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STATISTICAL ANALYSIS PLAN

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
Protocol Number:	D-US-60090-001
Protocol Version/Date:	Version 1.0/18 October 2018 Version 1.1/20 December 2018 Version 1.2/21 December 2018 Version 2.0/24 May 2019 Version 3.0/10 December 2019
Investigational Product:	IPN60090
Sponsor:	IPSEN Bioscience, Ipsen Group 650 East Kendall Street, Cambridge MA 02142, USA Tel: PPD
SAP Version/Date:	Version 2.0/17 December 2020

SIGNATURE PAGE

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Protocol Number:	IPN60090
SAP Version/Date:	Version 2.0/17 December 2020

We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

Signature	**Date**
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eSignature PPD ***Ipsen***	
PPD PPD ***Medpace, Inc.***	
PPD PPD ***Ipsen***	

VERSION HISTORY

Version	Version Date	Description
1.0	26 July 2019	Original signed version
2.0	17 December 2020	• Updates to be consistent with protocol version 3.0 from protocol version 2.0. • Section 3.3.7 add actual cumulative dose in mg for IPN60090 descriptive summary • Section 2.3.2.1 PFS includes clinical disease progression collected at end of treatment • Section 3.3.2 add COVID-19 analysis impact language.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Antidrug antibodies
AE	Adverse event
ALK	Anaplastic Lymphoma Kinase
ANC	Absolute Neutrophil Count
ASNS	Asparagine synthetase
$ASNS^{low}$	Low protein expression level of asparagine synthetase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic class
AUC	Area under the plasma concentration time curve
AUC0-last	Area under the plasma concentration time curve from time 0 to the last time point with quantifiable concentrations
BID	Bis in die (twice daily)
BOIN	Bayesian Optimal Interval
BOR	Best overall response
CBR	Clinical benefit rate
CD8	Cluster of differentiation 8
cfDNA	Circulating free deoxyribonucleic acid
CI	Confidence interval
CL/F	Apparent total clearance from plasma
Cmax	Maximum observed plasma drug concentration
Cmin	Minimum observed plasma concentration
CPI	Checkpoint inhibitor
CR	Complete response
CSR	Clinical Study Report
C_{trough}	Trough plasma concentration
DAP	Data Analysis Plan
DCR	Disease control rate
DL	Dose level
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	Epidermal growth factor receptor
Glu:Gln	glutamate:glutamine ratio
GLS1	Glutaminase-1
HCC	Hepatocellular carcinoma
HGSOC	High-grade serous ovarian cancer
HGSCC	Head and neck squamous cell carcinoma
iCR	immune complete response
iCPD	immune confirmed progressive disease
iPFS	immune progression-free survival
iPR	immune partial response

Abbreviation	Definition
iRECIST	immune-related Response Evaluation Criteria in Solid Tumours
ISAC	Independent safety assessment committee
iSD	immune stable disease
iUPD	Immune unconfirmed progressive disease
i.v.	intravenous
KEAP1	Kelch-like ECH-associated protein 1
KRAS	Kirsten Rat Sarcoma Viral Oncogene Homolog
LEVF	Left Ventricle Ejection Fraction
LKB1	Liver kinase B1
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
MUGA	Multigated acquisition
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NSCLC	Non-small cell lung cancer
ORR	Objective response rata
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
PD	Pharmacodynamics
PD-1	Programmed cell death protein 1
PFS	Progression free survival
PK	Pharmacokinetics
Q3W	Every 3 weeks
PR	Partial response
RD	Recommended dose
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SRC	Safety review committee
STK11	Serine/threonine kinase 11
$T_{1/2}$	Elimination half life
TEAE	Treatment-emergent adverse event
T_{max}	time to maximum observed drug concentration
T_{reg}	regulatory T-cells
V/F	Apparent volume of distribution
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from the study with protocol number D-US-60090-001. The initial version of SAP was finalized prior to the end of Part A. Any deviations from the SAP will be documented in SAP amendments before database lock and in the final Clinical Study Report (CSR) after database lock.

2 STUDY OVERVIEW

2.1 Study Objectives

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.

2.1.1 Primary Objective

- 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, the recommended dose (RD) of IPN60090 as a single agent (Part A) and in combination therapy with pembrolizumab (Part B) or paclitaxel (Part C).

2.1.2 Secondary Objectives

- 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.

2.1.3 Exploratory Objectives

- 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).

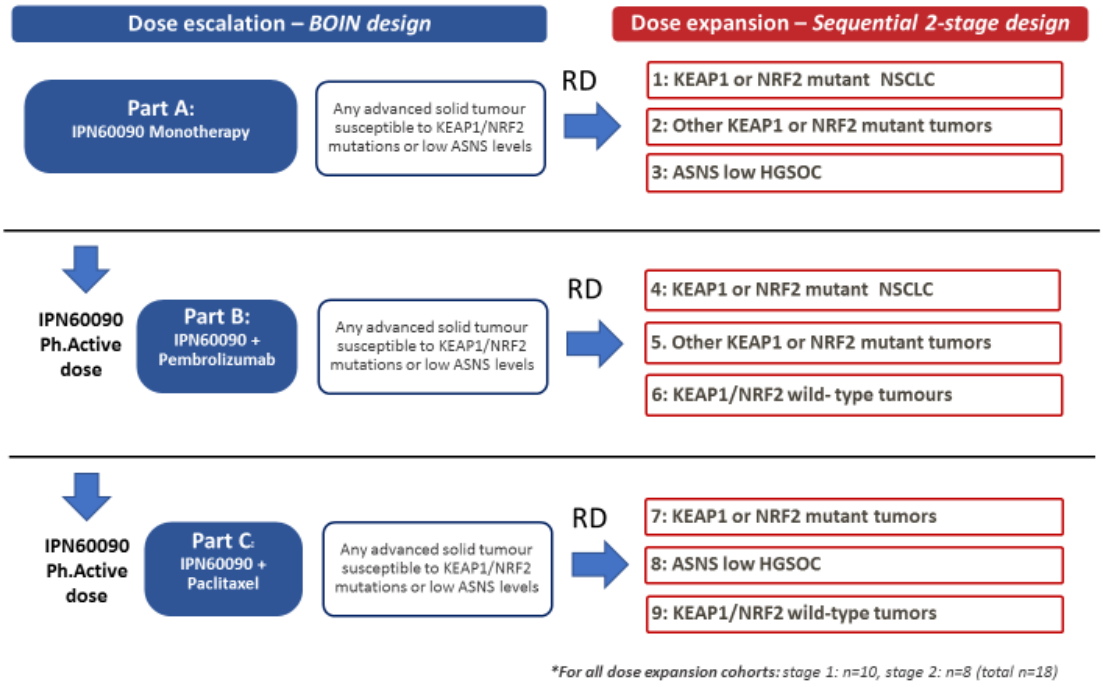
2.2 Study Design

2.2.1 Overview

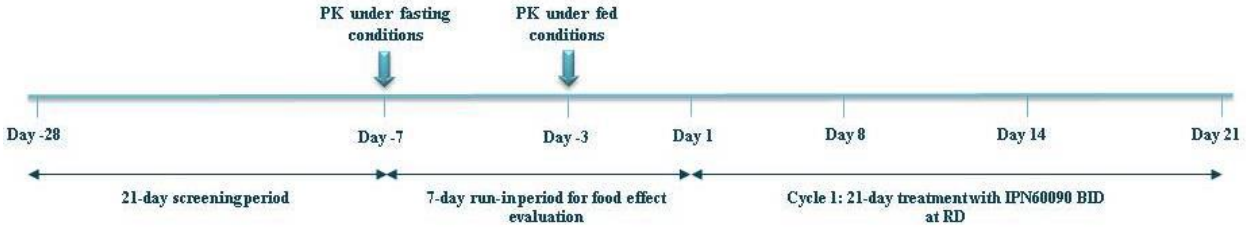
This is a phase I first in human, open-label, dose-escalation and expansion study of IPN60090 as a single agent and in combination in patients with advanced solid tumours.

As summarized in Figure 1, the study will be divided into three parts.

Figure 1 IPN60090: Summary of Early Clinical Development



PART D



ASNS=asparagine synthetase; BOIN=Bayesian Optimal Interval; CPI=checkpoint inhibitor; 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 PBMC (peripheral blood mononuclear cells)) 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 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 (EGFR), anaplastic lymphoma kinase (ALK), 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% 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 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 sensitive to GLS1 inhibition will explore 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 potential to boost response via increase of 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's early clinical data from CB-839 that indicate preliminary anti-tumour activity of the combination in 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 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 biomarker-unselected patient population across approved tumour types, based on early clinical data from CB-839 which indicate 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 tumour growth inhibition (at 50 and 100 mg/kg BID) was observed when at least 50% up to 96% inhibition of 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 SRC.

2.2.2 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 one of dose expansion and 72 patients in stage two). Section 2.2.7.3 explains the details of 2-stage design for expansion phase.

2.2.3 Dose Escalations

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

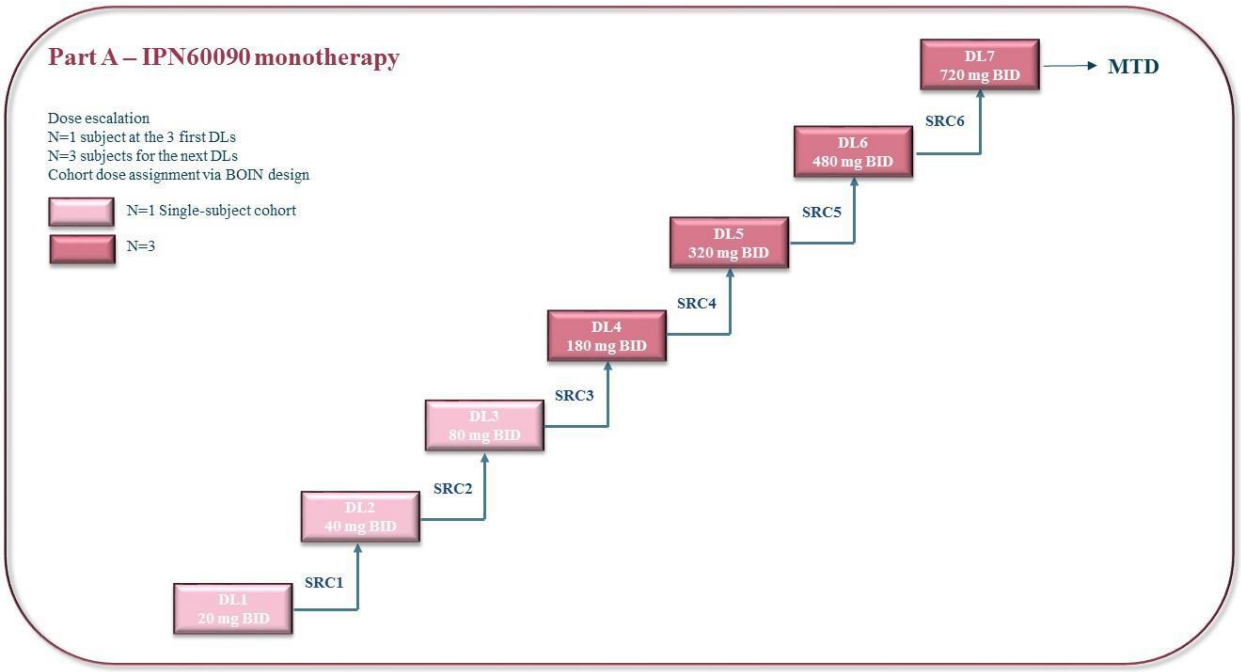
The dose escalation portion of Part A is to evaluate the safety, tolerability, PK and PD of IPN60090 given as a BID oral dose (every 12 hours), during or after a meal, over a 21-day cycle.

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 (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 2). The study will follow a BOIN design for dose escalation and de-escalation (Liu S and Yuan Y, 2015). Dose levels provided are examples and after the starting dose, the dose level to be tested 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.

Figure 2 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.
Dose levels are examples; after the starting dose, dose level will be determined by each SRC meeting. After each SRC meeting, dose level can be escalated,de-escalated, expanded or eliminated as permitted by the BOIN design.

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 1.

Table 1 Dose Escalation Phase I-Part A in Monotherapy

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).

Part A monotherapy dose-escalation will enroll 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 any 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. 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 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%. The decision

rules for dose-escalation and de-escalation from a local BOIN design are defined in Table 4 in section 2.2.7.1. At any point, additional patients may be enrolled for required safety and/or biomarker analysis.

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 Safety Review Committee (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.

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/mm3 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 alkaline phosphatase (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 aspartate amino transferase/alanine amino transferase (ALT/AST) and/or bilirubin, with the following exceptions:
  - for patients with Grade 1 ALT/AST at baseline (>upper limit of normal (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 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.
- 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 non-evaluable 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. Patients who received less than 75% of total planned dose due to DLT will be included for dose-escalation decisions. Noncompliant (<75% without DLT) 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.

2.2.3.2 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 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 2.

Table 2 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 enroll 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. The decision rules for dose-escalation and de-escalation from a local BOIN design is defined in Table 4 in section 2.2.7.1.

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.

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/mm3 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 non-evaluable 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. Patients who received less than 75% of total planned dose due to DLT will be included for dose-escalation decisions. Noncompliant (<75% without DLT) 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.

2.2.3.3 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 starting from Day 1 of each cycle. The predefined dose-escalation plan is described in Table 3.

Table 3 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/m^2 Q3W [b]	175 or 135 mg/m^2 Q3W [b]	175 or 135 mg/m^2 Q3W [b]	175 or 135 mg/m^2 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 enroll 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. The decision rules for dose-escalation and de-escalation from a local BOIN design is defined in Table 4in section 2.2.7.1.

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 DL-1.

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/mm3 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 which 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 non-evaluable 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. Patients who received less than 75% of total planned dose due to DLT will be included for dose-escalation decisions. Noncompliant (<75% without DLT) 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 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.

2.2.3.4 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, and will be followed for safety and efficacy in a separate cohort.

2.2.4 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.
- • 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.

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 disease progression on the 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.

2.2.5 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 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 enroll 10 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.

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.

2.2.6 Study Drug

2.2.6.1 IPN60090

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.

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

During 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 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.

During 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. 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 paclitaxel infusion and at least 2 hours prior to H2 blocker administration.

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

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.

2.2.6.2 Part B: Pembrolizumab

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 (Day 1 of every cycle).

2.2.6.3 Part C: Paclitaxel

IPN60090 intake should be performed at least 2.5 hours before the start of 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.

2.2.7 Sample Size Determination

2.2.7.1 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 4, 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 4 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 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 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 5). From each scenario, %MTD identified at dose level with true DLT at 30% is the highest and the average number of patients treated at MTD dose level is between 4.1 and 7.0 patients.

Table 5 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

2.2.7.2 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 enroll 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 trial 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.

2.2.7.3 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.

2.2.7.4 Sample Size Determination for the 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 enroll 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 Part 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 6 shows the operating characteristics for a range of true CBRs.

Table 6 Operating Characteristics for True CBRs

True CBR	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

For expansion phase, 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 analyzed 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.

2.3 Study Endpoints

2.3.1 Primary Endpoints

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:

- The incidence of DLTs (Parts A, Part B and Part C) during the DLT assessment period in order to determine the MTD.

  MTD is further defined in section 2.2.3 using a BOIN design. DLT is further defined in section 2.2.3. The DLT assessment period will be the first 21 days of treatment (one cycle). The BOIN design described in section 2.2.7.1

- Safety, PK and PD parameters (Parts A, Part B, Part C) in order to determine the RD.

2.3.2 Secondary Endpoints

2.3.2.1 Efficacy Endpoints

- Anti-tumour activity parameters assessed locally for dose escalation and centrally for dose expansion and collected on eCRF using Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 (Appendix B, Eisenhauer EA, 2009) for Parts A, C, and D and immune-related RECIST (iRECIST) (Appendix C, Seymour L, 2017) 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
    - The BOR for Parts A, C, and D is defined as the best response designation (in the order of CR, PR, SD, PD) for each subject that is recorded between the date of the first dose of the study drug and the date of documented disease progression per RECIST 1.1 or the date of subsequent anticancer therapy whichever occurs first.

- The BOR for Part B is defined as the best response designation (in the order of iCR, iPR, iSD, iUPD, iCPD) for each subject that is recorded between the date of the first dose of the study drug and the date of documented disease progression per iRECIST or the date of subsequent anticancer therapy whichever occurs first.

- 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) for Parts A, C, and D is defined as the time from first dose of study medication to the first documented objective disease progression (for RECIST), clinical disease progression collected at end of treatment, or death due to any cause, whichever occurs first.

  Progression free survival (PFS) for Part B is defined as the time from first dose of study medication to the first confirmed objective disease progression (for iRECIST), clinical disease progression collected at end of treatment or death due to any cause, whichever occurs first.

  PFS (months) = (event or censoring date – first dose date + 1)/30.4375

  PFS will be right-censored for patients who met one or more of the following conditions:

  - no baseline disease assessment or no evaluable post baseline disease assessments unless death occurred prior to the first planned assessment at post baseline (in which case death will be considered a PFS event).
  - amputation or surgical resection of tumour in the absence of documented disease progression.
  - subsequent anticancer therapy in the absence of documented disease progression.
  - died or documented disease progression after missing two or more consecutively scheduled disease assessment visits
  - alive and without documented disease progression on or before the data cutoff date

  If a patient meets more than one of these conditions, then the scenario that occurs first will be used for analysis. The progression or censoring date will be determined based on the conventions listed in Table 7:

Table 7: Date of Progression or Censoring for PFS

Situation	Date of event or censoring	Outcome
Death before first planned disease assessment	Date of death	Event
Death or disease progression (per RECIST 1.1 for Parts A, Part C, and Part D or iRECIST for Part B) or clinical disease progression collected at end of treatment between planned disease assessments	Date of death or first disease assessment showing disease progression, whichever occurs first	Event
No baseline disease assessment or no evaluable post-baseline disease assessments	Date of first dose of IPN60090	Censored
Surgical resection or subsequent anticancer treatment started before disease progression (per RECIST 1.1 for Parts A, Part C, and Part D or iRECIST for Part B) or clinical disease progression collected at end of treatment or death (without disease progression beforehand)	Date of last adequate disease assessment prior to surgery or start of subsequent anticancer treatment	Censored
Death or disease progression (per RECIST 1.1 for Parts A, Part C, and Part D or iRECIST for Part B) or clinical disease progression collected at end of treatment immediately after missing two scan intervals* consecutively scheduled disease assessments	Date of last adequate disease assessment visit without documentation of disease progression before the first missed visit	Censored
Alive and without disease progression	Date of last adequate disease assessment	Censored

*two scan interval is defined as 12 weeks + 2 weeks or 98 days.

The PFS time will always be derived based on scan dates and not visit dates. Scans contributing towards a particular visit may be performed on different dates. The following rules will be applied:

- Date of progression will be determined based on the earliest scan dates that triggered the progression per RECIST 1.1 or iRECIST criteria or clinical disease progression collected at end of treatment.
- When censoring a subject for PFS, the subject will be censored at the latest of the scan date for overall assessment.

For Part B, the event date to be used for calculation of PFS should be the first date that progression criteria are met (i.e. the date of immune unconfirmed progressive disease (iUPD)) providing that iCPD is confirmed at the next assessment. If iUPD occurs, but is disregarded because of later iSD, iPR or iCR, that iUPD date should not be used as the progression event date. If progression is not confirmed and there is no subsequent iSD, iPR or iCR then the iUPD date should still be used in the following scenarios: if the patient stops study treatment because they were not considered to be clinically stable, or no further response assessments are done (patient refusal or protocol non-compliance or patient death); the next time point responses are all iUPD, and immune confirmed progressive disease (iCPD) never occurs; or the patient dies of cancer.

- Overall survival (OS) is defined as the time from first dose of study medication to death due to any cause. Patients who were lost to follow-up or who were still alive at the time of analysis will be censored at the last day the patient was known to be alive or data cut-off date, whichever occurs first. OS will be calculated as follows:

  OS (months) = (Death or Censoring Date – First Dose Date + 1)/30.4375

2.3.2.2 Pharmacodynamic Endpoints

- Pharmacodynamic parameters and biomarkers, including:
  - 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 (ASNS level and $ASNS^{low}$ and $ASNS^{high}$)

2.3.2.3 Pharmacokinetic Endpoints

Pharmacokinetic parameters of IPN60090, including but not limited to maximum observed plasma 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) apparent volume of distribution (V/F) of IPN60090 (Parts A to D), 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) will be detailed in a separate Data Analysis Plan (DAP) and the PK report will be a standalone report.

2.3.3 Exploratory Endpoints

- Biomarkers of tumour biology parameters, including immune profiling, PD-L1 expression, nuclear antigen Ki67 (Ki67), phosphorylation of histone variant H2AX (γH2AX), LKB1 will be detailed in a separate DAP and reported as a standalone report.
- Exploratory IPN60090 concentrations in urine in Part A of dose escalation, including PK parameters, the amount of IPN60090 excreted in urine and renal clearance will also be detailed in the separate DAP and reported as a standalone report.

2.3.4 Biobanking

Biobanked for potential future exploratory biomarkers parameters, including PBMC, plasma, serum, circulating free DNA (cfDNA), paxgene DNA, paxgene ribonucleic acid (RNA), stools, and remaining material from tumour biopsies will be performed outside the scope of the main study and reported separately.

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Analysis Day Conventions

Analysis day will be calculated from the date of first dose of study drug. The day of the first dose of study drug will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0.

3.1.2 Analysis Visits

No study visit windows will be used for analyses.

3.1.3 Definition of Baseline

Baseline is defined as the last measurement prior to the first dose of study treatment.

3.1.4 Summary Statistics

Unless otherwise noted, data will be listed by dose level and part in the dose escalation phase and by cohort and part in the dose expansion phase. Data will be summarized by dose level, part and overall in the dose escalation phase and by cohort, part and overall in the dose expansion phase. Data will be also summarized for all the patients included in the study at the RD (dose escalation and dose expansion phases).

Categorical variables will be summarized by frequency distributions (number and percentages of patients). The 95% exact binomial confidence interval (CI) using the Clopper-Pearson method will be calculated when specified.

Continuous variables will be summarized by descriptive statistics (mean, standard deviation, median, minimum, and maximum).

Time-to-event variables will be summarized using the Kaplan-Meier estimates of the median and the corresponding 2-sided 95% confidence intervals using Greenwood's formula when specified.

3.1.5 Hypothesis Testing

No formal statistical testing will be carried out.

3.1.6 Evaluation of Site Effect

It is not planned to perform a subgroup analysis on individual or groups of centres.

3.1.7 Handling of Missing Data

Missing data will not be imputed. Only observed data will be used in the summaries and analyses.

In all listings, missing or incomplete dates should be left as they have been recorded. However, for calculation / sorting / assignation based on dates, the following methods will be used:

1) The most conservative approach will be systematically considered (i.e. if the onset date of an AE/concomitant medication is missing / incomplete, it is assumed to have occurred during the study (i.e. a TEAE for AEs) except if the partial onset date or other data [stop date, …] indicates differently).
2) A missing/incomplete date of medical history or disease diagnosis will be assumed to have occurred before any study treatment.
3) If a partial date and the associated information do not allow to state about the assignation to a group / category, all the possible groups / categories will be considered (i.e.: an AE could be assigned to several possible doses at event onset according to its partial onset date and stop date. Particularly an AE with missing start date will be assigned to each dose received before its end date. Similarly a medication with partial start and stop dates could be considered as prior and concomitant treatment).
4) Where this is possible, the derivations based on a partial date will be presented as superior inequalities (i.e.: for an AE started in FEB2004 after the administration performed on 31JAN2004, the days since last dose will be "≥2", similarly the duration of ongoing AEs or medication will be"≥xx" according to the start and last visit dates).

3.2 Analysis Populations

3.2.1 Screened Population

All patients screened (i.e. who signed the informed consent).

3.2.2 Safety Population

All patients who are exposed to (or started receiving) IPN60090 and/or the combination agents.

3.2.3 DLT Evaluable Population for Dose-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 who received less than 75% of total planned dose due to DLT will be included in this population. Patients in Part B and Part C need to have at least 1 dose of pembrolizumab or paclitaxel in order to be included in this population.

3.2.4 Efficacy Population

All patients who receive at least one dose of IPN60090.

3.2.5 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}, $AUC_{0\text{-}last}$).

3.2.6 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.

The NCA, the Pop PK and PK/PD modeling will be described in separate data analysis plans. Pharmacokinetic population for noncompartmental analysis and pharmacokinetic population for population PK modelling will be presented in standalone PK reports.

3.2.7 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 $AUC_{0\text{-}last}$).

3.2.8 Pharmacodynamic Population

All patients who have at least one PD endpoint measurement. PD endpoints refer to target engagement levels (Glu:Gln ratio in PBMC).

3.3 Patient Data and Study Conduct

3.3.1 Patient Disposition

The numbers and percentages of patients enrolled and included in each analysis population will be tabulated. The reasons for patient exclusions from each of the analysis populations will also be tabulated.

The numbers and percentages of patients screened, received study treatment, entered Cycle 2, Cycle 3, Cycle 4, and additional cycles will be summarized.

Primary reasons for discontinuation of study treatments (Part A: IPN60090, Part B: IPN60090 and pembrolizumab, Part C: IPN60090 and paclitaxel or Part D: IPN60090) and primary reasons for ending long-term follow-up will be tabulated.

The number and percentages of patients in Stage 1 and Stage 2 of the expansion phase will be summarized.

For Part A and Part D, the number and percentages of patients switched to Part B or Part C will be summarized.

3.3.2 Protocol Deviations

Any major protocol deviation will be documented as described in the protocol deviation plan, and its impact on population for any patient will be specified. The final list of protocol deviations impacting the analysis populations will be reviewed prior to database lock. Counts and percentages of patients with major protocol deviations by deviation category will be summarized.

Major protocol deviations related to COVID-19 will be flagged.

In addition, study visits not performed, performed remotely, performed at an alternative location, and visits delayed or partially completed will be listed. Patients or treatment discontinued related to COVID-19 will also be listed.

3.3.3 Analysis Populations

The analyses of safety data will be performed on the safety population and DLT evaluable population when applicable.

The analyses of anti-tumour activity and exploratory efficacy assessments will be performed on efficacy population.

The analyses of pharmacodynamic parameters will be performed on pharmacodynamic population.

3.3.4 Demographic and Baseline Characteristics

All demographic and baseline characteristics will be listed for all screened patients.

Summary statistics will be provided for demographic and baseline characteristics for the safety population and repeated for each analysis population if they are different from the safety population.

Demographic characteristics will include

- age (years),
- sex (male, female),
- ethnicity (Hispanic or Latino, Not Hispanic or Latino, not reported),
- race (Asian, American Indian or Alaska Native, Black or African American, Native Hawaiian or Other Pacific Islander, White, not reported, Other),
- weight (kg),
- height (cm)
- body mass index (BMI) in kg/m^2,
- ECOG performance status (0, 1, 2, 3, 4)
- Baseline disease characteristics will include
    - primary disease cancer type (breast cancer, ovarian cancer, renal cell carcinoma, non-small cell lung cancer, head and neck cancer, urothelial carcinoma, hepatocellular carcinoma, other)

- time from initial diagnosis of primary disease until the informed consent date (months)
- time from first relapse after last treatment until the informed consent date (months)
- Classification of Malignant Tumours (TNM) Staging for tumour, node, metastasis at diagnosis and at screening
- mutations prior screening assessment (wild type, mutated, not tested)
- ASNS grade (0, 1, 2, 3)
- ASNS H-score (0-300)
- prior chemotherapy for cancer (yes, no)
- prior hormonal therapy for cancer (yes, no)
- prior immunotherapy for cancer (yes, no)
- prior radiotherapy for cancer (yes, no)
- prior surgical procedures for cancer (yes, no)
- Best response to prior chemotherapy, hormonal, immunotherapy (CR, PR, SD, progressive disease (PD), inevaluable (NE), not available (NA))
- pembrolizumab antibody (positive, negative) for Part B only

3.3.5 Medical or Surgical History

Medical and surgical history will be coded initially using the latest version of MedDRA in use in Ipsen system.

Listings will present the preferred term and verbatim text.

A frequency table of the number and percentage of patients will be provided for medical and surgical history by primary system organ class and preferred term.

3.3.6 Concomitant Medications

Prior or concomitant therapy or medications. Prior, concomitant, and post-treatment medications are defined as following:

- Prior medications will include medications which started prior to the first IPN60090 administration date.
- Concomitant medications will include medications taken any time from the first IPN60090 administration date through 30 days following the last IPN60090 administration date or until the start of a subsequent anticancer therapy, whichever is earlier. Medications that started prior to the first dose of study drug but continued into treatment are considered concomitant.
- Post-treatment medications will include medications taken any time after from the first IPN60090 administration date through 30 days following the last IPN60090 administration date or until the start of a subsequent anticancer therapy, whichever is earlier.

Prior and concomitant therapies will be coded using the latest version of WHO-Drug Dictionary in use in Ipsen system. The therapeutic class will correspond to the second level of ATC code, which is, corresponding to the first 3 figures of ATC code.

Listings will be presented for the therapeutic class, preferred term and verbatim text.

A frequency table of the number and percentage of patients will be provided for concomitant therapies by therapeutic class and preferred name for each cohort and cancer type. Prior, concomitant, and post-treatment medications will be summarized separately.

Anticancer treatment collected in eCRF during the follow-up period will be summarized separately.

3.3.7 Study Drug Exposure and Compliance

Number of treatment cycles completed by each patients will be summarized for each study drug (IPN60090, pembrolizumab, and paclitaxel).

The number and percentage of patients with dose interruptions, missed doses, intra-subject dose escalations, intra-subject dose de-escalations, actual cumulative dose in mg for IPN60090 will be summarized. The number and percentage of patients with interruptions in i.v. infusion for pembrolizumab or paclitaxel will be summarized.

All information collected on the eCRF related to IPN60090 administration, pembrolizumab infusion, and paclitaxel infusion including any dose interruptions or modifications, pembrolizumab infusion and paclitaxel infusion will be listed.

3.4 Efficacy Assessment

3.4.1 Anti-tumour Activity Evaluation

Overall response at each time point captured on the tumour response eCRF will be used for the analysis and will not be programmatically derived using target and non-target lesions data. BOR will be derived at each time point.

Overall response and BOR at each time point will be presented in data listings.

The efficacy proportions CBR, ORR and DCR will be summarized using descriptive statistics and will be graphically displayed if appropriate. The corresponding exact binomial 95% CI using the Clopper-Pearson method will be provided.

In addition to the analyses described above, the best overall response (CR, PR, SD, PD, and NE for Part A, Part C, and Part D, and iCR, iPR, iSD, iUPD, iCPD and NE for Part B) will be summarized descriptively to show the number and percentage of subjects in each response category.

The baseline and the best change (%) or largest reduction (%) from baseline in tumour size (sum of the diameters) of the target lesion will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum). Waterfall plots will be used to depict graphically for individual patients of their best change (%) or largest reduction (%) from baseline in the sum of the diameters in target lesions. Spider and swimmer plots will be used to display the change in tumour burden over time for individual patients and the occurrence of clinical outcomes of interest (e.g., tumour response, disease progression, treatment discontinuation, death).

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% CI for median duration using Greenwood's formula will be provided.

3.5 Pharmacodynamic parameters

3.5.1 Target Engagement

The target engagement or PD levels (Glu:Gln ratio in peripheral blood mononuclear cells (PBMC)) at each time point will be summarized descriptively. The number and percentage of patients with at least 50%, 60%, 70%, 80%, and 90% inhibition of Glu:Gln ratio will be summarized. The maximum target

engagement will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum).

The correlation between the level of maximum target engagement Glu:Gln ratio and clinical outcome (efficacy and safety) will be explored.

3.5.2 Biomarkers of Patient Stratification

The number and percentage of patients in KEAP1/NRF2 mutant versus wild type will be summarized. The numbers and percentages of patients with all mutations for each indication collected from the eCRF will be summarized.

The number and percentage of patients for the expression levels of ASNS, which could be presented as a grade from 0 to 3; and/or as a H-Score from 0 to 300, and/or as % of positive cells, will be summarized.

Clinical outcomes (efficacy and safety) will be summarized by biomarker positive patients, biomarker negative patients and by tumor type.

These will be summarized (1) by study part for dose escalation phase and by study part for expansion phase, (2) by pooling Parts A, Part B and Part C in escalation phase and pooling Parts A, Part B and Part C expansion phase, and (3) by pooling escalation phase, expansion phase and food effect cohort.

Pharmacodynamic parameter tables will be presented in section 14.2.

3.6 Pharmacokinetic Assessment and PK/PD Assessment

3.6.1 PK Assessment Using NCA

The PK data analysis will be detailed in a separate DAP and reported as a standalone report.

3.6.2 PK Modeling

The PK modeling data analysis will be detailed in a separate DAP and reported as a standalone report.

3.6.3 PK/PD Modeling

PK/PD modeling will be performed as feasible, to describe the relationships between relevant selected biomarkers, efficacy parameters, safety parameters, safety parameters and/or PK descriptors. The PK/PD plan will be detailed in the PK modeling plan and reported in the same standalone report than the PK modeling report.

There will be two separate PK data analysis plans and reported as standalone reports, the NCA PK data analysis plan and Pop PK modeling and PK/PD modeling (including PK/QT modeling if needed).

3.6.4 Dose Response Analysis

A dose response will be performed to describe any relationship between the dose received and markers of the activity or of the response. This analysis will be performed for the dose escalation in Parts A, B and C. Part D data may be included in the dose response analysis. The dose response analysis will be detailed in a separate DAP and reported as a standalone report.

3.7 Safety Assessment

Unless otherwise specified, the safety analyses will be carried out on patients in the safety population.

3.7.1 Adverse Events (AEs)

Adverse events will be monitored from the time that the patient gives informed consent and throughout the study. Adverse events will be coded using the latest version of MedDRA in use in Ipsen system and graded according to NCI-CTCAE version 5.0.

TEAE is defined as any AE that occurs during 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 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 study.

An overall summary table of all adverse events will be presented, which will summarize the number and percentages of patients and number of events of the following categories:

- Any AEs,
- Any TEAEs,
- Any study treatment – related TEAEs,
- NCI CTCAE grade 3/4/5 TEAEs,
- Study treatment –related NCI CTCAE grade 3/4/5 TEAEs,
- DLT TEAEs,
- Deaths due to TEAEs,
- Study treatment-related TEAEs leading to death,
- Treatment-emergent SAEs,
- Study treatment-related treatment-emergent SAEs,
- Discontinuation of study treatment due to TEAEs,
- Discontinuation of study treatment due to study treatment-related TEAEs,
- Dose reduction due to TEAEs,
- Dose reduction due to study treatment-related TEAEs,
- Dose interruption due to TEAEs,
- Dose interruption due to study treatment-related TEAEs,
- Dose increased due to TEAEs,
- Dose increased due to study treatment-related TEAEs,

Summary tables of adverse events in each above category will be provided with the number and percentage of patients with adverse events and the number of events classified by primary system organ class, and preferred term and associated NCI/CTC worst grade. System organ classes are sorted by decreasing frequency. Preferred terms are sorted by decreasing frequency within each system organ class. In the event of multiple occurrences of the same adverse events being reported by the same patient, the

maximum intensity (Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > missing > not applicable) and the most serious causality (related) will be chosen.

Listings will be presented specifically for all adverse events, SAEs and TEAEs leading to discontinuation of study drug.

3.7.2 Dose Limiting Toxicity

DLTs during Cycle 1 will be summarized by cohort/dose level with the number and percentage of patients with DLTs classified by primary system organ class and preferred term. The number of occurrences of a DLT will also be presented.

Listings of all DLTs will also be presented.

DLTs will be captured in AEs eCRF page and used in the analysis. Programming check will be performed and reconciled prior to each SRC, database lock and analysis generation.

3.7.3 Clinical Laboratory Tests

During dose escalation part, all clinical safety laboratory tests will be performed at local laboratories. During dose expansion part, safety blood samples will be analysed centrally.

Clinical laboratory parameters, including

- Haematology: red blood cell count, haemoglobin, haematocrit, mean corpuscular volume, mean corpuscular, haemoglobin, mean corpuscular haemoglobin concentration, white blood cell (WBC) count, with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils and others) and platelet count.
- Biochemistry: 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 modification of diet in renal disease (MDRD) formula.
- Urinalysis: pH, protein, ketones, bilirubin, blood, urobilinogen, nitrites, leukocytes, glucose and specific gravity by dipstick.

A separate listing of normal ranges for SI units will be provided by gender and age where relevant.

Hematological and biochemistry toxicities when available will be recorded and graded according to the NCI-CTC criteria, version 5.0. Laboratory data must be listed in Standard International (SI) units and also be listed in local units. Abnormal values will be flagged (High, [H], Low [L], clinically significant [C], NCI-CTC grade (G)) where applicable. Any unscheduled laboratory assessments will be flagged [U] in the listings.

Descriptive statistics will be provided for selected clinical laboratory test results (hematology, coagulation, and chemistry) and changes from baseline for the minimum post-baseline value, maximum post-baseline value, and last post-baseline value. Both scheduled and unscheduled post-baseline values will be considered for the summaries.

Directional shifts in laboratory toxicity grades (comparing baseline grade with worst post-baseline grade) will be analyzed using standard shift tables, presenting number and proportion of patients and their maximum grade shift for selected laboratory parameters (ALT, AST, total bilirubin, ALP, creatinine,

hemoglobin, absolute neutrophils, platelet counts, white blood cell counts, aPTT, and INR). Plots over time will also be presented for these selected laboratory parameters.

The number and percentage of patients with the following potentially clinically significant abnormal liver function tests will be summarized:

- ALT ≥3xULN, ≥5xULN, ≥10xULN, and ≥20xULN
- AST ≥3xULN, ≥5xULN, ≥10xULN, and ≥20xULN
- Total bilirubin ≥2xULN
- ALT/AST ≥3×ULN with total bilirubin ≥2×ULN without elevation of ALP (< 2xULN)
- ALT or AST ≥3xULN, total bilirubin ≥2xULN, and ALP ≥2xULN

3.7.4 Vital Signs

Baseline values will be defined as the last vital signs measurement collected prior to the first dose of study treatment.

Vital signs include blood pressures, heart rate, respiratory rate and temperature.

Summary statistics will be presented for baseline and changes from baseline for the minimum post-baseline value, maximum post-baseline value.

Vital signs will be listed at each assessment. Any unscheduled vital signs will be flagged [U] in the listing.

3.7.5 Electrocardiograms

Baseline will be defined as the last ECG measurement collected prior to the first dose of study treatment.

Standard 12-lead ECG parameters include sinus rhythm (yes/no), RR interval, PR interval, QRS duration, QT interval, QTcF interval, QTcB interval, and interpretation of clinical significance.

QTcB is the duration of the QT interval corrected for heart rate by Bazett's formula: QTcB = QT/(RR)½; and QTcF is the duration of the QT interval corrected for heart rate by Fridericia's formula: QTcF = QT/(RR)1/3.

Number and percentage of patients with QTcF and QTcB intervals in the categories below will be provided.

- Absolute QTc interval >450 msec,
- Absolute QTc interval >480 msec,
- Absolute QTc interval >500 msec.
- Change from baseline QTc interval increase >30 msec,
- Change from baseline QTc interval increase >60 msec.

For continuous ECG parameters, summary statistics will be presented for baseline and changes from baseline for the minimum post-baseline value and maximum post-baseline value.

For interpretation of clinical significance (normal / abnormal, not clinically significant / abnormal, clinically significant / not evaluable), a frequency table will be presented at each post-dose assessment and for the worst value between post-dose assessments (abnormal, clinically significant > abnormal, not clinically significant > not evaluable).

ECG results will be listed at each assessment. Any unscheduled ECG will be flagged [U] in the listings. For RR interval, PR interval, QRS duration, QT interval, QTcF interval, QTcB interval and the average of the three triplicate measurements will be used for summary. ECG results will be listed at each assessment.

3.7.6 Physical Examinations

Physical examinations include overall assessment and neurological status assessments (abnormal, not clinically significant / abnormal, clinically significant /normal).

A frequency table will be presented at each post-dose assessment and for the worst value between post-dose assessments (abnormal, clinically significant > abnormal, not clinically significant > normal > not evaluable).

3.7.7 Local Tolerance at Infusion site

Local tolerance of pembrolizumab or paclitaxel infusions for Parts B and C include assessments for characteristics such as tenderness, erythema, swelling, rash, pain, itching, induration, haematoma, ulceration or necrosis, and the extent of erythema, haematoma, rash, ulceration or necrosis using the measurement of maximum length and maximum width.

For Parts B and C, number and percentage of patients with any infusion site reactions and each type of infusion site reaction (tenderness, erythema, swelling, rash, pain, itching, induration, haematoma, ulceration or necrosis) will be tabulated.

3.7.8 ECOG Performance Status

The frequency and percentage of patients with each performance status score will be displayed by visit. A shift table presenting the shift from baseline to worst post-baseline score will also be presented.

A listing of ECOG will be provided.

3.7.9 Echocardiogram

Echocardiogram (ECHO) or multigated acquisition (MUGA) parameters include left ventricle ejection fraction (LVEF) (%) and interpretation of clinical significance.

For echocardiogram assessments (abnormal, not clinically significant / abnormal, clinically significant /normal), a frequency table will be presented at each post-dose assessment and for the worst value between post-dose assessments (abnormal, clinically significant > abnormal, not clinically significant > normal > not evaluable).

For LVEF (%), summary statistics will be presented at each scheduled assessment for actual values and changes from baseline. The number and percentage of patients with LVEF less than 50% will be summarized at Screening and the end of study.

3.7.10 Antidrug Antibodies for Pembrolizumab (Part B only)

Antidrug antibodies (ADA) for pembrolizumab (Part B), anti-pembrolizumab antibodies, include both binding and neutralizing.

The number and percentage of patients with the presence of anti-pembrolizumab antibodies (both binding and neutralizing) at baseline will be summarized. The number of seroconverters (patients having a negative result at Screening and at least one positive result at any post-treatment timepoint) for binding and neutralizing antibodies will be summarized.

3.8 Exploratory Assessments

The exploratory biomarker data analysis will be detailed in a separate DAP and reported as a standalone report.

Exploratory IPN60090 concentrations in urine in Part A of dose escalation data analysis will be detailed in a separate DAP and reported as a standalone report also.

3.9 Biobanking

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

3.10 Subgroups

Clinical outcomes (efficacy and safety) will be summarized by the following subgroups:

- biomarker positive and negative
- tumor type.

Additional subgroups could be considered if needed. All patients treated at PD active doses (i.e. at least 50% inhibition of Glu:Gln ratio in PBMCs at C_{trough} on Day 14 of Cycle 1 in 66% of patients treated at this dose level) will be pooled by Part in the escalation and the expansion phases.

Subgroups analyses will also be performed for patients treated at PD active doses (1) by pooling Part A, Part B and Part C in escalation phase, (2) by pooling Parts A, Part B and Part C in expansion phase, and (3) by pooling escalation phase, expansion phase and food effect cohort.

4 DATA SAFETY MONITORING BOARD

4.1 Safety Review Committee

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 organized. The composition of the SRC and its specific working procedures are described in a separate SRC charter established prior to the screening of the first patient.

BOIN 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 dose escalation. This group will also determine when to implement predefined stopping rules.

4.2 Independent Safety Assessment Committee

An independent safety assessment committee (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 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 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.

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.

5 INTERIM ANALYSIS

An interim analysis will be performed at the end of the dose escalation to characterize the safety and define the RD but also to investigate preliminary anti-tumour activity in biomarker selected and unselected patients.

As the expansion phase study will follow a 2-stage design, an interim analysis will be performed after the first 10 patients enrolled and 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 to inform a decision on moving to Stage 2, prior to all patients being enrolled. Details of the 2-stage design is described in section 2.2.7.3 and section 4.2.

6 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

No changes affecting the statistical analysis defined in the protocol are made.

7 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.3 or higher. All available data will be presented in patient data listings which will be sorted by patient and visit date as applicable. Detailed Programming Specifications will be provided in a separate document.

APPENDIX A: REFERENCES

1. Brookmeyer R, Crowley J. A Confidence Interval for the Median Survival Time. 1982: 38: 29-41.
2. Eisenhauera EA, Therasseb P, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 2009; 45: 228 –247.
3. Seymour L, Bogaerts J, Perrone A, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol 2017;18(3):e143-e152.
4. Liu S and Yuan Y. Bayesian Optimal Interval Designs for Phase I Clinical Trials, Journal of the Royal Statistical Society. 2015. Series C. 64. 507-523.

APPENDIX B: ASSESSMENT OF DISEASE RESPONSE USING RECIST, VERSION 1.1

A summary of the overall tumor response calculation made by the investigator at each time point is summarized in Table B-1 for patients with target (± nontarget) disease, and Table B-2 for patients with nontarget disease only. When no imaging/measurement is done at all at a particular time point, the patients will be considered inevaluable (NE) at that point. If only a subset of target or nontarget lesion measurements are made at an assessment, the patient will be considered NE at that time point unless the contribution of the individual missing lesion(s) would not change the assigned time point response (eg, if a patient has a baseline sum of 50 mm with 3 measured lesions and at a follow-up time point only 2 lesions are assessed, but these give a sum of 80 mm, the patient will have achieved progressive disease status, regardless of the contribution of the missing lesion).

Table B-1: Time Point Response (Overall Response) for Patients with Target ± Nontarget Disease (Lesions)

Target lesions	Nontarget lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD/not all evaluated	No	PR
Stable	Non-PD/not all evaluated	No	Stable
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; NE = inevaluable; PD = progressive disease; PR = partial response

Source: Eisenhauer 2009

Table B-2: Time Point Response (Overall Response) for Patients with Nontarget Disease Only (Non Target Lesions)

Nontarget lesions	New lesions	Overall response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD[1]
Not all evaluated	No	NE
PD	Yes or No	PD
Any	Yes	PD

CR = complete response; NE = inevaluable; PD = progressive disease
Non-CR/Non-PD refers to stable disease

Source: Eisenhauer 2009

A summary of the best overall tumor response calculation is provided in Table B-3

Unless specified otherwise, tumor assessments will be excluded from the BOR calculation if they occur after the start of other anticancer therapy or surgical intervention.

BOR will be classified as NE for patients with early progression or early death. Early progression will include patients who discontinue study drug due to worsening disease but without objective evidence of disease progression, and their BOR cannot be determined because tumor assessments were either incomplete or were never performed or not repeated. Similarly, early death will include patients who die without objective evidence of disease progression beforehand, and their BOR cannot be determined because tumor assessments were either incomplete or were never performed or were not repeated.

Table B-3: Best Overall Response

Overall response First time point	Overall response Subsequent time point	Best overall response
CR	CR	CR
CR	PR	Stable, PD, or PR[1]
CR	Stable	Stable provided that minimum criteria for Stable duration met. Otherwise PD.
CR	PD	Stable provided that minimum criteria for Stable duration met. Otherwise PD.
CR	NE	Stable provided that minimum criteria for Stable duration met. Otherwise PD.
PR	CR[2]	PR
PR	PR	PR
PR	Stable	Stable
PR	PD	Stable provided that minimum criteria for Stable duration met. Otherwise PD.
PR	NE	Stable provided that minimum criteria for Stable duration met. Otherwise PD.
NE	NE	NE

CR = complete response; NE = inevaluable; PD = progressive disease; PR = partial response

[1] If a CR is *truly* met at a first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response will depend on whether minimum duration of Stable is met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient has PR, not CR at the first time point. Under these circumstances, the original CR will be changed to PR and the best response is PR.

[2] Every effort will be made to confirm the CR. For such cases where CR is not subsequently confirmed, then best overall response is PR.

Source: Eisenhauer 2009

APPENDIX C: ASSESSMENT OF DISEASE RESPONSE USING IRECIST

The principles used to establish objective tumor response are largely unchanged from RECIST 1.1, but the major change for iRECIST is the concept of resetting the bar if RECIST 1.1 progression is followed at the next assessment by tumor shrinkage. iRECIST define iUPD on the basis of RECIST 1.1 principles; however, iUPD requires confirmation, which is done on the basis of observing either a further increase in size (or in the number of new lesions) in the lesion category in which progression was first identified in (ie, target or non-target disease), or progression (defined by RECIST 1.1) in lesion categories that had not previously met RECIST 1.1 progression criteria. However, if progression is not confirmed, but instead tumor shrinkage occurs (compared with baseline), which meets the criteria of iCR, iPR, or iSD, then the bar is reset so that iUPD needs to occur again (compared with nadir values) and then be confirmed (by further growth) at the next assessment for iCPD to be assigned. If no change in tumor size or extent from iUPD occurs, then the timepoint response would again be iUPD. This approach allows atypical responses, such as delayed responses that occur after pseudoprogression, to be identified, further understood, and better characterized.

Table C-1: Comparison Between RECIST 1.1 and iRECIST

	RECIST 1.1	**iRECIST**
Definition of measurable and non-measurable disease; numbers and site of target disease	Measurable lesions are ≥10 mm in diameter (≥15 mm for nodal lesions); maximum of 5 lesions (2 per organ); all other disease is considered non-target (must be ≥10 mm in short axis for nodal disease)	No change from RECIST 1.1; however, new lesions are assessed as per RECIST 1.1 but are recorded separately on the case report form (but not included in the sum of lesions for target lesions identified at baseline)
CR, PR, or SD	Cannot have met criteria for progression before CR, PR, or SD	Can have had iUPD (1 or more instances), but not iCPD, before iCR, iPR, or iSD
Confirmation of CR or PR	Required	As per RECIST 1.1
Confirmation of SD	Not required	Not required
New lesions	Result in progression; recorded but not measured	New lesions should be assessed and categorized as measurable or non-measurable using RECIST 1.1. New lesions result in iUPD, but iCPD is only assigned on the basis of this category if at the next assessment, additional new lesions appear or an increase in size of new lesions is seen (≥5 mm for the sum of new lesion target or any increase in new lesion non-target); the appearance of new lesions, when none have previously been recorded, can also confirm iCPD.
Confirmation of progression	Not required (unless equivocal)	The next imaging assessment should be performed at ≥4 weeks but ≤8 weeks after iUPD. Progression is confirmed if the next imaging assessment confirms a further increase in size of at least 5 mm in the lesion category in which progression was first identified, or progression in a lesion category that had not previously met RECIST 1.1 progression criteria, or development of new lesions. However, the criteria for iCPD (after iUPD) are not considered to have been met if iCR, iPR, or iSD criteria (compared with baseline and as defined by RECIST 1.1) are met at the next assessment after iUPD. The status is then reset and iCR, iPR, or iSD should be documented.
Consideration of clinical status	Not included in assessment	Clinical stability is considered when deciding whether treatment is continued after iUPD
Abbreviations: CR, complete response; iCPD, confirmed progression assigned using iRECIST; iCR, complete response assigned using iRECIST; iPR, partial response assigned using iRECIST; iSD, stable disease assigned using iRECIST; iUPD, unconfirmed progression assigned using iRECIST; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.		

Table C-2: Assignment of Timepoint Response Using iRECIST

	Timepoint response with no previous iUPD in any category	**Timepoint response with previous iUPD in any category***
Target lesions: iCR; non-target lesions: iCR; new lesions: no	iCR	iCR
Target lesions: iCR; non-target lesions: non-iCR/non-iUPD; new lesions: no	iPR	iPR
Target lesions: iPR; non-target lesions: non-iCR/non-iUPD; new lesions: no	iPR	iPR
Target lesions: iSD; non-target lesions: non-iCR/non-iUPD; new lesions: no	iSD	iSD
Target lesions: iUPD with no change, or with a decrease from last timepoint; non-target lesions: iUPD with no change, or decrease from last timepoint; new lesions: yes	Not applicable	New lesions confirm iCPD if new lesions were previously identified and they have increased in size (≥5 mm in sum of measures for new lesion target or any increase for new lesion non-target) or number; if no change is seen in new lesions (size or number) from last timepoint, assignment remains iUPD
Target lesions: iSD, iPR, iCR; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in the size of non-target disease (does not need to meet RECIST 1.1 criteria for unequivocal progression)
Target lesions: iUPD; non-target lesions: non-iCR/non-iUPD, or iCR; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in sum of measures ≥5 mm; otherwise, assignment remains iUPD
Target lesions: iUPD; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed based on a further increase in previously identified target lesion iUPD in sum of measures ≥5 mm or non-target lesion iUPD (previous assessment need not have shown unequivocal progression)
Target lesions: iUPD; non-target lesions: iUPD; new lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in previously identified target lesion iUPD sum of measures ≥5 mm, previously identified non-target lesion iUPD (does not need to be unequivocal), or an increase in the size or number of new lesions previously identified
Target lesions: non-iUPD or progression; non-target lesions: non-iUPD or progression; new lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of an increase in the size or number of new lesions previously identified
Target lesions, non-target lesions, and new lesions defined according to RECIST 1.1 principles; if no pseudoprogression occurs, RECIST 1.1 and iRECIST categories for complete response, partial response, and stable disease would be the same. *Previously identified in assessment immediately before this timepoint. "i" indicates immune responses assigned using iRECIST. iCR=complete response. iPR=partial response. iSD=stable disease. iUPD=unconfirmed progression. non-iCR/non-iUPD=criteria for neither CR nor PD have been met. iCPD=confirmed progression. RECIST=Response Evaluation Criteria in Solid Tumours.		

Table C-3: Scenarios of assignments of best overall response using iRECIST

	Timepoint response 1	Timepoint response 2	Timepoint response 3	Timepoint response 4	Timepoint response 5	iBOR
Example 1	iCR	iCR, iPR, iUPD, or NE	iCR, iPR, iUPD, or NE	iUPD	iCPD	iCR
Example 2	iUPD	iPR, iSD, or NE	iCR	iCR, iUPD, or NE	iCR, iPR, iSD, iUPD, iCPD, or NE	iCR
Example 3	iUPD	iPR	iPR, iSD, iUPD, or NE	iPR, iSD, iUPD, NE, or iCPD	iPR, iSD, iUPD, NE, or iCPD	iPR
Example 4	iUPD	iSD or NE	iPR	iPR, iSD, iUPD, or NE	iPR, iSD, iUPD, iCPD, or NE	iPR
Example 5	iUPD	iSD	iSD, iUPD, or NE	iSD, iUPD, iCPD, or NE	iSD, iUPD, iCPD, or NE	iSD
Example 6	iUPD	iCPD	Any	Any	Any	iCPD
Example 7	iUPD	iUPD (no iCPD)	iCPD	Any	Any	iCPD
Example 8	iUPD	NE	NE	NE	NE	iUPD

Eight examples are presented for patients with target disease at baseline, but many more scenarios exist following the same principles. Table assumes a randomised study in which confirmation of complete response or partial response is not required. For patients with non-target disease only at baseline, only iCR or non-complete response or non-progression of disease can be assigned at each timepoint (not shown in the table for ease of presentation). "i" indicates immune responses assigned using iRECIST. iBOR=best overall response. iCR=complete response. iPR=partial response. NE=not evaluable. iUPD=unconfirmed progression. iCPD=confirmed progression. iSD=stable disease. RECIST=Response Evaluation Criteria in Solid Tumours.

Source: Seymour L, et al. 2017.