse PK samples for DLT assessment.** Criteria for DLTs are described in Section 3.1.2.1 for Part A, Section 3.1.2.2 for Part B, and Section 3.1.2.3 for Part C.
78	5.1	The schedule of procedures and assessments during the study is summarised in Table 12.	The schedule of procedures and assessments during the study is summarised in Table ~~12~~ **14 (Parts A to C) and Table 15 (Part D).**
79	5.1	Table 12 Study Procedures and Assessments	Table ~~12~~ **14** Study Procedures and Assessments **(Parts A to C)** Amended as follows:
83	5.1	New table	**Table 15 Study Procedures and Assessments (Part D)**

Table 14 Study Procedures and Assessments (Parts A to C)

Procedures and assessments	Protocol section	Screening	Treatment																		Follow-up		
			Cycle 1					Cycle 2			Cycle 3			Cycle 4			All Cycles after Cycle 4			EOS/EW	Safety FU	Survival FU
		D -28 to -1	D1	D2	D8	D14	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	30 days (Parts A and C) or 90 days (Part B) after last dose	Up to 180 days after last dose	Every 3 months after safety FU
		D1	D1	D2	D8	D14	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	Dx	Dx	Dx			
Visit window (days)		**N/A**	**N/A**		**±1**			**±3**			**±3**			**±3**			**±3**			**±3**	**±14**	**±14**
Baseline documentation and physical examination																							
Informed consent		X																					
Medical and disease history		X																					
Demographics and height		X																					
Physical examination		X	X[a]		X	X		X			X			X			X			X		
Body weight		X	X[a]		X	X		X			X			X			X			X		
Vital signs		X	X[a]		X	X		X			X			X			X			X		
ECOG performance status		X	X[a]					X			X			X			X			X		
RMH status		**X**																					
Enrolment																							
Inclusion/Exclusion criteria		X	X																				
End of phase disposition		X	X																	X		X
Safety/Laboratory assessments																							
Haematology		X	X[a]	X	X	X		X	X		X			X			X			X		
Chemistry (including liver function tests)		X	X[a]	X	X	X		X	X		X			X			X			X		
INR		X	X[a]								Day 1 of every 3rd cycle starting with Day 1 (i.e. Day 1, Cycle 6 Day 1, etc.)									X		
TSH (Part B only)		X	X[a]								Day 1 of every 3rd cycle starting with Day 1 (i.e. Day 1, Cycle 6 Day 1, etc.)									X		
Urinalysis		X	X[a]					X			X			X			X			X		
Serum pregnancy test		X																					
Urine pregnancy test								X			X			X			X			X		
ECHO/MUGA		X																		X		
Triplicate ECG (12-lead)		X	X[b]					X [b] [c]			X[c]			X[c]			As clinically indicated			X		

Procedures and assessments	Protocol section	Screening	Treatment																	Follow-up		
			Cycle 1					Cycle 2			Cycle 3			Cycle 4			All Cycles after Cycle 4			EOS/EW	Safety FU	Survival FU
		D -28 to -1	D1	D2	D8	D14	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	30 days (Parts A and C) or 90 days (Part B) after last dose	Up to 180 days after last dose	Every 3 months after safety FU
			D1	D2	D8	D14	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	Dx	Dx	Dx			
Visit window (days)		**N/A**	**N/A**			**±1**			**±3**			**±3**			**±3**			**±3**		**±3**	**±14**	**±14**
PK/Biomarkers																						
Blood sampling for PK of IPN60090			X[d]	X [c]		X[d]	X[e]	X[f]			X[f]			X[f]			**X[f]**			**X**		
Blood sampling for PK of combined drug: Pembrolizumab **(Part B only)**			X[c]					X[c]			X[c]			X[c]			X[c]					
Blood sampling for PK of combined drug: paclitaxel **(Part C only)**			X[g]					X[g]			X[g]											
Urine sampling for PK (Part A dose escalation only)			X[h]			X[h]																
Blood/PBMC samples for PD biomarker[i]			X[j]			X[j]	X~~[f]~~**[e]**													~~X[f]~~		
Serum Ca-125			X[k]								X[k]						X[k]					
~~C~~cfDNA		X[c]					X[c]				X[c]						X**[c]** [l]			X~~[c]~~		
Fresh tumour biopsy[m]		X[n][o]					X[n][p]													X[n][q]		
Archival tumour biopsies**[r]**		X																				
ADA samples for pembrolizumab (binding and neutralising) **(Part B only)**		X									X[c]						X[c]			X		
Biobanking (optional)																						
Biobanking serum[s]			X[t]				X	X			X			X			X			X		
Biobanking PBMC[s]			Remaining and not used PBMC for PD biomarker should be biobanked																			
Biobanking plasma[s]			X[t]				X	X			X			X			X			X		
Biobanking paxgene RNA[s]			X[t]				X	X			X			X			X			X		
Biobanking paxgene DNA[s]			X**[c]**																			
Biobanking stools[s]			X**[c]**				X**[c]**													X		

Procedures and assessments	Protocol section	Screening	Treatment																	Follow-up		
			Cycle 1					Cycle 2			Cycle 3			Cycle 4			All Cycles after Cycle 4			EOS/EW	Safety FU	Survival FU
		D -28 to -1	D1	D2	D8	D14	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	30 days (Parts A and C) or 90 days (Part B) after last dose	Up to 180 days after last dose	Every 3 months after safety FU
			D1	D2	D8	D14	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	Dx	Dx	Dx			
Visit window (days)		N/A	N/A		±1			±3			±3			±3			±3			±3	±14	±14
Biobanking cfDNA[s]			X[c]				X[c]	Blood collection for cfDNA should occur at the same time as efficacy assessments. Every 6 weeks from Cycle 1 Day 1[c].												X[c]		
Biobanking ~~remaining~~ **leftover tissue material and additional biopsies obtained from fresh frozen** biopsies[s]		Remaining ~~and not used tumour materials from~~ biopsies **from biomarkers collection** should be biobanked **along with any additional tumour material collected at these visits (archival and/or fresh).**																				
Tumour assessments																						
CT/MRI chest, abdomen, pelvis, or other (if clinically indicated)		X	Images required every 6 weeks (±1 week) from Cycle 1 Day 1 for the first 24 weeks of treatment, and every 12 weeks (±2 weeks) thereafter. To ensure image consistency, the same imaging modalities and acquisition protocols used at screening are to be used for subsequent tumour assessments.																X	X	
CT/MRI brain			Required in patients with documented, treated brain metastasis. As clinically indicated for patients with suspected brain metastasis. Images required every 6 weeks (±1 week) from Cycle 1 Day 1 for the first 24 weeks of treatment, and every 12 weeks (±2 weeks) thereafter. To ensure image consistency, the same imaging modalities and acquisition protocols used at screening are to be used for subsequent tumour assessments.																X (if applicable)	X	
Other clinical assessments																						
Adverse events			Document new or worsening AEs from informed consent through 30 days after the date of the decision to permanently discontinue study treatment. AE information will be collected at study visits and may also be collected at any time over the phone or by spontaneous patient report. Certain AEs and all SAEs that are ongoing 30 days after of the date of the decision to permanently discontinue study treatment are to be followed until resolution or determination by the investigator that the event is stable or irreversible.																		
Prior and concomitant medication/procedures/non-drug therapies			Document prior~~,~~ and concomitant medication taken from 28 days before first dose of study treatment through 30 days after the date of the decision to discontinue study treatment.																		
Further anti-tumour treatment																				X	X	X
IPN60090			Daily BID starting on Cycle 1 Day 1. Dose will be determined by phase and cohort.																			

Procedures and assessments	Protocol section	Screening	Treatment																Follow-up		
			Cycle 1					Cycle 2			Cycle 3			Cycle 4			All Cycles after Cycle 4			EOS/EW	Safety FU	Survival FU
		D -28 to -1	D1	D2	D8	D14	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	30 days (Parts A and C) or 90 days (Part B) after last dose	Up to 180 days after last dose	Every 3 months after safety FU
			D1	D2	D8	D14	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	Dx	Dx	Dx			
Visit window (days)		**N/A**	**N/A**		**±1**			**±3**			**±3**			**±3**			**±3**			**±3**	**±14**	**±14**
Pembrolizumab			200 mg (or per approved label) every 21 days (Day 1 of every cycle) as i.v. infusion.																		
Paclitaxel			175 mg/m^2 or 135 mg/m^2 (or per approved label) every 21 days (Day 1 of every cycle) i.v. infusion.																		

ADA=antidrug antibodies; AE=adverse events; BID=bis in die (twice daily); cfDNA=circulating free DNA; CT=computed tomography; D=day; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; EOS=end of study; EW=early withdrawal; FU=follow-up; HGSOC= high-grade serous ovarian cancer; INR=international normalised ratio; i.v.=intravenous; MRI=magnetic resonance imaging; MUGA=multigated acquisition; N/A=not applicable; PBMC=peripheral blood mononuclear cells; PD=pharmacodynamics; PK=pharmacokinetics; **RMH=Royal Marsden Hospital;** RNA=ribonucleic acid; SAE=serious adverse event; TSH=thyroid stimulating hormone

a assessment does not need to be repeated if done within 3 days of first dose.

b ~~thirty~~ **30** minutes **(±15 minutes)**, 1 **hour (±15 minutes)**, 2 **hours (±15 minutes)**, 4 **hours (±15 minutes)**, 8 **hours (±15 minutes)** and 12 hours **(±15 minutes)** postdose.

c predose.

d predose, 30 minutes **(±5 minutes)**, 1 **hour (±5 minutes)**, 2 **hours (±5 minutes)**, 4 **hours (±10 minutes)**, 8 **hours (±30 minutes)** and 12 hours **(±1 hour)** postdose.

e predose, and between 2 to 4 hours postdose.

f predose, 2 hours **(±5 minutes)** postdose.

g two time points: immediately before paclitaxel infusion and at the end of the paclitaxel infusion i.e. 3 hours after the start of the infusion.

h ~~twenty four hour interval urine~~ **0-12 h urine time** collection **interval** (only performed for Part A Dose Escalation).

i see Table ~~28~~ **32** for more details on collection timepoints and volumes.

j predose, 2 and 12 hours postdose.

k serum Ca-125 assessments will be performed at baseline, on Day 1 of Cycle 3 and then on Day 1 of every other cycle. This assessment will be performed in patients with HGSOC only.

l cfDNA sample on Day 1 of every other cycle after Cycle 3.

m remaining tumour materials should be biobanked.

n cfDNA should be collected at the same day of biopsy, if feasible.

o fresh tumour must be available for mutation and biomarker analysis unless KEAP1/NRF2 mutations were present in any previous biopsy, in which case, no further biopsy is required. For ovarian cancer patients, fresh biopsies must be collected in addition to the archival biopsies. Procedures to obtain biopsy should only be performed if the risk is minimal (no greater than 2% risk of serious or severe complications).

p performed 2 to 4 hours postdose.

q the EOS fresh biopsy is optional.

r **archival biopsies collected after the completion of the last line of treatment until study entry and archival biopsies from initial diagnosis if available.**

s biobanking samples will only be collected for subjects who have signed the optional biobanking informed consent form.

t predose and 12 hours postdose.

Table 15 Study Procedures and Assessments (Part D)

Procedures and assessments	Protocol section	Screening	Run-in		Treatment																		Follow-up		
					Cycle 1					Cycle 2			Cycle 3			Cycle 4			All cycles after Cycle 4					
		D -28 to D -8	D -7	D -3	D1	D2	D8	D14	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	EOS/EW	Safety FU	Survival FU
					D1	D2	D8	D14	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	Dx	Dx	Dx	30 days after last dose	Up to 180 days after last dose	Every 3 months after safety FU
Visit windows (days)		N/A	N/A	N/A	N/A		±1			±3			±3			±3			±3			±3	±14	±14
Baseline documentation and physical examination																								
Informed consent		X																						
Medical and disease history		X																						
Demographics and height		X																						
Physical examination		X			X[a]		X	X		X			X			X			X			X		
Body weight		X			X[a]		X	X		X			X			X			X			X		
Vital signs		X			X[a]		X	X		X			X			X			X			X		
ECOG performance status		X			X[a]					X			X			X			X			X		
RMH status		X																						
Enrolment																								
Inclusion/Exclusion criteria		X			X																			
End of phase disposition		X			X																	X		X
Safety/Laboratory assessments																								
Haematology		X	X	X	X[a]	X	X	X		X	X		X			X			X			X		
Chemistry (including liver function tests)		X	X	X	X[a]	X	X	X		X	X		X			X			X			X		
INR		X			X[a]								Day 1 of every 3rd cycle starting with Day 1 (i.e. Day 1, Cycle 6 Day 1, etc.)									X		
Urinalysis		X			X[a]					X			X			X			X			X		
Serum pregnancy test		X																						
Urine pregnancy test										X			X			X			X			X		
ECHO/MUGA		X																				X		
Triplicate ECG (12-lead)		X	X[b]	X[b]	X[c]					X[c] [d]			X[d]			X[d]			As clinically indicated			X		
PK/Biomarkers																								
Blood sampling for PK of IPN60090			X[e]	X[e]	X[f]	X[d]		X[f]	X[g]	X[h]			X[h]			X[h]			X[h]			X		
Blood/PBMC samples for PD biomarker[i]					X[j]			X[j]	X[g]															

Procedures and assessments	Protocol section	Screening	Run-in		Treatment																		Follow-up		
					Cycle 1					Cycle 2			Cycle 3			Cycle 4			All cycles after Cycle 4					
		D -28 to D -8	D -7	D -3	D1	D2	D8	D14	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	EOS/EW	Safety FU	Survival FU
					D1	D2	D8	D14	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	Dx	Dx	Dx	30 days after last dose	Up to 180 days after last dose	Every 3 months after safety FU
Visit windows (days)		N/A	N/A	N/A	N/A		±1			±3			±3			±3			±3			±3	±14	±14
Serum Ca-125					X[k]								X[k]						X[k]					
cfDNA		X[d]							X[d]				X[d]						X[d][l]			X		
Fresh tumour biopsy[m]		X[n][o]							X[n][p]													X[n][q]		
Archival tumour biopsies[r]		X																						
Biobanking (optional)																								
Biobanking serum[s]					X[t]				X	X			X			X			X			X		
Biobanking PBMC[s]					Remaining and not used PBMC for PD biomarker should be biobanked																			
Biobanking plasma[s]					X[t]				X	X			X			X			X			X		
Biobanking paxgene RNA[s]					X[t]				X	X			X			X			X			X		
Biobanking paxgene DNA[s]					X[d]																			
Biobanking stools[s]					X[d]				X[d]													X		
Biobanking cfDNA[s]					X[d]				X[d]	Blood collection for cfDNA should occur at the same time as efficacy assessments. Every 6 weeks from Cycle 1 Day 1[d].												X[d]		
Biobanking leftover material and additional biopsies obtained from fresh frozen biopsies[s]		Remaining biopsies from biomarkers collection should be biobanked along with any additional tumour material collected at these visits (archival and/or fresh)																						
Tumour assessments																								
CT/MRI chest, abdomen, pelvis, or other (if clinically indicated)		X			Images required every 6 weeks (±1 week) from Cycle 1 Day 1 for the first 24 weeks of treatment, and every 12 weeks (±2 weeks) thereafter. To ensure image consistency, the same imaging modalities and acquisition protocols used at screening are to be used for subsequent tumour assessments.																	X	X	
CT/MRI brain					Required in patients with documented, treated brain metastasis. As clinically indicated for patients with suspected brain metastasis. Images required every 6 weeks (±1 week) from Cycle 1 Day 1 for the first 24 weeks of treatment, and every 12 weeks (±2 weeks) thereafter. To ensure image consistency, the same imaging modalities and acquisition protocols used at screening are to be used for subsequent tumour assessments.																	X (if applicable)	X	

Procedures and assessments	Protocol section	Screening	Run-in		Treatment																		Follow-up		
					Cycle 1					Cycle 2			Cycle 3			Cycle 4			All cycles after Cycle 4					
		D -28 to D -8	D -7	D -3	D1	D2	D8	D14	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	EOS/EW	Safety FU	Survival FU
					D1	D2	D8	D14	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	Dx	Dx	Dx	30 days after last dose	Up to 180 days after last dose	Every 3 months after safety FU
Visit windows (days)		N/A	N/A	N/A	N/A		±1			±3			±3			±3			±3			±3	±14	±14
Other clinical assessments																								
Adverse events			Document new or worsening AEs from informed consent through 30 days after the date of the decision to permanently discontinue study treatment. AE information will be collected at study visits and may also be collected at any time over the phone or by spontaneous patient report. Certain AEs and all SAEs that are ongoing 30 days after of the date of the decision to permanently discontinue study treatment are to be followed until resolution or determination by the investigator that the event is stable or irreversible.																				
Prior and concomitant medication/procedures/non-drug therapies					Document prior and concomitant medication taken from 28 days before first dose of study treatment through 30 days after the date of the decision to discontinue study treatment.																			
Further anti-tumour treatment																						X	X	X
IPN60090			X[u]	X[u]	Daily BID starting on Cycle 1 Day 1. Dose will be at the RD (as defined by the SRC at the end of Part A dose escalation)																			

Procedures and assessments	Protocol section	Screening	Run-in		Treatment																	Follow-up		
					Cycle 1					Cycle 2			Cycle 3			Cycle 4			All cycles after Cycle 4					
		D -28 to D -8	D -7	D -3	D1	D2	D8	D14	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	EOS/EW	Safety FU	Survival FU
					D1	D2	D8	D14	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	Dx	Dx	Dx	30 days after last dose	Up to 180 days after last dose	Every 3 months after safety FU
Visit windows (days)		N/A	N/A	N/A	N/A		±1			±3			±3			±3			±3			±3	±14	±14
Pembrolizumab					200 mg (or per approved label) every 21 days (Day 1 of every cycle) as i.v. infusion.																			
Paclitaxel					175 mg/m^2 or 135 mg/m^2 (or per approved label) every 21 days (Day 1 of every cycle) i.v. infusion.																			

AE=adverse events; BID=bis in die (twice daily); cfDNA=circulating free DNA; CT=computed tomography; D=day; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; EOS=end of study; EW=early withdrawal; FU=follow-up; HGSOC=high-grade serous ovarian cancer; INR=international normalised ratio; i.v.=intravenous; MRI=magnetic resonance imaging; MUGA=multigated acquisition; N/A=not applicable; PBMC=peripheral blood mononuclear cells; PD=pharmacodynamics; PK=pharmacokinetics; RMH=Royal Marsden Hospital; RNA=ribonucleic acid; SAE=serious adverse event

a assessment does not need to be repeated if done within 3 days of first dose.
b 1 hour (±15 minutes), 2 hours (±15 minutes) and 4 hours (±15 minutes) postdose.
c 30 minutes (±15 minutes), 1 hour (±15 minutes), 2 hours (±15 minutes), 4 hours (±15 minutes), 8 hours (±15 minutes) and 12 hours (±15 minutes) postdose.
d predose.
e predose, 30 minutes (±5 minutes), 1 hour (±5 minutes), 2 hours (±5 minutes), 4 hours (±10 minutes), 8 hours (±30 minutes), 12 hours (±1 hour), 24 hours (±2 hours), 48 hours (±2 hours) and 72 hours (±2 hours) postdose.
f predose, 30 minutes (±5 minutes), 1 hour (±5 minutes), 2 hours (±5 minutes), 4 hours (±10 minutes), 8 hours (±30 minutes) and 12 hours (±1 hour) postdose.
g predose, and between 2 to 4 hours postdose.
h predose, 2 hours (±5 minutes) postdose.
i see Table 32 for more details on collection timepoints and volumes.
j predose, 2 and 12 hours postdose.
k serum Ca-125 assessments will be performed at baseline, on Day 1 of Cycle 3 and then on Day 1 of every other cycle. This assessment will be performed in patients with HGSOC only.
l cfDNA sample on Day 1 of every other cycle after Cycle 3.
m remaining tumour materials should be biobanked.
n cfDNA should be collected at the same day of biopsy, if feasible.
o fresh tumour must be available for mutation and biomarker analysis unless KEAP1/NRF2 mutations were present in any previous biopsy, in which case, no further biopsy is required. For ovarian cancer patients, fresh biopsies must be collected in addition to the archival biopsies. Procedures to obtain biopsy should only be performed if the risk is minimal (no greater than 2% risk of serious or severe complications).
p performed 2 to 4 hours postdose.
q the EOS fresh biopsy is optional.
r archival biopsies collected after the completion of the last line of treatment until study entry and archival biopsies from initial diagnosis if available.
s biobanking samples will only be collected for subjects who have signed the optional biobanking informed consent form.
t predose and 12 hours postdose.
u morning dose only.

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87	5.2	The schedule of visits and main procedures at each visit are summarised in Table 12.	The schedule of visits and main procedures at each visit are summarised in **Table ~~12~~ 14 (Parts A to C) and Table 15 (Part D)**.
87	5.3	The total volume of blood collected for all evaluations throughout this study varies depending on the study Part, and will reach a maximum of approximately 215.0 mL per month for any one patient (in Part B) (Table 13). An additional 50.5 mL of blood will be collected from patients who have signed the optional biobanking informed consent. Therefore, the maximum total blood volume collected per month from any one patient will not reach more than 265.5 mL per patient over the study duration.	The total volume of blood collected for all evaluations throughout this study varies depending on the study Part, and will reach a maximum of approximately ~~215.0~~ **278.0** mL per month for any one patient (in Part ~~B~~ **D**) (Table ~~13~~ **16 and Table 17**). An additional ~~50.5~~ **60.5** mL of blood will be collected from patients who have signed the optional biobanking informed consent. Therefore, the maximum total blood volume collected per month from any one patient will not reach more than ~~265.5~~ **338.5** mL per patient over the study duration.
88	5.3	Table 13 Total Blood Volume for All Evaluations	Table ~~13~~ **16** Total Blood Volume for All Evaluations **(Parts A to C)** Amended as follows:

Table 16 Total Blood Volume for All Evaluations (Parts A to C)

Assessments	Volume per sample (mL)	Max number of samples/month	Total max volume/month (mL)
Laboratory assessments			
Haematology	2	6	~~14~~ **12**
Chemistry (including liver function tests)	5	6	~~35~~ **30**
INR	2	2	4
TSH (Part B only)	2	2	4
Serum pregnancy test	2	1	2
PK and Biomarkers			
Blood sampling for PK of IPN60090	2	17	34
Blood sampling for PK of paclitaxel **(Part C only)**	2.5	2	5
Blood sampling for PK of pembrolizumab **(Part B only)**	2	1	2
Blood sampling for ADA against pembrolizumab **(Part B only)**	6	1	6
Blood sampling for Ca-125 (HGSOC only)	2	2	4
Blood/PBMC samples	~~5~~ **6**	18	~~90~~ **108**
~~C~~**c**fDNA	10	~~2~~ 3	~~20~~ **30**
Total volume Part A			~~**203**~~ **224**
Total volume Part B			~~**215**~~ **236**
Total volume Part C			~~**208**~~ **229**
Biobanking (optional)			
Biobanking serum	2.5	4	10
Biobanking plasma	2	4	8
Biobanking paxgene RNA	2.5	4	10
Biobanking paxgene DNA	2.5	1	2.5
Biobanking cfDNA	10	~~2~~ 3	~~20~~ 30
Total biobanking			~~**50.5**~~ **60.5**
Maximum Total			~~**265.5**~~ **296.5**

ADA=antidrug antibody; ~~BAbs=binding antibodies;~~ cfDNA=circulating free deoxyribonucleic acid; DNA=deoxyribonucleic acid; HGSOC=high-grade ~~serious~~ **serous** ovarian cancer; INR=international normalised ratio; **max=maximum;** ~~NAbs=neutralising antibodies~~; PBMC=peripheral blood mononuclear cells; PK=pharmacokinetic; RNA=ribonucleic acid; TSH=thyroid stimulating hormone.

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89	5.3	New table	**Table 17 Total Blood Volume for All Evaluations (Part D Only)**

Table 17 Total Blood Volume for All Evaluations (Part D)

Assessments	Volume per sample (mL)	Max number of samples/month	Total max volume/month (mL)
Laboratory assessments			
Haematology	2	8	16
Chemistry (including liver function tests)	5	8	40
INR	2	2	4
Serum pregnancy test	2	1	2
PK and Biomarkers			
Blood sampling for PK of IPN60090	2	37	74
Blood sampling for Ca-125 (HGSOC only)	2	2	4
Blood/PBMC samples	6	18	108
cfDNA	10	3	30
Total volume Part D			278
Biobanking (optional)			
Biobanking serum	2.5	4	10
Biobanking plasma	2	4	8
Biobanking paxgene RNA	2.5	4	10
Biobanking paxgene DNA	2.5	1	2.5
Biobanking cfDNA	10	3	30
Total biobanking			60.5
Maximum Total			338.5

cfDNA=circulating free deoxyribonucleic acid; DNA=deoxyribonucleic acid; HGSOC=high-grade serous ovarian cancer; INR=international normalised ratio; max=maximum; PBMC =peripheral blood mononuclear cells; PK=pharmacokinetic; RNA=ribonucleic acid.

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89	5.3	Technical instructions will be provided in a separate laboratory manual. During dose escalation, all samples will be analysed locally except urine PK samples for IPN60090, PK samples for pembrolizumab and paclitaxel analyses and anti-pembrolizumab ADA samples. During dose expansion, all samples will be sent for central analysis (with the exception of laboratory safety tests for clinical decision making, which will be analysed locally).	Technical instructions will be provided in a separate laboratory manual. During dose escalation **(Parts A to C) and during Part D**, all samples will be analysed locally except ~~urine PK samples for IPN60090,~~ PK samples for pembrolizumab and paclitaxel analyses and anti-pembrolizumab ADA samples. During dose expansion, all samples will be sent for central analysis (with the exception of laboratory safety tests for clinical decision making, which will be analysed locally).

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91	6.2.1	Patients in all Parts (A, B and C) should take IPN60090 BID (every 12 hours), during or after a meal. IPN60090 will be administered in the clinic on the first treatment day so that each patient can be observed for initial tolerability. Subsequent doses will be self-administered at home by taking IPN60090 BID at the same time each day until next visit. Patients will be given a medication diary to record day and time of administration, missed administration if any with related reasons if available or retake medication in case of rejection if applicable. Any unused study treatment must be returned to the study site for drug accountability and disposal.	**Patients in Part D will receive IPN60090 as a single dose in the morning on Day -7 and Day -3 as described in Section 3.1.3.** Patients in all Parts (A, B**,** ~~and~~ C **and D [from Day 1]**) should take IPN60090 BID (every 12 hours), during or after a meal. IPN60090 will be administered in the clinic on the first treatment day so that each patient can be observed for initial tolerability. Subsequent doses will be self-administered at home by taking IPN60090 BID at the same time each day until next visit. Patients will be given a medication diary to record day and time of administration, missed administration if any with related reasons if available or retake medication in case of rejection if applicable. Any unused study treatment must be returned to the study site for drug accountability and disposal.
92	6.2.1	New text	**During Part D, the administered dose during the run-in period (Day -7 and Day -3) will be the RD (morning dose only) as defined by the SRC at the end of Part A dose escalation. Then, starting from Day 1, IPN60090 will be administered at the RD BID during or after a meal.**
92	6.2.2.1	Pembrolizumab will be supplied as 100 mg/4 mL (25 mg/mL) solution in single-use vial to be diluted for infusion. It is a sterile, preservative-free, clear to slightly opalescent, colourless to slightly yellow solution that requires dilution for i.v. infusion. It is supplied in a vial as a white-to off-white lyophilised powder. Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg) and water for injection.	Pembrolizumab will be supplied as 100 mg/4 mL (25 mg/mL) solution in single-use vial to be diluted for infusion. It is a sterile, preservative-free, clear to slightly opalescent, colourless to slightly yellow solution that requires dilution for i.v. infusion. ~~It is supplied in a vial as a white-to off-white lyophilised powder.~~ **Each vial contains 100 mg of pembrolizumab in 4 mL of solution.** Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg) and water for injection**, USP**.

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92	6.2.2.1	Pembrolizumab dose will be fixed at 200 mg (or according to the approved local label for particular tumour types) administered as an i.v. infusion over 30 minutes every 21 days (Day 1 of every cycle) through an i.v. line containing a sterile, non-pyrogenic, low-protein binding 0.2 µm to 5 µm in-line or add-on filter. Premedication with antipyretic and antihistamine may be considered. Reconstitution and preparation of pembrolizumab solution for infusion should be done as per locally-approved product information.	Pembrolizumab dose will be fixed at 200 mg (or according to the approved local label for particular tumour types) administered as an i.v. infusion over 30 minutes every 21 days **(±1 day in Cycle 1 and ±3 days in all other cycles)** (Day 1 of every cycle) through an i.v. line containing a sterile, non-pyrogenic, low-protein binding 0.2 µm to 5 µm in-line or add-on filter. Premedication with antipyretic and antihistamine may be considered. Reconstitution and preparation of pembrolizumab solution for infusion should be done as per locally-approved product information.
92	6.2.2.1	New text	**Unopened vials must be stored under refrigeration between 2°C to 8°C.**
93	6.2.2.2	The dose of paclitaxel will be fixed at 175 mg/m² or 135 mg/m² (or according to the local approved label for particular tumour types) administered as an i.v. infusion every 21 days.	The dose of paclitaxel will be fixed at 175 mg/m² or 135 mg/m² (or according to the local approved label for particular tumour types) administered as an i.v. infusion every 21 days **(±1 day in Cycle 1 and ±3 days in all other cycles)**.
94	6.3.1	New text	**H2 blockers, proton pump inhibitors and antacids are prohibited during the run-in period (Day -7 to Day -3) of Part D.**
94	6.3.2	Caution should be exercised when administering IPN60090 concomitantly with medicines known to be moderate inhibitors of CYP3A4 or CYP2D6. Administering IPN60090 concomitantly with medicines known to be moderate inducers of CYP3A4 is not recommended. The lists of moderate inhibitors of CYP3A4 and of CYP2D6 are provided in Appendix 3 and Appendix 4.The list of moderate inducers of CYP3A4 is provided in Appendix 3.	Caution should be exercised when administering IPN60090 concomitantly with medicines known to be moderate inhibitors of CYP3A4 or CYP2D6. Administering IPN60090 concomitantly with medicines known to be moderate inducers of CYP3A4 is not recommended. **Moreover, moderate inhibitors/inducers of CYP2C8 should also be used with caution for Part C as well as immunosuppressive agents for Part B.** The lists of moderate inhibitors of CYP3A4 and of CYP2D6 are provided in Appendix ~~3~~ **4** and Appendix ~~4~~ **5**. The list of moderate inducers of CYP3A4 is provided in Appendix ~~3~~ **4**. **The lists of moderate inhibitors/inducers of CYP2C8 are provided in Appendix 7. The list of immunosuppressive agents is provided in Appendix 8.**

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95	6.3.3	• Drugs used to control bone loss (e.g. bisphosphonates and denosumab) are allowed if started prior to screening activities but may not be initiated or exchanged during the course of the study and require sponsor approval.	• Drugs used to control bone loss (e.g. bisphosphonates and denosumab) are allowed if started prior to screening**.** ~~activities but may not~~ **If indicated to** be initiated or exchanged during the course of the study**,** ~~and require~~ sponsor**'s** approval **is required**.
101	6.4.5	Patients enrolled in monotherapy Part A may receive combination treatment with either pembrolizumab or with paclitaxel upon progression on IPN60090 monotherapy at the discretion of the investigator and with the approval of the sponsor, once the safe dose level for the combination is determined. These patients will need to satisfy eligibility criteria for combination therapy prior to initiating treatment, and will be followed for safety and efficacy in a separate cohort.	Patients enrolled in monotherapy Part A **and Part D** may receive combination treatment with either pembrolizumab or with paclitaxel upon progression on IPN60090 monotherapy at the discretion of the investigator and with the approval of the sponsor, once the safe dose level for the combination is determined. These patients will need to satisfy eligibility criteria for combination therapy prior to initiating treatment, and will be followed for safety and efficacy in a separate cohort.
102	7.1.1	*7.1.1 Dose Escalation (Part A - Monotherapy and Parts B and C - Combinations)*	*7.1.1 Dose Escalation (Part A - Monotherapy and Parts B and C - Combinations)* ***and Food Effect Cohort (Part D)***
102	7.1.1	Secondary tumour activity endpoints and evaluations planned during the dose escalation phase are summarised in Table 22. All tumour endpoints will be assessed locally.	Secondary tumour activity endpoints and evaluations planned during the dose escalation phase **and food effect cohort** are summarised in Table ~~22~~ **26**. All tumour endpoints will be assessed locally.
102	7.1.1	Table 22 Efficacy Endpoints and Evaluations During Dose Escalation	Table ~~22~~ **26** Efficacy Endpoints and Evaluations During Dose Escalation **and Food Effect Cohort** Amended as follows:

Table 26 Efficacy Endpoints and Evaluations During Dose Escalation and Food Effect Cohort

Measure	Timepoint	Variable	Endpoint
Tumour size (longest diameter)	Parts A~~, B and~~ C **and D**: Baseline and every 6 weeks	Tumour response according to RECIST v1.1	CBR ORR PFS DCR OS
	Part B: Baseline and every 6 weeks	Tumour response according to iRECIST	CBR ORR DCR iPFS OS

CBR=clinical benefit rate; DCR=disease control rate; iPFS=immune progression-free survival; ORR=objective response rate; OS=overall survival; PFS=progression free survival

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102	7.1.1	Table 23 Efficacy Endpoints and Evaluations During Dose Escalation	Table ~~23~~ **27** Efficacy Endpoints and Evaluations During Dose Escalation Amended as follows:

Table 27 Efficacy Endpoints and Evaluations During Dose Expansion

Measure	Timepoint	Variable	Endpoint
Tumour size (longest diameter)	Parts A, ~~B~~ and C: Baseline and every 6 weeks	Tumour response according to RECIST v1.1	CBR ORR PFS DCR OS
	Part B: Baseline and every 6 weeks	Tumour response according to iRECIST	CBR ORR DCR iPFS OS

CBR=clinical benefit rate; DCR=disease control rate; iPFS=immune progression-free survival; ORR=objective response rate; OS=overall survival; PFS=progression free survival

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106	8.1.4	All SAEs (as defined below), regardless of treatment group or suspected relationship to IMP, must be reported immediately (within 24 hours of the investigator's knowledge of the event) using the email specified at the beginning of this protocol. If the immediate report is submitted by telephone, this must be followed by detailed written reports using the SAE report form.	All SAEs (as defined below), regardless of treatment group or suspected relationship to IMP, must be reported immediately (within 24 hours of the investigator's knowledge of the event) **via the electronic data capture (EDC) system or** using the email specified at the beginning of this protocol **in case the EDC is not available**. If the immediate report is submitted by telephone, **or if the EDC was not available at initial reporting,** this must be followed by detailed written reports using the SAE ~~report~~ form **in the eCRF**.

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107	8.1.4	Any SAE must be reported immediately (within 24 hours), using the email specified at the beginning of this protocol, independent of the circumstances or suspected cause, if it occurs or comes to the attention of the investigator at any time during the study period.	Any SAE must be reported immediately (within 24 hours) **in the eCRF or** using the email specified at the beginning of this protocol **in case the EDC system is not available**, independent of the circumstances or suspected cause, if it occurs or comes to the attention of the investigator at any time during the study period.
107	8.1.4	The additional information included in the SAE form must be provided to the sponsor or representative as soon as it is available. The investigator should always provide an assessment of causality for each event reported to the sponsor. Upon receipt of the initial report, the sponsor will ask for the investigator's causality assessment if it was not provided with the initial report.	The additional information included in the SAE form must be ~~provided to the sponsor or representative~~ **collected in the eCRF** as soon as it is available. The investigator should always provide an assessment of causality for each event reported to the sponsor. Upon receipt of the initial report, the sponsor will ask for the investigator's causality assessment if it was not provided ~~with the initial report~~ **initially**.
108	8.1.5	Information regarding pregnancies must be collected on the AE page of the eCRF and reported to the sponsor as an SAE. The sponsor will request further information from the investigator as to the course and outcome of the pregnancy using the Standard Pregnancy Outcome Report Form.	Information regarding pregnancies must be collected on the AE/**SAE** page of the eCRF and reported to the sponsor as an SAE **via the EDC system**. The sponsor will request further information from the investigator as to the course and outcome of the pregnancy using the Standard Pregnancy Outcome Report Form.
109	8.2	During dose escalation part, all clinical safety laboratory tests listed below will be performed at local laboratories. A list of laboratory normal ranges should be provided to the sponsor. Any change in laboratory normal ranges during the trial will be forwarded to the sponsor. During dose expansion part, safety blood samples will also be analysed centrally.	During dose escalation part, all clinical safety laboratory tests listed below will be performed at local laboratories **(except anti-pembrolizumab antibodies)**. A list of laboratory normal ranges should be provided to the sponsor. Any change in laboratory normal ranges during the trial will be forwarded to the sponsor. During dose expansion part, safety blood samples will also be analysed centrally.
110	8.2.5	*Antipembrolizumab Antibody Testing*	*Antipembrolizumab Antibody Testing* ***(Part B Only)***

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110	8.2.5	The determination of putative antibodies against pembrolizumab will be evaluated using a validated method by at Kymos Pharma Services S.L., Parc Tecnòlogic del Vallès, Ronda de Can Fatjó 7-B, 08290 Cerdanyola del Vallès, Barcelona, Spain.	The determination of putative antibodies against pembrolizumab will be evaluated using ~~a~~ validated method**s** ~~by at Kymos Pharma Services S.L., Parc Tecnòlogic del Vallès, Ronda de Can Fatjó 7-B, 08290 Cerdanyola del Vallès, Barcelona, Spain~~ **ElectroChemiLuminiscence Assay (ECLA) electrochemiluminescent bridging assay for binding antibodies and cell-based assay for neutralising antibodies**.
111	8.6	Table 24 Electrocardiograms Timepoints	Table ~~24~~ **28** Electrocardiograms Timepoints Amended as follows:

Table 28 Electrocardiograms Timepoints

Visit	Timepoint	Method
Screening	Day (D) -28 to D -1 **(Parts A to C) and D -28 to D -8 (Part D)**	Triplicate
Run-in, Day -7 and Day -3 (Part D only)	**1 hours postdose**	**Triplicate**
	2 hours postdose	**Triplicate**
	4 hours postdose	**Triplicate**
Cycle 1, Day 1	30 minutes postdose	Triplicate
	1 hours postdose	Triplicate
	2 hours postdose	Triplicate
	4 hours postdose	Triplicate
	8 hours postdose	Triplicate
	12 hours postdose	Triplicate
Cycle 2, Day 1	Predose	Triplicate
	30 minutes postdose	Triplicate
	1 hours postdose	Triplicate
	2 hours postdose	Triplicate
	4 hours postdose	Triplicate
	8 hours postdose	Triplicate
	12 hours postdose	Triplicate
Cycle 3, Day 1	Predose	Triplicate
Cycle 4, Day 1	Predose	Triplicate
End of treatment	30 days after last dose	Triplicate

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112	9.1.1	Table 25 Timepoints for IPN60090 PK Blood Sample Determination	Table ~~25~~ **29** Timepoints for IPN60090 PK Blood Sample Determination Amended as follows:

Table 29 Timepoints for IPN60090 PK Blood Sample Determination

Visit	Timepoint	Volume
Run-in phase Day -7 (Part D only)	**Predose**	**2.0 mL**
	30 minutes postdose	**2.0 mL**
	1 hour postdose	**2.0 mL**
	2 hours postdose	**2.0 mL**
	4 hours postdose	**2.0 mL**
	8 hours postdose	**2.0 mL**
	12 hours postdose	**2.0 mL**
	24 hours postdose	**2.0 mL**
	48 hours postdose	**2.0 mL**
	72 hours postdose	**2.0 mL**
Run-in phase Day -3 (Part D only)	**Predose**	**2.0 mL**
	30 minutes postdose	**2.0 mL**
	1 hour postdose	**2.0 mL**
	2 hours postdose	**2.0 mL**
	4 hours postdose	**2.0 mL**
	8 hours postdose	**2.0 mL**
	12 hours postdose	**2.0 mL**
	24 hours postdose	**2.0 mL**
	48 hours postdose	**2.0 mL**
	72 hours postdose	**2.0 mL**
Cycle 1, Day 1	Predose	2.0 mL
	30 minutes postdose	2.0 mL
	1 hour postdose	2.0 mL
	2 hours postdose	2.0 mL
	4 hours postdose	2.0 mL
	8 hours postdose	2.0 mL
	12 hours postdose	2.0 mL
Cycle 1, Day 2	Predose	2.0 mL
Cycle 1, Day 14	Predose	2.0 mL
	30 minutes postdose	2.0 mL
	1 hour postdose	2.0 mL
	2 hours postdose	2.0 mL
	4 hours postdose	2.0 mL
	8 hours postdose	2.0 mL
	12 hours postdose	2.0 mL
Cycle 1, Day 15	Predose	2.0 mL
	2 to 4 hours postdose	2.0 mL
Cycle 2, Day 1	Predose	2.0 mL
	2 hours postdose	2.0 mL
Cycle 3, Day 1	Predose	2.0 mL
	2 hours postdose	2.0 mL
Cycle 4, Day 1	Predose	2.0 mL
	2 hours postdose	2.0 mL
All cycles after Cycle 4	**Predose**	**2.0 mL**
	2 hours postdose	**2.0 mL**
End of study		**2.0 mL**

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113	9.1.1.3	The time points for sampling are indicated in Table 12 and Table 26. Blood should be collected (2.0 mL) collected at each time point with serum clot activator for the determination of serum pembrolizumab levels. Blood samples should be collected from the contralateral arm used for the study drug infusion, or from another anatomical site. After blood collection, the tubes should be inverted 8 times and left for 30 minutes (for a maximum of 60 minutes) at ambient temperature and then centrifuged for 10 minutes at 1300*g* at 4°C. The resulting serum should be transferred into two aliquots in 2.0 mL cryovials (0.5 mL for the determination of the PK of pembrolizumab and <0.5 mL for backup samples). Samples should be stored at ≤-20°C.	The time points for **blood** sampling **for pembrolizumab determination** are indicated in Table ~~12~~ **14** and Table ~~26~~ **30**. Blood should be collected (2.0 mL) ~~collected~~ at each time point with serum clot activator for the determination of serum pembrolizumab levels. Blood samples should be collected from the contralateral arm used for the study drug infusion, or from another anatomical site. After blood collection, the tubes should be inverted 8 times and left for 30 minutes (for a maximum of 60 minutes) at ambient temperature and then centrifuged for 10 minutes at 1300*g* at 4°C. The resulting serum should be transferred into two aliquots in 2.0 mL cryovials (0.5 mL for the determination of the PK of pembrolizumab and <0.5 mL for backup samples). Samples should be stored at ≤-20°C **prior to shipment to the analysis laboratory: Kymos Pharma Services, Spain for pembrolizumab level determination**.
113	9.1.1.3	Pembrolizumab blood levels will be determined using a validated analytical method by at Kymos Pharma Services S.L., Parc Tecnòlogic del Vallès, Ronda de Can Fatjó 7-B, 08290 Cerdanyola del Vallès, Barcelona, Spain.	Pembrolizumab blood levels will be determined using a validated**,** ~~analytical method by at Kymos Pharma Services S.L., Parc Tecnòlogic del Vallès, Ronda de Can Fatjó 7-B, 08290 Cerdanyola del Vallès, Barcelona, Spain~~ **specific and sensitive solid phase enzyme-linked immunosorbent assay (ELISA) based on the sandwich principle**.
113	9.1.1.4	Blood samples for the determination of IPN60090 are described in Table 27.	Blood samples for the determination of ~~IPN60090~~ **paclitaxel** are described in Table ~~27~~ **31**.
114	9.1.1.4	Blood should be collected (2.5 mL) from the uninfused arm, in an EDTA tube at each time point and gently inverted eight times. The samples should be centrifuged at 4°C for 10 minutes. The resulting plasma will be stored at -80°C +/- 10°C in polypropylene tubes as two 500 µL aliquots (primary and back-up) prior to shipment to the analysis laboratory: Kymos Pharma Services, Spain for paclitaxel level determination.	Blood should be collected (2.5 mL) from the uninfused arm, in ~~an~~ **a K2-**EDTA tube at each time point and gently inverted eight times. The samples should be centrifuged **at 2000*g*** 4°C for 10 minutes. The resulting plasma will be stored at -80°C ~~+/-~~ ±10°C in polypropylene tubes as two 500 µL aliquots (primary and back-up) prior to shipment to the analysis laboratory: Kymos Pharma Services, Spain for paclitaxel level determination.

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114	9.1.2	Plasma samples will be analysed to determine concentrations of IPN60090 during dose expansion and paclitaxel (dose escalation and dose expansion) using a validated, specific and sensitive LC-MS/MS method at Kymos Pharma Services.	Plasma samples will be analysed to determine concentrations of IPN60090 during dose expansion and paclitaxel (dose escalation and dose expansion) using a validated, specific and sensitive LC-MS/MS method ~~at Kymos Pharma Services~~.
114	9.1.2	Serum samples will be analysed to determine concentrations of pembrolizumab using a validated, specific and sensitive solid phase enzyme-linked immunosorbent assay (ELISA) based on the sandwich principle.	Serum samples will be analysed to determine concentrations of pembrolizumab using a validated, specific and sensitive solid phase ~~enzyme-linked immunosorbent assay (~~ELISA~~)~~ based on the sandwich principle.
114	9.1.2	An analytical method for the determination of the presence of binding antibodies to pembrolizumab in human serum by ElectroChemiLuminiscence Assay (ECLA) in a bridging format will be developed and validated.	An analytical method for the determination of the presence of binding antibodies to pembrolizumab in human serum by ~~ElectroChemiLuminiscence Assay (~~ECLA~~)~~ in a bridging format will be developed and validated.
115	9.2	9.2 Biomarkers Evaluation Pharmacodynamic biomarkers with the evaluation of Glu:Gln ratio will be assessed in PBMC at the timepoints shown in Table 28.	9.2 **Pharmacodynamic** Biomarkers ~~Evaluation~~ Pharmacodynamic ~~biomarkers~~ **endpoints** with the evaluation of Glu:Gln ratio will be assessed in PBMC at the timepoints shown in Table ~~28~~ **32**.
115	9.2	Table 28 Collection Time Points for PD evaluation in PBMC	Table ~~28~~ **32** Collection Time Points for PD evaluation in PBMC Amended as follows:

Table 32 Collection Time Points for PD evaluation in PBMC

Visit	Timepoint	Volume
Cycle 1, Day 1	Predose	4 tubes x ~~5~~ **6** mL for PBMC isolation
	2 hours postdose	2 tubes x ~~5~~ **6** mL for PBMC isolation
	12 hours postdose	2 tubes x ~~5~~ **6** mL for PBMC isolation
Cycle 1, Day 14	Predose	2 tubes x ~~5~~ **6** mL for PBMC isolation
	2 hours postdose	2 tubes x ~~5~~ **6** mL for PBMC isolation
	12 hours postdose	2 tubes x ~~5~~ **6** mL for PBMC isolation
Cycle 1, Day 15 ~~and EOS/EW~~	Predose	2 tubes x ~~5~~ **6** mL for PBMC isolation
	2 to 4 hours postdose	2 tubes x ~~5~~ **6** mL for PBMC isolation

~~EOS=end of study; EW=early withdrawal~~

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115	9.2	Two tubes of 5 ml collections per timepoint are needed to ensure the possibility of running the assay by purifying a sufficient number of PBMCs for analysis and procuring a back-up pellet for biobanking. At Cycle 1 Day 1 predose only, two additional tubes of 5 mL blood are needed to be used as QC samples. In this case, a total of four tubes of 5 mL of blood are required at Cycle 1 Day 1 predose and at end of study (EOS)/early withdrawal (EW). Biomarkers of patient stratification such as tumour mutation status (e.g. KEAP1/NRF2) and tumour ASNS expression will be evaluated in archival and/or fresh biopsies available at screening and could be also re-assessed on biopsies collected on Cycle 1 Day 15 if data are not conclusive at screening and/or if needed. A panel of mutations including NRF2 could be also explored in collected cfDNA at screening, at Cycle 1 Day 15 and at EOS/EW. In HGSOC patients, blood samples (2 mL) will also be collected for serum Ca-125 assessment at Baseline, on Day 1 of Cycle 3 and then on Day 1 of every other cycle.	Two tubes of ~~5 ml~~ **6 mL** collections per timepoint are needed to ensure the possibility of running the assay by purifying a sufficient number of PBMCs for analysis and procuring a back-up pellet for biobanking. At Cycle 1 Day 1 predose only, two additional tubes of ~~5~~ **6** mL blood are needed to be used as QC samples. In this case, a total of four tubes of ~~5~~ **6** mL of blood are required at Cycle 1 Day 1 predose ~~and at end of study (EOS)/early withdrawal (EW)~~. **At Cycle 1 Day 14 and Cycle 1 Day 15, two tubes of 6 mL will be collected at each time point.** ~~Biomarkers of patient stratification such as tumour mutation status (e.g. KEAP1/NRF2) and tumour ASNS expression will be evaluated in archival and/or fresh biopsies available at screening and could be also re-assessed on biopsies collected on Cycle 1 Day 15 if data are not conclusive at screening and/or if needed. A panel of mutations including NRF2 could be also explored in collected cfDNA at screening, at Cycle 1 Day 15 and at EOS/EW.~~ ~~In HGSOC patients, blood samples (2 mL) will also be collected for serum Ca-125 assessment at Baseline, on Day 1 of Cycle 3 and then on Day 1 of every other cycle.~~
116	10	10 EXPLORATORY BIOMARKERS AND BIOBANKING 10.1 Exploratory Biomarkers Biomarkers of tumour biology evolution under treatment (e.g. immune profiling, PD-L1 expression, Ki67, phosphorylation of histone variant H2AX (γH2AX), LKB1, etc) may be evaluated and correlated with clinical outcome.	10 ~~EXPLORATORY~~ BIOMARKER~~S~~ **EVALUATION** AND BIOBANKING 10.1 ~~Exploratory~~ Biomarker~~s~~ **Evaluation** ~~Biomarkers of tumour biology evolution under treatment (e.g. immune profiling, PD-L1 expression, Ki67, phosphorylation of histone variant H2AX (γH2AX), LKB1, etc) may be evaluated and correlated with clinical outcome.~~ ***10.1.1 Collection of Biopsies for Biomarker Analysis*** **Fresh and/or archival tumour tissue from the biopsy obtained between the completion of the most recent line of treatment until study entry must be available for mutation and**

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			biomarker analysis unless KEAP1/NRF2 mutations were present in any previous biopsy, in which case, no further biopsy is required. For ovarian cancer patients, both archival biopsies obtained between the completion of the most recent line of treatment until study entry and fresh biopsies must be available to evaluate the evolution of ASNS levels over time. Fresh tumour biopsy is performed at the screening visit, Cycle 1 Day 15, and end of study/early withdrawal (EOS/EW [separate consent is required]). The EOS fresh biopsy is optional and requires an additional informed consent for collection. If available, biopsy at initial diagnosis will be also collected for biomarker analysis. ***10.1.2 Collection of cfDNA for Biomarker Analysis*** **Blood (10 mL) will be collected in cfDNA (Streck tubes) for plasma isolation and will be used for biomarker analysis. Sampling is done at screening, on Cycle 1 Day 15 (predose), Cycle 3 Day 1 (predose), then on Day 1 of every other cycle after Cycle 3 (predose) and at EOS/EW.** ***10.1.3 Biomarkers of Patient Stratification*** **KEAP1/NRF2 mutations and ASNS levels will be evaluated in fresh and/or archival biopsies and will be correlated with clinical outcome.** ***10.1.4 Biomarkers of Disease Evolution Under Treatment*** **In HGSOC patients, blood samples (2 mL) will also be collected for serum Ca-125 assessment at Baseline, on Day 1 of Cycle 3 and then on Day 1 of every other cycle.**
117	10.3.4	*10.2.4 Blood for DNA for Biobank* Blood (2.5 mL) will be collected in PAXgene RNA tubes and frozen for storage Sampling is done on Cycle 1 Day 1 predose only	~~*10.2.4*~~ ***10.3.4*** *Blood for DNA for Biobank* Blood (2.5 mL) will be collected in PAXgene ~~RNA~~ **DNA** tubes and frozen for storage**.** Sampling is done on Cycle 1 Day 1 predose only**.**

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117	10.3.5	*10.2.5 Blood for CfDNA for Biobank* Blood (10 mL) will be collected in CfDNA (Streck tubes) for plasma isolation and frozen for storage. Sampling is done on Cycle 1 Day 1, Cycle 1 Day 15, Cycle 3 Day 1, then on Day 1 of every other cycle after Cycle 3 EOS/EW.	~~*10.2.5*~~ ***10.3.5*** *Blood for CfDNA for Biobank* Blood (10 mL) will be collected in CfDNA (Streck tubes) for plasma isolation and frozen for storage. Sampling is done on Cycle 1 Day 1, Cycle 1 Day 15, Cycle 3 Day 1, then on Day 1 of every other cycle after Cycle 3 **and at** EOS/EW.
117	10.3.6	*10.2.6 Blood for PBMC* Remaining and not used PBMC for PD biomarker evaluation (see Section 9.2) should be biobanked. Sampling is done on Cycle 1 Day 1 (predose, and 2 and 12 hours postdose), Cycle 1 Day 14 (predose, and 2 and 12 hours postdose), Cycle 1 Day 15 (predose, and 2 hours postdose), and EOS/EW (predose and 2 hours postdose).	~~*10.2.6*~~ ***10.3.6*** *Blood for PBMC* Remaining and not used PBMC for PD biomarker evaluation (see Section 9.2) should be biobanked. Sampling is done on Cycle 1 Day 1 (predose, and 2 and 12 hours postdose), Cycle 1 Day 14 (predose, and 2 and 12 hours postdose), and Cycle 1 Day 15 (predose, and 2 **to 4** hours postdose)~~,~~ ~~and EOS/EW (predose and 2 hours postdose)~~.
117	10.3.7	*10.2.7 Stools* Sampling procedure will be outlined in a laboratory manual. Sampling is done on Cycle 1 Day 1 (predose and postdose), Cycle 1 Day 15, Day 1 of each following Cycle and EOS/EW	~~*10.2.7*~~ ***10.3.7*** *Stools* Sampling procedure will be outlined in a laboratory manual. Sampling is done on Cycle 1 Day 1 (predose~~ and postdose~~), Cycle 1 Day 15 **(predose)**~~, Day 1 of each following Cycle~~ and EOS/EW.

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	10.3.8	*10.2.8 Biopsies* Fresh or archival tumour tissue must be available for mutation and biomarker analysis. Fresh tumour biopsy is performed at the screening visit, Cycle 1 Day 15, and EOS/EW (separate consent is required). Archival tumour tissue post the most recent line of treatment is acceptable in lieu of fresh biopsy at screening. In case no archival tumour tissue is available in a patient, fresh biopsy should be performed only if the procedure to obtain biopsy has a serious/severe complication risk no greater than 2%. Procedures more invasive than core biopsy should not be used. The EOS fresh biopsy is optional and requires an additional informed consent for collection. Any limitations in tissue availability and sampling in patients with known KEAP1/NRF2 or ASNS status should be discussed with the sponsor. Remaining tumour material from biopsies should be biobanked (separate check box on the Biobanking ICF compared to blood sampling for biobanking).	~~*10.2.8*~~ ***10.3.8 Leftover Tissue Material and Additional*** *Biopsies* ***for Biobanking*** ~~Fresh or archival tumur tissue must be available for mutation and biomarker analysis. Fresh tumour biopsy is performed at the screening visit, Cycle 1 Day 15, and EOS/EW (separate consent is required). Archival tumour tissue post the most recent line of treatment is acceptable in lieu of fresh biopsy at screening. In case no archival tumour tissue is available in a patient, fresh biopsy should be performed only if the procedure to obtain biopsy has a serious/severe complication risk no greater than 2%. Procedures more invasive than core biopsy should not be used. The EOS fresh biopsy is optional and requires an additional informed consent for collection. Any limitations in tissue availability and sampling in patients with known KEAP1/NRF2 or ASNS status should be discussed with the sponsor.~~ ~~Remaining tumour~~ **Leftover tissue** material from **mandatory** biopsies **used for biomarker analysis (e.g. remaining formalin-fixed paraffin-embedded blocks) and additional fresh biopsies (fine-needle aspiration and/or core biopsies) collected will** ~~should~~ be used for ~~biobanked~~ **biobanking** (~~separate~~ **if patient consent is on the** check box ~~on~~ **for** the Biobanking **in the** ICF ~~compared to blood sampling for biobanking~~).

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119	11.1	New text	• **Food effect population: All patients in Part D who have received IPN60090 under fasting and fed conditions (Day -7 and Day -3), have consumed ≥80% of the moderate fat meal in approximately 30 minutes on Day -3, and who have no major protocol deviation affecting the PK variables and who have a sufficient number of IPN60090 plasma concentrations to estimate the main PK parameters (C_{max}, T_{max} and $AUC_{0\text{-}last}$)** • **Pharmacodynamic population: All patients who have at least one PD endpoints measurement. PD endpoints refer to target engagement levels (Glu:Gln ratio in PBMC).**
120	11.1.1	New text	**The analyses of PD parameters will be performed on the PD population. The analyses of food effect PK parameters will be performed on the food effect population.**
120	11.2	11.2 Statistical Methods for Dose Escalation Phase	11.2 Statistical Methods for Dose Escalation Phase **and Food Effect**
123	11.2.1.3	New text	***11.2.1.3 Sample Size for Part D*** **The sample size (n=8) is not based on statistical calculation. A sample size of eight patients allows for a preliminary assessment of the potential effect of food on the PK of IPN60090.**

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125	11.2.3.6	New text	***11.2.3.6 Food Effect Assessment*** **The assessment of food effect will be based upon the ratio of the population geometric means (fed versus fasted, i.e. Day -3 versus Day -7) for the PK parameters (C_{max} and AUC). The data will be transformed prior to analysis using a logarithmic transformation. T_{max} between fed and fasted states will be compared using a non-parametric test such as the Wilcoxon test. Descriptive statistics of other PK parameters will be presented both in fasting and fed conditions.**
128	11.3.4	New text	**The ISAC will meet after 1 year of the start of the study or at the end of the dose escalation, whichever occurs first.**
141	18	New text	**23 Arkenau HT, Barriuso J, Olmos D, et al. Prospective Validation of a Prognostic Score to Improve Patient Selection for Oncology Phase I Trials. J Clin Oncol 2009;27(16):2692-6.**
150/151	Appendix 2	New text	**Appendix 2 ROYAL MARSDEN HOSPITAL SCORE**

Royal Marsden Hospital Prognostic Score

Variable	Score	Hazard Ratio[a]
LDH		**1.85**
≤ULN	**0**	
>ULN	**1**	
Albumin, g/L		**1.83**
≥35	**0**	
<35	**1**	
Sites of metastasis		**1.54**
0-2	**0**	
>2	**1**	

LDH=lactate dehydrogenase; ULN=upper limit of normal
The prognostic score ranges from 0 to 3. The good-prognosis group comprises patients with a score of 0 to 1, and the poor-prognosis group comprises patients with a score of 2 to 3.
a hazard ratios are based on the retrospective analysis
Source: Arkenau et al [23]

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160/161	Appendix 7	New text	**Appendix 7 LIST OF MODERATE INHIBITORS AND INDUCERS OF CYP2C8**

Paclitaxel is mainly metabolised by CYP2C8. Therefore, inhibitors and inducers of CYP2C8 may have an impact on the AUC of paclitaxel.

A moderate inhibitor for a specific CYP450 enzymes is defined as an inhibitor which increases the AUC of a sensitive substrate for that CYP450 enzymes by 2-fold or greater, but less than 5-fold.

A moderate inducer: decreases the AUC of a victim drug between 50% to 80%.

Moderate Inhibitors of CYP2C8
Letermovir **Teriflunomide** **Deferasirox**
Moderate Inducers of CYP2C8
Rifampin **Carbamazepin** **Ivosidenib** **Hormonal contraceptives**

This above table is not all inclusive.

The above lists were compiled from the Indiana University School of Medicine's "P450 Drug Interaction Table – Clinically Relevant Table" [21], supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (October 2017) and the University of Washington's Drug Interaction Database (January 2017). These lists are not comprehensive and are only meant to be used as a guide.

The sponsor should be contacted in case of any doubt. If a medication appears on both the list of prohibited and the list of medications to be used with caution, the medication is prohibited.

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162	Appendix 8	New text	**APPENDIX 8 LIST OF IMMUNOSUPPRESSIVE AGENTS**

Immunosuppressants	**Azathioprine** **Betamethasone** **Dexamethasone** **Hydrocortisone** **Hydroxychloroquine** **Leflunamide** **Methotrexate** **Methylprednisolone** **Prednisolone** **Triamcinolone** **Tenflunomide**
Anti-rejection agents	**Ciclosporin** **Everolimus** **Mycophenolic acid** **Tacrolimus** **Sirolimus**

Biological agents	**Abatacept** **Adalimumab** **Alemtuzumab** **Anakinra** **Apremilast** **Basiliximab** **Bevacizumab** **Canakinumab** **Certolizumab** **Daclizumab** **Eculizumab** **Erlotinid** **Etanercept** **Golimumab** **Infliximab** **Imatinib** **Ixekizumab** **Natalizumab** **Nilotinib** **Perfenidone** **Pomalidomide** **Rituximab** **Secukinumab** **Siltuximab** **Sortatinib** **Thalidomide** **Tocilizumab** **Ustenkinumab** **Vedolizumab** **Fingolimod** **Lenalidomide**
Cytotoxic chemotherapy agents	**Paclitaxel** **Capecitabine** **Fludarabine** **Etoposide** **Bendamustine** **Busulfan** **Carmustine** **Chlorambucil** **Dacarbazine** **Ifosfamide** **Melphalan** **Temozolamide** **Thiotepa** **Treosulfan** **Daunorubicin** **Doxorubicin** **Epirubicin** **Idarubicin** **Mitoxanthrone** **Azacitidine** **Cladribine** **Clofarabine** **Cytarabine** **Decitabine** **Fluorouracil** **Gemcitabine** **Mercaptopurine** **Nelarabine** **Pemetrexed** **Tioguanine** **Crisantaspase** **Eribulin** **Hydroxycarbamide (previously hydroxyurea)** **Mitotane** **Raltitrexed**

	Bleomycin **Mitomycin** **Pentostatin** **Carboplatin** **Cisplatin** **Trabectedin** **Oxaliplatin** **Cabazitaxel** **Docetaxel** **Irinotecan** **Topotecan** **Vinblastine** **Vincristine** **Vinorelbine** **Vinflunine**
Others	**Carbimazole** **Clozapine** **Deferiprone** **Olanzapine** **Phenytoin** **Phenobarbital** **Propylthiouracil**

The above list can be found on: https://www.hse.ie/eng/services/publications/clinical-strategy-and-programmes/list-of-immunosuppressant-medication.pdf

SUMMARY & OUTCOME OF CHANGES:

STUDY NUMBER	D-US-60090-001		
AMENDED PROTOCOL VERSION NUMBER & DATE	Amendment 1.0, Version 2.0, 24 May 2019		
SUBSTANTIAL ☒	**NON-SUBSTANTIAL** ☐		
REASONS FOR CHANGES	To implement comments from the FDA including food effect Part D. Minor changes were made to resolve inconsistencies within the protocol.		
OTHER ACTION REQUIRED?	CRF UPDATE	Yes No	☒ ☐ *(tick one)*
	LOCAL CONSENT FORM UPDATE	Yes No	☒ ☐ *(tick one)*
	DATABASE UPDATE	Yes No	☒ ☐ *(tick one)*
	REPORTING & ANALYSIS PLAN (RAP) UPDATE	Yes No	☒ ☐ *(tick one)*

STUDY NUMBER:	D-US-60090-001
PROTOCOL TITLE:	A PHASE I OPEN LABEL, DOSE ESCALATION AND DOSE EXPANSION STUDY TO INVESTIGATE THE SAFETY, PHARMACOKINETICS, PHARMACODYNAMICS AND ANTI-TUMOUR ACTIVITY OF IPN60090 AS SINGLE AGENT AND IN COMBINATION IN PATIENTS WITH ADVANCED SOLID TUMOURS
AMENDED PROTOCOL VERSION NUMBER & DATE	Amendment 2.0, Version 3.0, 10 December 2019

THE FOLLOWING AMENDMENT(S) IS/ARE PROPOSED: Minor formatting, typographical errors and rephrasing of text to enhance clarity have not been recorded. Any new or amended text added to the protocol is indicated in **bold**. Removed text is shown as ~~strikethrough~~.

Section	VERSION 2.0 24 MAY 2019 WAS	VERSION 3.0 10 DECEMBER 2019 IS	RATIONALE FOR CHANGE
Title Page	**Sponsor Signatory and Medical Monitor:** PPD	**Sponsor Signatory, Medical Monitor and Emergency Contact:** PPD	Administrative update
Title Page	**Emergency Contact:** PPD	**Pharmacovigilance Contact:** PPD	Administrative update
Title Page	Fax: PPD (for serious adverse event (SAE) reporting and pregnancy notification)	~~Fax:~~ PPD ~~(for serious adverse event (SAE) reporting and pregnancy notification)~~	To provide clarifications and specifications regarding SAE reporting requirements.
Title Page	For SAE reporting and pregnancy notification: E-mail: PPD	~~For SAE reporting and pregnancy notification:~~ ~~E-mail:~~ PPD **All serious adverse events (SAEs) and pregnancies must be reported immediately using the electronic data capture (EDC) system. If the EDC system is not available, the SAE form must be emailed to** PPD **or faxed to** PPD **(if not possible to email).**	To provide clarifications and specifications regarding SAE reporting requirements.

Section	VERSION 2.0 24 MAY 2019 WAS	VERSION 3.0 10 DECEMBER 2019 IS	RATIONALE FOR CHANGE
Title Page	**Sponsor Clinical Pharmacologist:** PPD Ipsen Innovation Global Drug Development ZI de Courtaboeuf, 5, Avenue du Canada, 91940 Les Ulis, France PPD	~~**Sponsor Clinical Pharmacologist:**~~ PPD ~~Ipsen Innovation~~ ~~Global Drug Development~~ ~~ZI de Courtaboeuf, 5, Avenue du Canada,~~ ~~91940 Les Ulis, France~~ PPD	Administrative update
Synopsis (exploratory objectives), 2.2.3	To analyse exploratory biomarkers including biomarkers of response or resistance to the treatment and associate them with clinical outcome.	To analyse exploratory biomarkers **in archival and fresh biopsy samples,** including biomarkers of response or resistance to the treatment**,** and associate them with clinical outcome.	Clarification
Synopsis, 3.1.2.1	Any other clinically significant or persistent toxicity (including those outside the DLT assessment period) may be considered a DLT following review by the SRC.	~~Any o~~ **O**ther clinically significant or persistent toxicit**ies**~~y (including those outside the DLT assessment period)~~ may be considered a DLT following review by the SRC.	Reworded to clarify the DLT determination for the clinically significant or persistent toxicities
Synopsis, 3.1.2.1	Any patient who does not complete the DLT assessment period for any reason other than a DLT will be considered nonevaluable for dose escalation decisions and MTD assessment and will be replaced at that same dose level. Patients will be considered eligible for the DLT assessment only if they were able to receive ≥75% of the total planned IPN60090 dose over the DLT assessment period. Noncompliant patients will also be replaced.	Any patient who does not complete the DLT assessment period for any reason other than a DLT will be considered nonevaluable for dose escalation decisions and MTD assessment and will be replaced **by an additional patient** at that same dose level. Patients will be considered eligible for the DLT assessment only if they were able to receive ≥75% of the total planned IPN60090 dose over the DLT assessment period. Noncompliant patients will also be replaced. **The SRC may decide to enrol additional patients based on the safety, PK or PD data.**	Clarification

Section	VERSION 2.0 24 MAY 2019 WAS	VERSION 3.0 10 DECEMBER 2019 IS	RATIONALE FOR CHANGE
Synopsis, 3.1.2.2	Any patient who does not complete the DLT assessment period for any reason other than a DLT will be considered nonevaluable for dose-escalation decisions and MTD assessment and will be replaced by an additional patient at that same dose level. Moreover, patients will be considered eligible for the DLT assessment only if they received ≥75% of the total planned IPN60090 dose and one infusion of pembrolizumab over the DLT assessment period. Noncompliant patients will also be replaced.	Any patient who does not complete the DLT assessment period for any reason other than a DLT will be considered nonevaluable for dose escalation decisions and MTD assessment and will be replaced by an additional patient at that same dose level. Moreover, patients will be considered eligible for the DLT assessment only if they received ≥75% of the total planned IPN60090 dose and one infusion of pembrolizumab over the DLT assessment period. Noncompliant patients will also be replaced. **The SRC may decide to enrol additional patients based on the safety, PK or PD data.**	Clarification
Synopsis, 3.1.2.3	Any patient who does not complete the DLT assessment period for any reason other than a DLT will be considered nonevaluable for dose escalation decisions and MTD assessment and will be replaced by an additional patient at that same dose level. Moreover, patients will be considered eligible for the DLT assessment only if they were able to receive ≥75% of the total planned IPN60090 dose and one infusion of paclitaxel over the DLT assessment period.	Any patient who does not complete the DLT assessment period for any reason other than a DLT will be considered nonevaluable for dose escalation decisions and MTD assessment and will be replaced by an additional patient at that same dose level. Moreover, patients will be considered eligible for the DLT assessment only if they were able to receive ≥75% of the total planned IPN60090 dose and one infusion of paclitaxel over the DLT assessment period. **The SRC may decide to enrol additional patients based on the safety, PK or PD data.**	Clarification
Synopsis, 3.1.4	Enrolment into dose expansion cohorts will occur simultaneously and independently of each other.	Enrolment into dose expansion cohorts will occur ~~simultaneously and~~ independently of each other.	Clarification

Section	VERSION 2.0 24 MAY 2019 WAS	VERSION 3.0 10 DECEMBER 2019 IS	RATIONALE FOR CHANGE
Synopsis (inclusion criteria), 4.1.1	(3) Histologically or cytologically confirmed advanced solid tumours including tumours known to harbour KEAP1 and NRF2 mutations or have low ASNS expression levels (IHC Grade 0 or 1). - In dose escalations of all Parts, patients may be KEAP1/NRF2 wild-type or mutated and have tumours with any level of ASNS expression. For dose expansions, see specific inclusion criteria per Part below.	(3) Histologically or cytologically confirmed advanced solid tumours including tumours known to harbour KEAP1 and/**or** NRF2 mutations or have low ASNS expression levels ~~(IHC Grade 0 or 1)~~. - In dose escalations of all **p**arts, patients may be KEAP1 **and** /NRF2 wild-type or mutated and have tumours with any level of ASNS expression. For dose expansions, see specific inclusion criteria per part below.	Amended for consistency with the immunohistochemistry cut-off investigation.
Synopsis (inclusion criteria), 4.1.1	(8) Eastern Cooperative Oncology Group Performance Status ≤1 and a Royal Marsden Hospital score of 0 or 1≤1.	(8) Eastern Cooperative Oncology Group Performance Status ≤1 ~~and a Royal Marsden Hospital score of 0 or 1≤1~~.	Requested by the principal investigator.
Synopsis (inclusion criteria), 4.1.1	(9) Adequate organ function as indicated by the following laboratory values independent of transfusion within 2 weeks before first study treatment:	(9) Adequate organ function as indicated by the following laboratory values ~~independent of transfusion within 2 weeks before first study treatment~~:	No counter-indication for transfusions prior to study entry
Synopsis (Part A specific inclusion criteria), 4.1.2	(A2) Patients with following tumour types will be recruited: (a) NSCLC KEAP1/NRF2 mutant (b) KEAP1/NRF2 other tumours (c) HGSOC ASNS^{low}	(A1) Patients with **the** following tumour types will be recruited: (a) NSCLC KEAP1 **and**/**or** NRF2 mutant (b) KEAP1 **and**/**or** NRF2 **mutant** other tumours (c) HGSOC ASNS^{low}	Clarification

Section	VERSION 2.0 24 MAY 2019 WAS	VERSION 3.0 10 DECEMBER 2019 IS	RATIONALE FOR CHANGE
Synopsis (Part B specific inclusion criteria), 4.1.3	New text.	(B2) Patients may have received previous treatment with any anti-programmed cell death protein 1 (PD-1)/programmed death-ligand 1 PD-L1) monoclonal antibody (mAb) administered either as monotherapy, or in combination with other checkpoint inhibitors or other therapies. PD-1 treatment progression is defined by meeting all of the following criteria: (a) Has received at least 2 doses of an approved anti-PD-1/L1 mAb. (b) Has demonstrated disease progression after PD-1/L1 as defined by iRECIST v1.1. The initial evidence of disease progression is to be confirmed by a second assessment no less than four weeks from the date of the first documented disease progression, in the absence of rapid clinical progression.	Added per Merck requirement.
Synopsis (Part B specific inclusion criteria), 4.1.3	(B2) Patients with following tumour types will be recruited during the dose expansion only: (a) NSCLC KEAP1 or NRF2 mutant (b) Other KEAP1 or NRF2 mutant tumours (c) KEAP1 or NRF2 wild type tumours with any level of ASNS expression	(B3) Patients with **the** following tumour types will be recruited during the dose expansion only: (a) NSCLC KEAP1 **and**/or NRF2 mutant (b) Other KEAP1 **and**/or NRF2 mutant tumours (c) KEAP1 **and** ~~or~~ NRF2 wild type tumours with any level of ASNS expression	Clarification

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Synopsis (Part B specific exclusion criteria), 4.2.3	New text	**(B4) Patient has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are 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 are allowed; however, intranasal influenza vaccines (e.g. FluMist®) are live attenuated vaccines and are not allowed.**	Pembrolizumab administration requirement
Synopsis (test product, dose, mode of administration)	IPN60090 intake should be performed at least 2 hours before the start of pembrolizumab infusion.	IPN60090 intake should be performed at least **1** ~~2~~ hour~~s~~ before the start of pembrolizumab infusion.	Clarification due to the PK blood sampling schedule
Synopsis (primary endpoint), 3.2.1	The safety and tolerability of IPN60090 as a single agent (Part A and Part D) and in combination with pembrolizumab (Part B) or paclitaxel (Part C) will be assessed by continuous reporting of AEs and serious AEs (SAEs), clinical laboratory test results, the presence of anti-pembrolizumab antidrug antibodies (ADA; Part B only), vital signs measurements, ECG and physical examination results and concomitant medication usage.	The safety and tolerability of IPN60090 as a single agent (Part A and Part D) and in combination with pembrolizumab (Part B) or paclitaxel (Part C) will be assessed by ~~continuous reporting~~ the **rate** of **DLTs at each dose level in the dose escalation, and the rate of** AEs **and the rate of Grade 3 and higher AEs in the dose escalation and dose expansion. Continuous monitoring of AEs and** serious AEs (SAEs), clinical laboratory test results, the presence of anti -pembrolizumab antidrug antibodies (ADA; Part B only), vital signs measurements, **electrocardiogram (**ECG**)** and physical examination results and concomitant medication usage **will be performed**.	Clarification.

Section	VERSION 2.0 24 MAY 2019 WAS	VERSION 3.0 10 DECEMBER 2019 IS	RATIONALE FOR CHANGE
Synopsis (secondary endpoints), 3.2.2	Tumour mutation status (for example KEAP1/NRF2, serine/threonine kinase 11, Kirsten Rat Sarcoma Viral Oncogene Homolog and Myc overexpression and/or amplification, etc)	Tumour mutation status (for example KEAP1/NRF2, serine/threonine kinase 11, Kirsten Rat Sarcoma Viral Oncogene Homolog and ~~Myc overexpression and/or amplification, etc~~ **other mutations**) **and correlation with clinical outcome**	Amended as this is not collected in the EDC.
Synopsis (safety endpoint), 3.2.4	The safety and tolerability of IPN60090 will be assessed by continuous monitoring of the rate of AEs and SAEs, clinical laboratory test results, the presence of anti-pembrolizumab ADA (Part B only), vital signs measurements, ECG and physical examination results, and concomitant medication usage.	The safety and tolerability of IPN60090 will be assessed by ~~continuous monitoring of~~ the rate of **DLTs at each dose level in the dose escalation, and the rate of** AEs and **the rate of Grade 3 and higher AEs in the dose escalation and dose expansion. Continuous monitoring of AEs and** SAEs, clinical laboratory test results, the presence of anti-pembrolizumab ADA (Part B only), vital signs measurements, ECG and physical examination results, and concomitant medication usage **will be performed**.	Clarification
Synopsis (statistical methods)	Food effect population: All patients in Part D who have received IPN60090 under fasting and fed conditions (Day 7 and Day 3), have consumed ≥80% of the moderate fat meal on Day 3, and who have no major protocol deviation affecting the PK variables and who have a sufficient number of IPN60090 plasma concentrations to estimate the main PK parameters (C_{max}, T_{max} and $AUC_{0\text{-}last}$).	Food effect population: All patients in Part D who have received IPN60090 under fasting and fed conditions (Day 7 and Day 3), have consumed ≥80% of the moderate fat meal **in approximately 30 minutes** on Day 3, and who have no major protocol deviation affecting the PK variables and who have a sufficient number of IPN60090 plasma concentrations to estimate the main PK parameters (C_{max}, T_{max} and $AUC_{0\text{-}last}$).	Amended for consistency with Section 11.1
Synopsis (statistical methods)	Duration of PFS is defined as time from first study drug to the earlier of either PD per RECIST 1.1, iPD per iRECIST or death from any cause.	~~Duration of PFS is defined as time from first study drug to the earlier of either PD per RECIST 1.1, iPD per iRECIST or death from any cause.~~	Will be defined in the Statistical Analysis Plan.

Section	VERSION 2.0 24 MAY 2019 WAS	VERSION 3.0 10 DECEMBER 2019 IS	RATIONALE FOR CHANGE
Synopsis	Based on the dose escalation data, the protocol may be amended to further define the dose expansion cohorts.	~~Based on the dose escalation data, the protocol may be amended to further define the dose expansion cohorts.~~	Deleted to remove duplication with later sentence
1.1	IPN60090 is currently in preclinical development with expected first treatment in humans by Q1 2019.	IPN60090 is currently in ~~pre~~clinical development ~~with expected~~ **and the** first treatment in humans ~~by Q1~~ **took place on 04 April 2019**.	Updated to reflect current status
2.2.2	To document the steady state concentrations of pembrolizumab and paclitaxel (Parts B and C).	To document the ~~steady state~~ concentrations of pembrolizumab and paclitaxel (Parts B and C).	Amended for consistency with the synopsis
3.1.2.2	At all dose levels, IPN60090 will be administered orally BID starting from Day 1 of each 21-day cycle and pembrolizumab will be administered as one intravenous (i.v.) infusion every 21 days (±1 day in Cycle 1 and ±3 days in all other cycles) starting from Day 1 of each cycle.	At all dose levels, IPN60090 will be administered orally BID starting from Day 1 of each 21-day cycle and pembrolizumab will be administered as one intravenous (i.v.) infusion every 21 days (±1 day in Cycle 1 and ±3 days in all other cycles) starting from Day 1 of each cycle. **The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumour type.**	Clarification of pembrolizumab administration

Section	VERSION 2.0 24 MAY 2019 WAS	VERSION 3.0 10 DECEMBER 2019 IS	RATIONALE FOR CHANGE
3.1.2.2	The DLT assessment period will consist of the first 21 days of treatment (one cycle). The SRC will evaluate safety, available PK and PD data in order to make a decision on dose escalation, and to determine the MTD and the RD. The safety data reviewed by the SRC will include the safety findings and DLTs observed during the DLT assessment period from the previous cohort. The SRC may decide to evaluate an intermediate, not predefined, previously evaluated or not previously-evaluated dose or a less frequent dosing schedule that will not exceed the MTD level if evaluation of toxicity at such a dose or schedule is desired.	The DLT assessment period **for IPN60090 in combination with pembrolizumab (Part B)** will consist of the first 21 days of treatment (one cycle). **An additional safety assessment for delayed onset AEs will be performed at 6 weeks (42 days), and at 12 weeks (84 days).** The SRC will evaluate safety **and** available PK and PD data in order to make a decision on dose escalation, and to determine the MTD and the RD. The safety data reviewed by the SRC will include the safety findings and DLTs observed during the DLT assessment period from the previous cohort. The SRC may decide to evaluate an intermediate, not predefined, previously evaluated or not previously-evaluated dose **of IPN60090** or a less frequent dosing schedule that will not exceed the MTD level if evaluation of toxicity at such a dose or schedule is desired.	Clarification of pembrolizumab AE assessment
3.1.2.2, 3.1.2.3	Any other clinically significant or persistent toxicity may be considered a DLT following review by the SRC.	~~Any o~~ **O**ther clinically significant or persistent toxicit**ies**~~y~~ may be considered a DLT following review by the SRC.	Reworded to clarify the DLT determination for the clinically significant or persistent toxicities
4.1.4	(C2) Patients with the following tumour types will be recruited during the dose expansion only: (a) KEAP1 or NRF2 mutant tumours (b) $ASNS^{low}$ tumours (c) KEAP1 or NRF2 wild type tumours with any level of ASNS expression	(C2) Patients with the following tumour types will be recruited during the dose expansion only: (a) KEAP1 or NRF2 mutant tumours (b) **HGSOC** $ASNS^{low}$ tumours (c) KEAP1 or NRF2 wild type tumours with any level of ASNS expression	Amended for consistency with the rest of the protocol

Section	VERSION 2.0 24 MAY 2019 WAS	VERSION 3.0 10 DECEMBER 2019 IS	RATIONALE FOR CHANGE
5.1	Table 14 Study Procedures and Assessments (Parts A to C) New assessment added	Ophthalmological examination at screening added.	Additional baseline safety evaluation
5.1	Table 14 Study Procedures and Assessments (Parts A to C) Assessment deleted	RMH status at screening deleted	Requested by the principal investigator.
5.1	Table 15 Study Procedures and Assessments (Part D) New assessment added	Ophthalmological examination at screening added.	Additional baseline safety evaluation
5.1	Table 15 Study Procedures and Assessments (Part D) Assessment deleted	RMH status at screening deleted	Requested by the principal investigator.
5.3	Table 16 Total Blood Volume for All Evaluations (Parts A to C) Blood sampling for PK of paclitaxel (Part C only): Volume per sample (mL): 2.5 Total max volume/month (mL): 5 Total volume (Part C): 229	Table 16 Total Blood Volume for All Evaluations (Parts A to C) Blood sampling for PK of paclitaxel (Part C only): Volume per sample (mL): **2** ~~2.5~~ Total max volume/month (mL): **4** ~~5~~ Total volume (Part C): **228** ~~229~~	Clarification of blood volume required for PK analysis.

Section	VERSION 2.0 24 MAY 2019 WAS	VERSION 3.0 10 DECEMBER 2019 IS	RATIONALE FOR CHANGE
6.2.2.1	IPN60090 capsules should be taken before the pembrolizumab infusion. Pembrolizumab dose will be fixed at 200 mg (or according to the approved local label for particular tumour types) administered as an i.v. infusion over 30 minutes every 21 days (±1 day in Cycle 1 and ±3 days in all other cycles) (Day 1 of every cycle) through an i.v. line containing a sterile, non-pyrogenic, low protein binding 0.2 µm to 5 µm in line or add on filter. Premedication with antipyretic and antihistamine may be considered. Reconstitution and preparation of pembrolizumab solution for infusion should be done as per locally approved product information.	IPN60090 capsules should be taken **at least 1 hour** before the pembrolizumab infusion. **The predose, 30-minute (±5 minutes) and 1-hour (±5 minutes) blood samples for PK analysis should be drawn before initiating the pembrolizumab infusion.** **The p**embrolizumab dose will be fixed at 200 mg (or according to the approved local label for particular tumour types) administered as an i.v. infusion over 30 minutes every 21 days (±1 day in Cycle 1 and ±3 days in all other cycles) (Day 1 of every cycle) through an i.v. line containing a sterile, non-pyrogenic, low protein binding 0.2 µm to 5 µm in line or add on filter. Premedication with antipyretic and antihistamine may be considered. Reconstitution and preparation of pembrolizumab solution for infusion should be done as per **the** locally approved product information. **Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (i.e. infusion time is 30 minutes (-5 minutes/+10 minutes).**	Clarification of pembrolizumab administration
6.4.4.1	New heading added	**6.4.4.1 Dose Adjustments and Modifications for Nonimmune Related Adverse Events**	Heading amended to allow for new Section 6.4.4.2.

Section	VERSION 2.0 24 MAY 2019 WAS	VERSION 3.0 10 DECEMBER 2019 IS	RATIONALE FOR CHANGE
6.4.4.2	New section added	**6.4.4.2 Dose Adjustments and Modifications for Immune-Related Adverse Events Associated with Pembrolizumab** **Adverse events associated with pembrolizumab exposure may represent an immune-related response. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm aetiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 24.**	Clarification of pembrolizumab AE assessment

Table 24 Dose Modification and Toxicity Management Guidelines for Immune-Related AEs Associated with Pembrolizumab

irAEs	Toxicity grade (CTCAE v5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhoea/colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (i.e. diarrhoea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e. peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhoea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhoea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via i.v. infusion
	Recurrent Grade 3 or Grade 4	Permanently discontinue		
AST or ALT elevation or increased bilirubin	Grade 2[a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3[b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or hyperglycaemia	New onset T1DM or Grade 3 or 4 hyperglycaemia associated with evidence of β-cell failure	Withhold[d]	• Initiate insulin replacement therapy for participants with T1DM • Administer antihyperglycaemic in participants with hyperglycaemia	• Monitor participants for hyperglycaemia or other signs and symptoms of diabetes

irAEs	Toxicity grade (CTCAE v5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (e.g. propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3, 4	Continue	• Initiate thyroid replacement hormones (e.g. levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm aetiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		

irAEs	Toxicity grade (CTCAE v5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
All other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm aetiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event[e]		
	Recurrent Grade 3 or 4	Permanently discontinue		

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; GI=gastrointestinal; irAE=immune-related adverse event; i.v.=intravenous; T1DM=Type 1 diabetes mellitus; ULN=upper limit of normal

[a] AST/ALT: >3.0 to 5.0 × ULN if baseline normal; >3.0 to 5.0 × baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 × ULN if baseline normal; >1.5 to 3.0 × baseline, if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 × ULN if baseline normal; >5.0 to 20.0 × baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 × ULN if baseline normal; >3.0 to 10.0 × baseline, if baseline abnormal

[c] AST/ALT: >20.0 × ULN if baseline normal; >20.0 × baseline, if baseline abnormal; bilirubin: >10.0 × ULN if baseline normal; >10.0 × baseline, if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include but are not limited to: Guillain-Barre Syndrome, encephalitis, Stevens-Johnson Syndrome and toxic epidermal necrolysis.

Section	VERSION 2.0 24 MAY 2019 WAS	VERSION 3.0 10 DECEMBER 2019 IS	RATIONALE FOR CHANGE
6.4.4.2	New text	**General instructions:** **(1) Severe and life-threatening irAEs should be treated with i.v. corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.** **(2) Pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab treatment.** **(3) The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue for at least 4 weeks.** **(4) If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤ Grade 1 after the corticosteroid taper.**	Clarification of pembrolizumab AE management

Section	VERSION 2.0 24 MAY 2019 WAS	VERSION 3.0 10 DECEMBER 2019 IS	RATIONALE FOR CHANGE
7.2.2	New text	**iRECIST is adapted to account for the unique tumour response seen with immunotherapeutic drugs. When clinically stable, patients should not be discontinued until progression is confirmed by the investigator. Some patients can have initial radiographic progressive disease due to a transient tumour flare in the first few months after the start of immunotherapy, and then experience subsequent disease response.** **Clinical stability is defined as the following:** • **absence of symptoms and signs indicating clinically significant progression of disease** • **no decline in ECOG performance status** • **no requirements for intensified management, including increased analgesia, radiation or other palliative care** **Any patient deemed clinically unstable should be discontinued from study treatment at first radiologic evidence of progressive disease and will not be required to have repeat tumour imaging for confirmation of progressive disease by iRECIST.** **Patients who are clinically stable and exhibit initial radiographic progressive disease may continue to receive study treatment and the tumour assessment should be repeated 4 to 6 weeks later to confirm progressive disease by iRECIST, per investigator assessment. If repeated imaging does not confirm progressive disease per iRECIST, as assessed by the investigator, and the patient continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If progressive disease is confirmed, patients will be discontinued from study treatment.** **If a patient has confirmed radiographic progression as defined in Appendix 10, study treatment should be discontinued; however, if the patient is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the sponsor. In this case, if study treatment is continued, tumour imaging should follow the 6-week tumour assessment schedule.** **A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 29.**	Clarification of pembrolizumab response assessment

Table 29 Imaging and Treatment after First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST v1.1	Repeat imaging at 4 to 8 weeks to confirm PD	May continue study treatment at the investigator's discretion while awaiting confirmatory tumour imaging by site by iRECIST	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only	Discontinue treatment
Repeat tumour imaging confirms PD (iCPD) by iRECIST per investigator assessment	No additional imaging required	Discontinue treatment (exception is possible upon consultation with sponsor)	No additional imaging required	Not applicable
Repeat tumour imaging shows iUPD by iRECIST per investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study treatment at the investigator's discretion	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only	Discontinue treatment
Repeat tumour imaging shows iSD, iPR or iCR by iRECIST per investigator assessment.	Continue regularly scheduled imaging assessments	Continue study treatment at the investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion. Next tumour imaging should occur according to the regular imaging schedule.

BICR=Blinded Independent Central Review; iCPD=iRECIST confirmed progressive disease; iCR=iRECIST complete response; iRECIST=modified Response Evaluation Criteria in Solid Tumors for immune-based therapeutics; iSD=iRECIST stable disease; iUPD=iRECIST unconfirmed progressive disease; PD=progressive disease; RECIST=Response Evaluation Criteria in Solid Tumors; VOP=verification of progression

Section	VERSION 2.0 24 MAY 2019 WAS	VERSION 3.0 10 DECEMBER 2019 IS	RATIONALE FOR CHANGE
8.1.1	The following is considered an event of special interest and must be reported to Ipsen within 24 hours of site awareness, irrespective of causality: serum aminotransferases ALT/AST >3×ULN, with increase in total serum bilirubin >2×ULN.	The following **events** ~~is considered an event of special interest and~~ must be reported to **the sponsor** ~~Ipsen~~ within 24 hours of **the** site**'s** awareness, irrespective of causality: serum aminotransferases ALT/AST >3×ULN, with increase in total serum bilirubin >2×ULN.	To provide clarifications and specifications regarding additional AEs that require immediate reporting to the sponsor from the site.
8.1.4	All SAEs (as defined below), regardless of treatment group or suspected relationship to IMP, must be reported immediately (within 24 hours of the investigator's knowledge of the event) via the electronic data capture (EDC) system or using the email specified at the beginning of this protocol in case the EDC is not available. If the immediate report is submitted by telephone, or if the EDC was not available at initial reporting, this must be followed by detailed written reports using the SAE form in the eCRF.	All SAEs (as defined below), regardless of treatment group or suspected relationship to IMP, must be reported immediately (within 24 hours of the investigator's knowledge of the event) ~~via~~ **using** the electronic data capture (EDC) system**. In instances where the EDC system is not available, the SAE form must be completed and sent to the email address or fax number (if not possible to email)** ~~or using the email~~ specified at the beginning of this protocol ~~in case the EDC is not available~~. If the immediate report is submitted by telephone, or if the EDC was not available at initial reporting, this must be followed by **the reporting of this SAE using the EDC system as soon as it becomes available** ~~detailed written reports using the SAE form in the eCRF~~.	To provide clarifications and specifications regarding SAE reporting requirements and timelines.

Section	VERSION 2.0 24 MAY 2019 WAS	VERSION 3.0 10 DECEMBER 2019 IS	RATIONALE FOR CHANGE
8.1.4	In addition to the above criteria, any additional AE that the sponsor or an investigator considers serious should be immediately reported to the sponsor and included in the corporate SAEs database system.	In addition to the above criteria**, the following events must be reported to the sponsor within 24 hours of the site's awareness, irrespective of causality: serum aminotransferases ALT/AST >3×ULN, with increase in total serum bilirubin >2×ULN** ~~any additional AE that the sponsor or an investigator considers serious should be immediately reported to the sponsor and included in the corporate SAEs database system.~~	To provide clarifications and specifications regarding additional AEs that require immediate reporting to the sponsor from the site.
8.1.4	Any SAE must be reported immediately (within 24 hours) in the eCRF or using the email specified at the beginning of this protocol in case the EDC system is not available, independent of the circumstances or suspected cause, if it occurs or comes to the attention of the investigator at any time during the study period.	Any SAE must be reported immediately (within 24 hours) **using the EDC system** ~~in the eCRF~~ or ~~using the~~ email **address or fax number (if not possible to email)** specified at the beginning of this protocol in case the EDC system is not available, independent of the circumstances or suspected cause, if it occurs or comes to the attention of the investigator at any time during the study period.	To provide clarifications and specifications regarding SAE reporting requirements.
8.1.4	New text	**All AEs meeting serious criteria, from the time of treatment/allocation through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever occurs first, must be reported by the investigator.** **Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to the sponsor if the event is considered to be drug-related.**	To provide clarifications and specifications regarding SAE reporting requirements and timelines.

Section	VERSION 2.0 24 MAY 2019 WAS	VERSION 3.0 10 DECEMBER 2019 IS	RATIONALE FOR CHANGE
8.1.5	Pregnancies with a conception date within 4 months after patient's last dose of IMP must also be reported to the investigator for onward reporting to the sponsor.	~~Pregnancies with a conception date within 4 months after patient's last dose of IMP must also be reported to the investigator for onward reporting to the sponsor.~~ **All pregnancies, from the time of treatment/allocation through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, must be reported by the investigator.**	To provide clarifications and specifications pregnancy reporting requirements and timelines.
9.1.1.3	Samples should be stored at ≤-20°C prior to shipment to the analysis laboratory: Kymos Pharma Services, Spain for pembrolizumab level determination.	Samples should be stored at ≤-20°C prior to shipment to the analysis laboratory~~: Kymos Pharma Services, Spain~~ for pembrolizumab level determination.	Details of CRO performing analysis not needed in the protocol.
9.1.1.4	Blood volumes in table updated. Was: 2.5 mL	Blood volumes in table: ~~2.5 mL~~ 2.**0** mL	Clarification of blood volume required for PK analysis.
9.1.1.4	Blood should be collected (2.5 mL) from the uninfused arm, in a K2 EDTA tube at each time point and gently inverted eight times. The samples should be centrifuged at 2000*g* at 4°C for 10 minutes. The resulting plasma will be stored at -80°C ±10°C in polypropylene tubes as two 500 µL aliquots (primary and back-up) prior to shipment to the analysis laboratory: Kymos Pharma Services, Spain for paclitaxel level determination.	Blood **samples (2.0 mL)** should be collected ~~(2.5 mL)~~ from the uninfused arm, in a K2 EDTA tube at each time point and gently inverted eight times. The samples should be centrifuged at 2000*g* at 4°C for 10 minutes. The resulting plasma will be stored at -80°C ±10°C in polypropylene tubes as two 500 µL aliquots (primary and back-up) prior to shipment to the analysis laboratory~~: Kymos Pharma Services, Spain~~ for paclitaxel level determination.	Clarification of blood volume required for PK analysis.

Section	VERSION 2.0 24 MAY 2019 WAS	VERSION 3.0 10 DECEMBER 2019 IS	RATIONALE FOR CHANGE
11.2.3.5	A TEAE is defined as any AE that occurs during the active phase of the study if: • It was not present prior to receiving the first administration of study drugs; or • It was present prior to receiving the first administration of study drugs but the intensity increased during the active phase of the study; or • It was present prior to receiving the first administration of one of the study drugs, the intensity is the same but the drug relationship became related during the active phase of the study.	A TEAE is defined as any AE that occurs during the ~~active phase of the~~ study if: • It was not present prior to receiving the first administration of study drugs; or • It was present prior to receiving the first administration of study drugs but the intensity increased during the active phase of the study; or • It was present prior to receiving the first administration of one of the study drugs, the intensity is the same but the drug relationship became related during the active phase of the study.	Removed reference to 'active phase' as term not used elsewhere in protocol.
14.3	As required by local regulations, the sponsor's Regulatory Affairs group (or its delegates) will ensure all legal regulatory aspects are covered and obtain approval of the appropriate regulatory bodies, prior to study initiation in regions where an approval is required.	As required by local regulations, the sponsor's Regulatory Affairs **and Clinical Operations** groups (or ~~its~~ **their** delegates) will ensure all legal regulatory aspects are covered and obtain approval of the appropriate regulatory bodies, prior to study initiation in regions where an approval is required.	Administrative update.
Appendix 2	Royal Marsden Hospital Score	Appendix deleted	Requested by the principal investigator.
Appendix 9	New appendix added	See below.	Clarification of pembrolizumab response assessment

Appendix 9 DESCRIPTION OF THE iRECIST PROCESS FOR ASSESSMENT OF DISEASE PROGRESSION

Assessment at Screening and Prior to RECIST 1.1 Progression

Until radiographic disease progression based on RECIST 1.1, there is no distinct iRECIST assessment.

Assessment and Decision at RECIST 1.1 Progression

For patients who show evidence of radiological progressive disease by RECIST v1.1 as determined by the investigator, the investigator will decide whether to continue a patient on study treatment until repeat imaging is obtained (using iRECIST for patient management). This decision by the investigator should be based on the patient's overall clinical condition.

Clinical stability is defined as the following:

- absence of symptoms and signs indicating clinically significant progression of disease
- no decline in ECOG performance status
- no requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any patient deemed **clinically unstable** should be discontinued from study treatment at site-assessed first radiologic evidence of progressive disease, and is not required to have repeat tumour imaging for confirmation of progressive disease by iRECIST.

If the investigator decides to continue treatment, the participant may continue to receive study treatment and the tumour assessment should be repeated 4 to 8 weeks later to confirm progressive disease by iRECIST, per investigator assessment. Images should continue to be sent in to the central imaging vendor for potential retrospective Blinded Independent Central Review.

Tumour flare may manifest as any factor causing radiographic progression per RECIST v1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥20% and ≥5 mm from nadir
  - Note: the iRECIST publication uses the terminology "sum of measurements", but "sum of diameters" will be used in this protocol, consistent with the original RECIST v1.1 terminology.
- Unequivocal progression of non-target lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including unconfirmed progressive disease (iUPD) and confirmed progressive disease (iCPD). For the purposes of iRECIST assessment, the first visit showing progression according to RECIST v1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and nontarget lesions identified at baseline by RECIST v1.1 will be assessed as usual.

New lesions will be classified as measurable or nonmeasurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST v1.1. From measurable new lesions, up to five lesions total (up to two per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated, and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Nontarget.

Assessment at the Confirmatory Imaging

On the confirmatory imaging, the patient will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening
  - For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm, compared to any prior iUPD timepoint
  - For nontarget lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD timepoint; this does not have to meet the "unequivocal" standard of RECIST v1.1
  - For new lesions, worsening is any of these:
    - An increase in the new lesion sum of diameters by ≥5 mm from a prior iUPD timepoint
    - Visible growth of new nontarget lesions
    - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST v1.1

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) remains above the initial progressive disease threshold (by RECIST v1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the imaging on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation imaging proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial progressive disease threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudoprogression, and the level of suspicion for progression is "reset". This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management Following the Confirmatory Imaging

If repeat imaging does not confirm progressive disease per iRECIST, as assessed by the investigator, and the patient continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, patients will be discontinued from study treatment.

NOTE: If a patient has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the sponsor. In this case, if study treatment is continued, tumour imaging should continue to be performed following the intervals previously outlined and submitted to the central imaging vendor.

Detection of Progression at Visits After Pseudoprogression Resolves

After resolution of pseudoprogression (i.e. achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
  - Sum of diameters reaches the progressive disease threshold (≥20% and ≥5 mm increase from nadir) either for the first time, or after resolution of previous pseudoprogression. The nadir is always the smallest sum of diameters seen during the entire study, either before or after an instance of pseudoprogression.
- Nontarget lesions
  - If nontarget lesions have never shown unequivocal progression, their doing so for the first-time results in iUPD.
  - If nontarget lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of nontarget lesions, taken as a whole.
- New lesions
  - New lesions appear for the first time
  - Additional new lesions appear

- Previously identified new target lesions show an increase of ≥5 mm in the new lesion sum of diameters, from the nadir value of that sum
- Previously identified nontarget lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, with one exception: if new lesions occurred at a prior instance of iUPD, and at the confirmatory imaging the burden of new lesions has increased from its smallest value (for new target lesions, the sum of diameters is ≥5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

Additional details about iRECIST are provided in the iRECIST publication.

SUMMARY & OUTCOME OF CHANGES:

STUDY NUMBER	D-US-60090-001		
AMENDED PROTOCOL VERSION NUMBER & DATE	Amendment 2.0, Version 3.0, 10 December 2019		
SUBSTANTIAL ☒	**NON-SUBSTANTIAL** ☐		
REASON(S) FOR CHANGES	Additional baseline safety evaluation added. Pembrolizumab standard text for administration, AE assessment and response assessment added per Merck requirements. Clarifications and specifications regarding SAE and pregnancy reporting requirements and timelines added.		
OTHER ACTION REQUIRED?	CRF UPDATE	Yes ☒ No ☐ *(tick one)*	
	LOCAL CONSENT FORM UPDATE	Yes ☒ No ☐ *(tick one)*	
	DATABASE UPDATE	Yes ☒ No ☐ *(tick one)*	
	STATISTICAL ANALYSIS PLAN (SAP) UPDATE	Yes ☒ No ☐ *(tick one)*	