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Sponsor

Novartis

Generic Drug Name

Capmatinib

Trial Indication(s)

Non-small cell lung cancer

Protocol Number

CINC280I12201

Protocol Title

A randomized, open label, multicenter phase II study evaluating the efficacy and safety of capmatinib (INC280) plus pembrolizumab versus pembrolizumab alone as first line treatment for locally advanced or metastatic non-small cell lung cancer with PD-L1≥ 50%

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase 4

Study Start/End Dates

Study Start Date: January 22, 2020 (Actual)
Primary Completion Date: January 14, 2022 (Actual)

Study Completion Date: February 07, 2023 (Actual)

Reason for Termination

The study that was terminated early on 07-Feb-2023 (last subject last visit). The enrollment to the study was halted on 21-Jan-2021 due to lack of tolerability observed in the capmatinib plus pembrolizumab arm. Following the enrollment halt, all ongoing subjects in the combination arm were discontinued from capmatinib treatment but were allowed to continue treatment with pembrolizumab.

Study Design/Methodology

This was a randomized, open-label, multicenter, phase II study evaluating the efficacy and safety of capmatinib plus pembrolizumab in comparison to pembrolizumab alone as first line treatment for locally advanced or metastatic non-small cell lung cancer (NSCLC) with programmed cell death ligand-1 (PD-L1) expression ≥ 50%, mesenchymal epithelial transition (MET) unselected, epidermal growth factor receptor (EGFR) wild type and anaplastic lymphoma kinase (ALK) negative.

All eligible subjects were randomized to one of the treatment arms in a 2:1 (capmatinib plus pembrolizumab: pembrolizumab alone) ratio. Participants in both treatment arms were to receive up to 35 cycles (approximately 24 months) of study treatment. The study enrollment was halted on 21-Jan-2021 per sponsor's decision. The enrollment halt decision was based on lack of tolerability observed in the capmatinib plus pembrolizumab arm.

Immediately following the enrollment halt, the below procedural changes were performed:

- Capmatinib treatment was discontinued in subjects on the combination arm. All ongoing subjects were allowed to continue receiving pembrolizumab single agent treatment as per investigator’s discretion until unacceptable toxicity, or disease progression, or up to 35 cycles of treatment, whichever occurred first.
- Termination of capmatinib pharmacokinetics (PK) sample collection.
- Termination of pembrolizumab PK/immunogenicity (IG) sample collection.

After the enrollment halt, the study protocol was amended (amendment 03) and the collection of efficacy data was stopped. As pembrolizumab is a registered and commercialized treatment for the study indication, the efficacy and safety assessments were to be performed as per each institution's standard of care and no longer captured in the electronic Case Report Form (eCRF) (except reporting of adverse events). Additionally, as single-agent pembrolizumab is a well-established standard treatment for the study indication, the requirement for post-treatment disease progression follow-up and survival follow-up were removed.

Centers

36 centers in 16 countries/regions: Malaysia(2), India(3), Australia(3), Spain(5), Belgium(1), Taiwan(2), Japan(2), France(3), Thailand(3), Hong Kong(1), Germany(2), Czech Republic(1), Italy(2), Greece(2), Netherlands(3), Canada(1)

Objectives:

The primary objective of the trial was to evaluate the efficacy of capmatinib plus pembrolizumab in comparison to pembrolizumab alone.

The secondary objectives of the trial were:

- To evaluate the anti-tumor activity of capmatinib plus pembrolizumab in comparison to pembrolizumab alone
- To characterize the safety profile of capmatinib plus pembrolizumab and pembrolizumab alone
- To characterize the pharmacokinetics of capmatinib and pembrolizumab
- To evaluate the prevalence and incidence of immunogenicity of pembrolizumab

Test Product (s), Dose(s), and Mode(s) of Administration

In this study, “study treatment” refers to capmatinib plus pembrolizumab or pembrolizumab alone. “Investigational drug” refers to the Novartis study drug, capmatinib (INC280).

Subjects were assigned to one of the following two treatment arms in a ratio of 2:1 (capmatinib plus pembrolizumab: pembrolizumab alone). A complete cycle of treatment was defined as 21 days of an infusion of pembrolizumab, with or without continuous capmatinib treatment. Subjects in both treatment arms were to receive up to 35 cycles (approximately 24 months) of study treatment. As per the original protocol study design, treatment beyond disease progression for subjects who had documented disease progression per RECIST 1.1 was allowed.

Capmatinib tablets were administered orally on a continuous twice daily (BID) dosing schedule at a dose level of 400 mg, from Day 1 until Day 21 of each 21-day cycle. Pembrolizumab (100 mg concentrate for solution for infusion or 50 mg lyophilized power for reconstitution for infusion) was administered intravenously at 200 mg once every 21 days.

Based on lack of tolerability observed in the capmatinib plus pembrolizumab arm, the study enrollment was halted per sponsor's decision. Capmatinib treatment was discontinued in subjects on the combination arm and all ongoing participants were allowed to continue receiving pembrolizumab single agent treatment. Following the approval of protocol amendment 03, treatment with pembrolizumab strictly adhered to the drug’s approved label for the study indication. Accordingly, pembrolizumab was administered until disease progression, unacceptable toxicity, or up to 35 cycles in participants without disease progression, whichever occurred first. Treatment beyond disease progression was no longer allowed as part of this study.

Statistical Methods

Analysis of the primary endpoint: Progression-Free Survival (PFS) was defined as the time from the date of randomization to the date of the first documented progression or death due to any cause.

There was 1 amendment to the statistical analysis plan (SAP), based on substantial changes to study conduct following the study enrollment halt. Due to the discontinuation of one of the investigational drugs (capmatinib) in all subjects in the combination arm and the stopping of efficacy data collection per protocol amendment 03, Kaplan-Meier (KM) analysis was used to report the primary endpoint PFS and not the initially planned Bayesian analysis. PFS was censored on the 21-Jan-2021 or the last adequate tumor assessment prior to that date for the capmatinib plus pembrolizumab arm.

Analysis of secondary endpoints: The secondary efficacy endpoints were Overall Response Rate (ORR), Disease Control Rate (DCR), Time to response (TTR), Duration of Response (DOR) as per RECIST 1.1 and Overall Survival (OS). ORR and DCR were presented by treatment arm, along with their accompanying 95% confidence intervals (CIs) based on the exact binomial distribution. TTR, DOR and OS were summarized by treatment arms using the KM estimators for the medians along with their accompanying 95% CIs. Similarly, 21-Jan-2021 or any last adequate tumor assessment prior to that date was considered as the end of evaluation period for BOR for the capmatinib plus pembrolizumab arm.

Pharmacokinetic (PK) samples for capmatinib were quantified using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) assay. The assay to quantify and assess the pembrolizumab PK and immunogenicity (IG) was a validated homogeneous enzyme-linked immunosorbent assay (ELISA). PK parameters were determined by non-compartmental methods using the PK profile of capmatinib.

Incidence of adverse events (AEs) and serious adverse events (SAEs), AEs leading to dose reduction/interruption and AEs leading to dose discontinuation were summarized by treatment arm.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Histologically confirmed and documented locally advanced stage III (not candidates for surgical resection or definitive chemo-radiation) or stage IV (metastatic) NSCLC (per AJCC/IASLC v.8) for treatment in the first-line setting
- Histologically or cytologically confirmed diagnosis of NSCLC that is both EGFR wild type status and ALK- negative rearrangement status
- Have an archival tumor sample or newly obtained tumor biopsy with high PD-L1 expression (TPS ≥ 50%)
- ECOG performance status score ≤ 1
- Have at least 1 measurable lesion by RECIST 1.1
- Have adequate organ function

Exclusion Criteria:

- Prior treatment with a MET inhibitor or HGF-targeting therapy
- Prior immunotherapy (e.g. anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways)
- Have untreated symptomatic central nervous system (CNS) metastases
- Clinically significant, uncontrolled heart diseases
- Prior palliative radiotherapy for bone lesions ≤ 2 weeks prior to starting study treatment

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Participant Flow Table

Overall Study

	Capmatinib 400mg BID + pembrolizumab 200mg Q3W	Pembrolizumab 200mg Q3W	Total
Arm/Group Description	Capmatinib (INC280) 400 mg orally twice daily (BID) in combination with pembrolizumab 200 mg intravenously every 3 weeks (Q3W)	Pembrolizumab 200 mg intravenously every 3 weeks (Q3W)	
Started	51	25	76
Entered post-treatment follow-up*	38	20	58
Completed	10	7	17
Not Completed	41	18	59
Adverse Event	10	2	12
Death	6	4	10
Lost to Follow-up	1	0	1
Physician Decision	3	1	4
Progressive Disease	19	9	28
Subject Decision	2	2	4

* Post-treatment disease progression follow-up and survival follow-up started on day 31 after last dose of study treatment. This was applicable until the implementation of Protocol Amendment 03.

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Baseline Characteristics

	Capmatinib 400mg BID + pembrolizumab 200mg Q3W	Pembrolizumab 200mg Q3W	Total
Arm/Group Description	Capmatinib (INC280) 400 mg orally twice daily (BID) in combination with pembrolizumab 200 mg intravenously every 3 weeks (Q3W)	Pembrolizumab 200 mg intravenously every 3 weeks (Q3W)	
Number of Participants [units: participants]	51	25	76
Baseline Analysis Population Description			
Age Continuous (units: years) Analysis Population Type: Participants Mean ± Standard Deviation			
	64.7±7.59	66.6±8.80	65.4±8.00
Sex: Female, Male (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)			
Female	16	9	25
Male	35	16	51
Race/Ethnicity, Customized (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)			
White	25	16	41
Asian	22	8	30
Unknown	4	1	5

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Primary Outcome Result(s)

Progression-Free Survival (PFS) by investigator assessment as per RECIST 1.1

Description	PFS is defined as the time from the date of randomization to the date of the first documented progression or death due to any cause. Tumor response was based on investigator assessment per Response Evaluation Criteria In Solid Tumors (RECIST) v1.1. If a patient did not have an event, PFS was censored at the date of the last adequate tumor assessment, the start of a subsequent anti-neoplastic therapy (if any) or the date of sponsor's decision to discontinue capmatinib (applicable only to subjects on the combination arm). Due to the discontinuation of one of the investigational drugs (capmatinib) in all subjects in the combination arm, PFS was censored on the 21-Jan-2021 or the last adequate tumor assessment prior to that date for the capmatinib plus pembrolizumab arm. PFS was analyzed using Kaplan-Meier estimates.
Time Frame	Up to 1.3 years
Analysis Population Description	All patients to whom study treatment had been assigned by randomization.

	Capmatinib 400mg BID + pembrolizumab 200mg Q3W	**Pembrolizumab 200mg Q3W**
Arm/Group Description	Capmatinib (INC280) 400 mg orally twice daily (BID) in combination with pembrolizumab 200 mg intravenously every 3 weeks (Q3W)	Pembrolizumab 200 mg intravenously every 3 weeks (Q3W)
Number of Participants Analyzed [units: participants]	51	25
Progression-Free Survival (PFS) by investigator assessment as per RECIST 1.1 (units: months)	**Median (95% Confidence Interval)**	**Median (95% Confidence Interval)**
	5.2 (2.0 to NA)[1]	5.1 (2.6 to NA)[1]

[1] Not estimable due to insufficient number of participants with events.

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Secondary Outcome Result(s)

Overall Response Rate (ORR) by investigator assessment as per RECIST 1.1

Description	Tumor response was based on local investigator assessment as RECIST v1.1. ORR per RECIST v1.1 is defined as the percentage of participants with a best overall response (BOR) of Complete Response (CR) or Partial Response (PR). For the capmatinib plus pembrolizumab arm, 21-Jan-2021 or any last adequate tumor assessment prior to that date was considered as the end of evaluation period for BOR. For RECIST v1.1, CR=Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm; PR= At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.
Time Frame	Up to 1.3 years
Analysis Population Description	All patients to whom study treatment had been assigned by randomization.

	Capmatinib 400mg BID + pembrolizumab 200mg Q3W	**Pembrolizumab 200mg Q3W**
Arm/Group Description	Capmatinib (INC280) 400 mg orally twice daily (BID) in combination with pembrolizumab 200 mg intravenously every 3 weeks (Q3W)	Pembrolizumab 200 mg intravenously every 3 weeks (Q3W)
Number of Participants Analyzed [units: participants]	51	25
Overall Response Rate (ORR) by investigator assessment as per RECIST 1.1 (units: Percentage of participants)	**Number (95% Confidence Interval)**	**Number (95% Confidence Interval)**
	9.8 (3.3 to 21.4)	40.0 (21.1 to 61.3)

Disease Control Rate (DCR) by investigator assessment as per RECIST 1.1

Description	Tumor response was based on local investigator assessment per RECIST v1.1. DCR is defined as the percentage of participants with a BOR of Complete Response (CR), Partial Response (PR), Stable Disease (SD), and non-CR/non-progressive disease (for subjects without target lesions). For the capmatinib plus pembrolizumab arm, 21-Jan-2021 or any last adequate tumor assessment prior to that date was considered as the end of evaluation period for BOR. For RECIST v1.1, CR=Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm; PR= At least a 30% decrease in the sum of diameter

of all target lesions, taking as reference the baseline sum of diameters; SD= Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for progression).

Time Frame: Up to 1.3 years

Analysis Population Description: All patients to whom study treatment had been assigned by randomization.

	Capmatinib 400mg BID + pembrolizumab 200mg Q3W	Pembrolizumab 200mg Q3W
Arm/Group Description	Capmatinib (INC280) 400 mg orally twice daily (BID) in combination with pembrolizumab 200 mg intravenously every 3 weeks (Q3W)	Pembrolizumab 200 mg intravenously every 3 weeks (Q3W)
Number of Participants Analyzed [units: participants]	51	25
Disease Control Rate (DCR) by investigator assessment as per RECIST 1.1 (units: percentage of participants)	**Number (95% Confidence Interval)**	**Number (95% Confidence Interval)**
	37.3 (24.1 to 51.9)	60.0 (38.7 to 78.9)

Time to response (TTR) by investigator assessment as per RECIST 1.1

Description: TTR is defined as the time from the date of randomization to the first documented response of either complete response or partial response, which must be subsequently confirmed (although initial date of response is used, not date of confirmation). TTR was analyzed using the Kaplan-Meier method as defined in the statistical analysis plan.

Time Frame: Up to 1.3 years

Analysis Population Description: All patients to whom study treatment had been assigned by randomization.

	Capmatinib 400mg BID + pembrolizumab 200mg Q3W	Pembrolizumab 200mg Q3W

Arm/Group Description	Capmatinib (INC280) 400 mg orally twice daily (BID) in combination with pembrolizumab 200 mg intravenously every 3 weeks (Q3W)	Pembrolizumab 200 mg intravenously every 3 weeks (Q3W)
Number of Participants Analyzed [units: participants]	51	25
Time to response (TTR) by investigator assessment as per RECIST 1.1 (units: months)	**Median (95% Confidence Interval)**	**Median (95% Confidence Interval)**
	NA (NA to NA)[1]	NA (NA to NA)[1]

[1] Not estimable due to insufficient number of participants with events.

Duration of Response (DOR) by investigator assessment as per RECIST 1.1

Description	DOR only applies to patients for whom best overall response is complete response (CR) or partial response (PR) based on local investigator assessment of overall lesion response according to RECIST v1.1. DOR is defined as the time from the date of first documented response (confirmed CR or confirmed PR) to the date of first documented disease progression or death due to any cause. If a patient not had an event, duration was censored at the date of last adequate tumor assessment before the start of a new anticancer therapy, if any. DOR was analyzed using the Kaplan-Meier method as defined in the statistical analysis plan.
Time Frame	Up to 1.3 years
Analysis Population Description	All patients to whom study treatment had been assigned by randomization and for whom best overall response was CR or PR as per RECIST v1.1 based on local investigator assessment.

	Capmatinib 400mg BID + pembrolizumab 200mg Q3W	**Pembrolizumab 200mg Q3W**
Arm/Group Description	Capmatinib (INC280) 400 mg orally twice daily (BID) in combination with pembrolizumab 200 mg intravenously every 3 weeks (Q3W)	Pembrolizumab 200 mg intravenously every 3 weeks (Q3W)
Number of Participants Analyzed [units: participants]	5	10
Duration of Response (DOR) by investigator assessment as per RECIST 1.1 (units: months)	**Median (95% Confidence Interval)**	**Median (95% Confidence Interval)**

	NA (NA to NA)[1]	NA (NA to NA)[1]

[1] Not estimable due to insufficient number of participants with events.

Overall survival (OS)

Description	OS is defined as the time from the date of randomization to the date of death due to any cause. The requirement for survival follow-up period was removed following the discontinuation of one of the investigational drugs (capmatinib) in all subjects in the combination arm and the implementation of Protocol Amendment 03. OS was analyzed using the Kaplan-Meier method as defined in the statistical analysis plan.
Time Frame	Up to 2.1 years
Analysis Population Description	All patients to whom study treatment had been assigned by randomization.

	Capmatinib 400mg BID + pembrolizumab 200mg Q3W	**Pembrolizumab 200mg Q3W**
Arm/Group Description	Capmatinib (INC280) 400 mg orally twice daily (BID) in combination with pembrolizumab 200 mg intravenously every 3 weeks (Q3W)	Pembrolizumab 200 mg intravenously every 3 weeks (Q3W)
Number of Participants Analyzed [units: participants]	51	25
Overall survival (OS) (units: months)	**Median** **(95% Confidence Interval)**	**Median** **(95% Confidence Interval)**
	NA (NA to NA)[1]	NA (NA to NA)[1]

[1] Not estimable due to insufficient number of participants with events.

Number of participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)

Description	Number of participants with AEs (any AE regardless of seriousness) and SAEs, including changes from baseline in vital signs, electrocardiograms and laboratory results qualifying and reported as AEs.
Time Frame	From first dose of study treatment to 30 days after last dose, up to 2.1 years

Analysis Population Description: All patients to whom study treatment had been assigned by randomization. Patients are analyzed according to the treatment they were randomized to.

	Capmatinib 400mg BID + pembrolizumab 200mg Q3W	**Pembrolizumab 200mg Q3W**
Arm/Group Description	Capmatinib (INC280) 400 mg orally twice daily (BID) in combination with pembrolizumab 200 mg intravenously every 3 weeks (Q3W)	Pembrolizumab 200 mg intravenously every 3 weeks (Q3W)
Number of Participants Analyzed [units: participants]	51	25
Number of participants with Adverse Events (AEs) and Serious Adverse Events (SAEs) (units: participants)	**Count of Participants (Percentage)**	**Count of Participants (Percentage)**
AEs	49 (96.08%)	25 (100%)
Treatment-related AEs	45 (88.24%)	18 (72%)
SAEs	31 (60.78%)	13 (52%)
Treatment-related SAEs	18 (35.29%)	1 (4%)
AEs leading to discontinuation	18 (35.29%)	5 (20%)
Treatment-related AEs leading to discontinuation	17 (33.33%)	2 (8%)
AEs leading to dose reduction/interruption	34 (66.67%)	7 (28%)
Treatment-related AEs leading to dose reduction/interruption	24 (47.06%)	2 (8%)

Maximum observed plasma concentration (Cmax) of capmatinib

Description	Pharmacokinetic (PK) parameters were calculated based on capmatinib plasma concentrations by using non-compartmental methods. Cmax is defined as the maximum (peak) observed plasma concentration following a dose.
Time Frame	pre-dose and 1, 2, 4 and 8 hours after morning dose on Cycle 2 Day 1. The duration of one cycle was 21 days.
Analysis Population Description	Patients in the capmatinib pharmacokinetic analysis set (INC-PAS) with an available value for the outcome measure. INC-PAS consists of all patients who provided at least one blood sample with measurable capmatinib PK data.

	Capmatinib 400mg BID + pembrolizumab 200mg Q3W
Arm/Group Description	Capmatinib (INC280) 400 mg orally twice daily (BID) in combination with pembrolizumab 200 mg intravenously every 3 weeks (Q3W)
Number of Participants Analyzed [units: participants]	25
Maximum observed plasma concentration (Cmax) of capmatinib (units: ng/mL)	**Geometric Mean (Geometric Coefficient of Variation)**
	2730 (155.9%)

Time to reach maximum plasma concentration (Tmax) of capmatinib

Description	PK parameters were calculated based on capmatinib plasma concentrations by using non-compartmental methods. Tmax is defined as the time to reach maximum (peak) plasma concentration following a dose. Actual recorded sampling times were considered for the calculations.
Time Frame	pre-dose and 1, 2, 4 and 8 hours after morning dose on Cycle 2 Day 1. The duration of one cycle was 21 days.
Analysis Population Description	Patients in the capmatinib pharmacokinetic analysis set (INC-PAS) with an available value for the outcome measure. INC-PAS consists of all patients who provided at least one blood sample with measurable capmatinib PK data.

Capmatinib 400mg BID + pembrolizumab 200mg Q3W

Arm/Group Description	Capmatinib (INC280) 400 mg orally twice daily (BID) in combination with pembrolizumab 200 mg intravenously every 3 weeks (Q3W)
Number of Participants Analyzed [units: participants]	25
Time to reach maximum plasma concentration (Tmax) of capmatinib (units: hours)	**Median (Full Range)**
	1.33 (0 to 4.00)

Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration (AUClast) of capmatinib

Description	PK parameters were calculated based on capmatinib plasma concentrations by using non-compartmental methods. The linear trapezoidal method was used for AUClast calculation.
Time Frame	pre-dose and 1, 2, 4 and 8 hours after morning dose on Cycle 2 Day 1. The duration of one cycle was 21 days.
Analysis Population Description	Patients in the capmatinib pharmacokinetic analysis set (INC-PAS) with an available value for the outcome measure. INC-PAS consists of all patients who provided at least one blood sample with measurable capmatinib PK data.

	Capmatinib 400mg BID + pembrolizumab 200mg Q3W
Arm/Group Description	Capmatinib (INC280) 400 mg orally twice daily (BID) in combination with pembrolizumab 200 mg intravenously every 3 weeks (Q3W)
Number of Participants Analyzed [units: participants]	25
Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration (AUClast) of capmatinib (units: hr*ng/mL)	**Geometric Mean (Geometric Coefficient of Variation)**
	4210 (232.8%)

Trough serum concentration (Ctrough) of pembrolizumab

Description	PK parameters were calculated based on pembrolizumab serum concentrations by using non-compartmental methods. Ctrough is defined as the concentration reached immediately before the next dose is administered. All drug concentrations below the lower limit of quantification were treated as zero for the calculation of PK parameters.
Time Frame	pre-dose on Cycle 2 Day 1, Cycle 3 Day 1, Cycle 6 Day 1 and Cycle 12 Day 1. The duration of one cycle was 21 days.
Analysis Population Description	Patients in the pembrolizumab pharmacokinetic analysis set (Pembro-PAS) with an available value for the outcome measure at each timepoint. Pembro-PAS consists of all patients who provided at least one blood sample with measurable pembrolizumab PK data.

	Capmatinib 400mg BID + pembrolizumab 200mg Q3W	**Pembrolizumab 200mg Q3W**
Arm/Group Description	Capmatinib (INC280) 400 mg orally twice daily (BID) in combination with pembrolizumab 200 mg intravenously every 3 weeks (Q3W)	Pembrolizumab 200 mg intravenously every 3 weeks (Q3W)
Number of Participants Analyzed [units: participants]	32	18
Trough serum concentration (Ctrough) of pembrolizumab (units: µg/mL)	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**
Cycle 2 Day 1 (n=32, 18)	11.8 (37.5%)	10.6 (34.8%)
Cycle 3 Day 1 (n=29, 18)	18.9 (51.9%)	18.2 (32.3%)
Cycle 6 Day 1 (n=14, 8)	27.6 (66.5%)	36.8 (26.0%)
Cycle 12 Day 1 (n=0, 2)		49.7 (10.0%)

Number of participants with anti-pembrolizumab antibodies

Description	Immunogenicity (IG) was evaluated in serum samples. The assay to quantify and assess the IG was a validated homogeneous enzyme-linked immunosorbent assay (ELISA). • ADA-negative at baseline: ADA-negative sample at baseline • ADA-positive at baseline: ADA-positive sample at baseline • ADA-negative post-baseline: patient with ADA-negative sample at baseline and at least 1 post baseline determinant sample, all of which are ADA-negative samples • ADA-positive post-baseline: patient with at least 1 ADA-positive sample post baseline
Time Frame	Baseline (pre-dose), up to 8 months

Analysis Population Description	All patients to whom study treatment had been assigned by randomization and who had a determinant baseline IG sample and at least one determinant post-baseline IG sample. A determinant sample is neither ADA-inconclusive nor unevaluable.

	Capmatinib 400mg BID + pembrolizumab 200mg Q3W	**Pembrolizumab 200mg Q3W**
Arm/Group Description	Capmatinib (INC280) 400 mg orally twice daily (BID) in combination with pembrolizumab 200 mg intravenously every 3 weeks (Q3W)	Pembrolizumab 200 mg intravenously every 3 weeks (Q3W)
Number of Participants Analyzed [units: participants]	42	20
Number of participants with anti-pembrolizumab antibodies (units: participants)	**Count of Participants (Percentage)**	**Count of Participants (Percentage)**
ADA-negative at baseline	37 (88.1%)	18 (90%)
ADA-positive at baseline	5 (11.9%)	2 (10%)
ADA-negative post-baseline	36 (85.71%)	18 (90%)
ADA-positive post-baseline	6 (14.29%)	2 (10%)

Post-Hoc Outcome Result(s)

All-Collected Deaths

Description	On-treatment deaths were collected from start of treatment to 30 days after last dose. Post-treatment survival follow-up deaths were collected from day 31 after last dose of study treatment until the requirement for survival follow-up was removed following the discontinuation of capmatinib in the combination arm (protocol amendment 03). All deaths refer to the sum of on-treatment deaths plus post-treatment survival follow-up deaths.
Time Frame	On-treatment: Up to 2.1 years after start of treatment. Post-treatment survival follow-up: Up to 1.3 years after start of treatment.

Analysis Population Description	All patients to whom study treatment had been assigned by randomization. Patients are analyzed according to the treatment they were randomized to.

	Capmatinib 400mg BID + pembrolizumab 200mg Q3W	Pembrolizumab 200mg Q3W
Arm/Group Description	Capmatinib (INC280) 400 mg orally twice daily (BID) in combination with pembrolizumab 200 mg intravenously every 3 weeks (Q3W)	Pembrolizumab 200 mg intravenously every 3 weeks (Q3W)
Number of Participants Analyzed [units: participants]	51	25
All-Collected Deaths (units: participants)		
On-treatment deaths (n=51, 25)	10	3
Post-treatment survival follow-up deaths (n=38, 20)	6	5
All deaths (n=51, 25)	16	8

Safety Results

Time Frame	Adverse events were collected from first dose of study treatment to 30 days after last dose, up to 2.1 years after start of treatment. Deaths were collected in the post-treatment survival follow-up from day 31 after last dose of study treatment until the requirement for survival follow-up was removed following the discontinuation of capmatinib in the combination arm (protocol amendment 03), up to 1.3 years after start of treatment. These are not considered AEs.
Additional Description	Patients were analyzed according to the treatment they actually received. Deaths in the post-treatment survival follow-up are not considered Adverse Events. The total number at risk in the post treatment survival includes patients that entered the post treatment survival follow-up period.
Source Vocabulary for Table Default	MedDRA (25.0)

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Collection Approach for Table Default	Systematic Assessment

All-Cause Mortality

	Capmatinib + pembrolizumab – On-treatment N = 51	Pembrolizumab after combination treatment – On-treatment N = 51	Pembrolizumab – On-treatment N = 25	Capmatinib + pembrolizumab – Post-treatment survival follow-up N = 38	Pembrolizumab – Post-treatment survival follow-up N = 20
Arm/Group Description	Capmatinib 400 mg BID in combination with pembrolizumab 200 mg Q3W. AEs collected during on-treatment period (up to 30 days after last dose).	Pembrolizumab single agent 200 mg Q3W after discontinuing capmatinib. AEs collected during on-treatment period (up to 30 days after last dose).	Pembrolizumab single agent 200 mg Q3W from study start. AEs collected during on-treatment period (up to 30 days after last dose).	Capmatinib 400 mg BID in combination with pembrolizumab 200 mg Q3W. Deaths collected in the post-treatment follow-up period (starting from day 31 after last dose). No AEs were collected during this period.	Pembrolizumab single agent 200 mg Q3W from study start. Deaths collected in the post-treatment follow-up period (starting from day 31 after last dose). No AEs were collected during this period.
Total Number Affected	8	2	3	6	5
Total Number At Risk	51	51	25	38	20

Serious Adverse Events

Time Frame	Adverse events were collected from first dose of study treatment to 30 days after last dose, up to 2.1 years after start of treatment. Deaths were collected in the post-treatment survival follow-up from day 31 after last dose of study treatment until the requirement for survival follow-up was removed following the discontinuation of capmatinib in the combination arm (protocol amendment 03), up to 1.3 years after start of treatment. These are not considered AEs.

Additional Description	Patients were analyzed according to the treatment they actually received. Deaths in the post-treatment survival follow-up are not considered Adverse Events. The total number at risk in the post treatment survival includes patients that entered the post treatment survival follow-up period.
Source Vocabulary for Table Default	MedDRA (25.0)
Collection Approach for Table Default	Systematic Assessment

	Capmatinib + pembrolizumab – On-treatment N = 51	**Pembrolizumab after combination treatment – On-treatment N = 51**	**Pembrolizumab – On-treatment N = 25**	**Capmatinib + pembrolizumab – Post-treatment survival follow-up N = 0**	**Pembrolizumab – Post-treatment survival follow-up N = 0**
Arm/Group Description	Capmatinib 400 mg BID in combination with pembrolizumab 200 mg Q3W. AEs collected during on-treatment period (up to 30 days after last dose).	Pembrolizumab single agent 200 mg Q3W after discontinuing capmatinib. AEs collected during on-treatment period (up to 30 days after last dose).	Pembrolizumab single agent 200 mg Q3W from study start. AEs collected during on-treatment period (up to 30 days after last dose).	Capmatinib 400 mg BID in combination with pembrolizumab 200 mg Q3W. Deaths collected in the post-treatment follow-up period (starting from day 31 after last dose). No AEs were collected during this period.	Pembrolizumab single agent 200 mg Q3W from study start. Deaths collected in the post-treatment follow-up period (starting from day 31 after last dose). No AEs were collected during this period.
Total # Affected by any Serious Adverse Event	26	9	13	0	0
Total # at Risk by any Serious Adverse Event	51	51	25	0	0
Blood and lymphatic system disorders					
Anaemia	1 (1.96%)	0 (0.00%)	0 (0.00%)		

Thrombocytopenia	1 (1.96%)	0 (0.00%)	0 (0.00%)
Cardiac disorders			
Cardiac failure	1 (1.96%)	0 (0.00%)	1 (4.00%)
Cardiac failure congestive	1 (1.96%)	0 (0.00%)	0 (0.00%)
Pericardial effusion	1 (1.96%)	2 (3.92%)	0 (0.00%)
Gastrointestinal disorders			
Abdominal pain upper	0 (0.00%)	1 (1.96%)	0 (0.00%)
Ileus	0 (0.00%)	0 (0.00%)	1 (4.00%)
Pancreatitis	0 (0.00%)	1 (1.96%)	0 (0.00%)
Pancreatitis acute	1 (1.96%)	0 (0.00%)	0 (0.00%)
Upper gastrointestinal haemorrhage	1 (1.96%)	0 (0.00%)	0 (0.00%)
Vomiting	1 (1.96%)	0 (0.00%)	0 (0.00%)
General disorders and administration site conditions			
Disease progression	1 (1.96%)	0 (0.00%)	0 (0.00%)
General physical health deterioration	1 (1.96%)	0 (0.00%)	1 (4.00%)
Pyrexia	3 (5.88%)	1 (1.96%)	0 (0.00%)
Hepatobiliary disorders			
Hepatotoxicity	1 (1.96%)	0 (0.00%)	0 (0.00%)
Hypertransaminasaemia	1 (1.96%)	0 (0.00%)	0 (0.00%)
Immune-mediated hepatitis	1 (1.96%)	0 (0.00%)	0 (0.00%)

Immune system disorders			
Hypersensitivity	1 (1.96%)	0 (0.00%)	0 (0.00%)
Infections and infestations			
Bronchitis	2 (3.92%)	0 (0.00%)	1 (4.00%)
Cellulitis	0 (0.00%)	1 (1.96%)	0 (0.00%)
Encephalitis	1 (1.96%)	0 (0.00%)	0 (0.00%)
Meningitis listeria	1 (1.96%)	0 (0.00%)	0 (0.00%)
Myelitis	0 (0.00%)	0 (0.00%)	1 (4.00%)
Pneumonia	2 (3.92%)	1 (1.96%)	2 (8.00%)
Sepsis	2 (3.92%)	1 (1.96%)	0 (0.00%)
Septic shock	1 (1.96%)	0 (0.00%)	0 (0.00%)
Injury, poisoning and procedural complications			
Anastomotic stenosis	0 (0.00%)	0 (0.00%)	1 (4.00%)
Radiation pneumonitis	1 (1.96%)	0 (0.00%)	0 (0.00%)
Investigations			
Transaminases increased	1 (1.96%)	0 (0.00%)	0 (0.00%)
Metabolism and nutrition disorders			
Decreased appetite	0 (0.00%)	0 (0.00%)	1 (4.00%)
Diabetic ketoacidosis	1 (1.96%)	0 (0.00%)	0 (0.00%)
Hyponatraemia	0 (0.00%)	0 (0.00%)	1 (4.00%)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pericardial effusion malignant	1 (1.96%)	0 (0.00%)	0 (0.00%)
Nervous system disorders			
Brain oedema	1 (1.96%)	0 (0.00%)	0 (0.00%)
Cerebrovascular accident	0 (0.00%)	1 (1.96%)	0 (0.00%)
Hydrocephalus	1 (1.96%)	0 (0.00%)	0 (0.00%)
Seizure	1 (1.96%)	0 (0.00%)	0 (0.00%)
Renal and urinary disorders			
Acute kidney injury	2 (3.92%)	0 (0.00%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure	0 (0.00%)	0 (0.00%)	1 (4.00%)
Atelectasis	0 (0.00%)	0 (0.00%)	1 (4.00%)
Bronchial obstruction	0 (0.00%)	0 (0.00%)	1 (4.00%)
Bronchospasm	1 (1.96%)	0 (0.00%)	0 (0.00%)
Chronic obstructive pulmonary disease	0 (0.00%)	0 (0.00%)	2 (8.00%)
Dyspnoea	0 (0.00%)	1 (1.96%)	2 (8.00%)
Haemoptysis	1 (1.96%)	0 (0.00%)	1 (4.00%)
Pleural effusion	1 (1.96%)	1 (1.96%)	0 (0.00%)
Pneumonitis	1 (1.96%)	0 (0.00%)	0 (0.00%)
Vocal cord polyp	0 (0.00%)	0 (0.00%)	1 (4.00%)

Skin and subcutaneous tissue disorders			
Skin reaction	1 (1.96%)	0 (0.00%)	0 (0.00%)
Vascular disorders			
Hypotension	1 (1.96%)	0 (0.00%)	0 (0.00%)
Peripheral ischaemia	0 (0.00%)	0 (0.00%)	1 (4.00%)

Other (Not Including Serious) Adverse Events

Time Frame	Adverse events were collected from first dose of study treatment to 30 days after last dose, up to 2.1 years after start of treatment. Deaths were collected in the post-treatment survival follow-up from day 31 after last dose of study treatment until the requirement for survival follow-up was removed following the discontinuation of capmatinib in the combination arm (protocol amendment 03), up to 1.3 years after start of treatment. These are not considered AEs.
Additional Description	Patients were analyzed according to the treatment they actually received. Deaths in the post-treatment survival follow-up are not considered Adverse Events. The total number at risk in the post treatment survival includes patients that entered the post treatment survival follow-up period.
Source Vocabulary for Table Default	MedDRA (25.0)
Collection Approach for Table Default	Systematic Assessment

Frequent Event Reporting Threshold 5%

	Capmatinib + pembrolizumab – On-treatment N = 51	Pembrolizumab after combination treatment – On-treatment N = 51	Pembrolizumab – On-treatment N = 25	Capmatinib + pembrolizumab – Post-treatment survival follow-up N = 0	Pembrolizumab – Post-treatment survival follow-up N = 0
Arm/Group Description	Capmatinib 400 mg BID in combination with pembrolizumab 200 mg Q3W. AEs collected during on-treatment period (up to 30 days after last dose).	Pembrolizumab single agent 200 mg Q3W after discontinuing capmatinib. AEs collected during on-treatment period (up to 30 days after last dose).	Pembrolizumab single agent 200 mg Q3W from study start. AEs collected during on-treatment period (up to 30 days after last dose).	Capmatinib 400 mg BID in combination with pembrolizumab 200 mg Q3W. Deaths collected in the post-treatment follow-up period (starting from day 31 after last dose). No AEs were collected during this period.	Pembrolizumab single agent 200 mg Q3W from study start. Deaths collected in the post-treatment follow-up period (starting from day 31 after last dose). No AEs were collected during this period.
Total # Affected by any Other Adverse Event	41	29	24	0	0
Total # at Risk by any Other Adverse Event	51	51	25	0	0
Blood and lymphatic system disorders					
Anaemia	4 (7.84%)	2 (3.92%)	0 (0.00%)		
Cardiac disorders					
Tachycardia	0 (0.00%)	0 (0.00%)	2 (8.00%)		
Endocrine disorders					
Hypothyroidism	1 (1.96%)	6 (11.76%)	1 (4.00%)		
Gastrointestinal disorders					
Abdominal pain	1 (1.96%)	1 (1.96%)	2 (8.00%)		
Abdominal pain upper	3 (5.88%)	3 (5.88%)	1 (4.00%)		

Constipation	5 (9.80%)	7 (13.73%)	4 (16.00%)
Diarrhoea	8 (15.69%)	4 (7.84%)	6 (24.00%)
Gastrooesophageal reflux disease	1 (1.96%)	0 (0.00%)	2 (8.00%)
Nausea	13 (25.49%)	1 (1.96%)	2 (8.00%)
Vomiting	14 (27.45%)	1 (1.96%)	2 (8.00%)
General disorders and administration site conditions			
Asthenia	4 (7.84%)	1 (1.96%)	5 (20.00%)
Chest pain	2 (3.92%)	2 (3.92%)	3 (12.00%)
Chills	3 (5.88%)	0 (0.00%)	0 (0.00%)
Fatigue	2 (3.92%)	3 (5.88%)	5 (20.00%)
Oedema peripheral	14 (27.45%)	6 (11.76%)	1 (4.00%)
Pyrexia	9 (17.65%)	2 (3.92%)	5 (20.00%)
Immune system disorders			
Hypersensitivity	0 (0.00%)	1 (1.96%)	2 (8.00%)
Infections and infestations			
COVID-19	0 (0.00%)	0 (0.00%)	2 (8.00%)
Investigations			
Alanine aminotransferase increased	11 (21.57%)	4 (7.84%)	3 (12.00%)
Amylase increased	4 (7.84%)	3 (5.88%)	2 (8.00%)
Aspartate aminotransferase increased	11 (21.57%)	2 (3.92%)	3 (12.00%)

Blood alkaline phosphatase increased	5 (9.80%)	0 (0.00%)	1 (4.00%)
Blood bilirubin increased	6 (11.76%)	1 (1.96%)	1 (4.00%)
Blood creatine phosphokinase increased	1 (1.96%)	3 (5.88%)	0 (0.00%)
Blood creatinine increased	7 (13.73%)	1 (1.96%)	1 (4.00%)
Blood lactate dehydrogenase increased	3 (5.88%)	1 (1.96%)	0 (0.00%)
Gamma-glutamyltransferase increased	4 (7.84%)	0 (0.00%)	2 (8.00%)
Lipase increased	2 (3.92%)	2 (3.92%)	2 (8.00%)
SARS-CoV-2 test negative	4 (7.84%)	0 (0.00%)	2 (8.00%)
Metabolism and nutrition disorders			
Decreased appetite	5 (9.80%)	2 (3.92%)	5 (20.00%)
Hypoalbuminaemia	6 (11.76%)	2 (3.92%)	2 (8.00%)
Hyponatraemia	5 (9.80%)	3 (5.88%)	0 (0.00%)
Musculoskeletal and connective tissue disorders			
Arthralgia	3 (5.88%)	5 (9.80%)	6 (24.00%)
Back pain	4 (7.84%)	2 (3.92%)	3 (12.00%)
Muscular weakness	0 (0.00%)	1 (1.96%)	2 (8.00%)
Myalgia	3 (5.88%)	0 (0.00%)	3 (12.00%)
Pain in extremity	0 (0.00%)	0 (0.00%)	2 (8.00%)
Nervous system disorders			
Dizziness	1 (1.96%)	1 (1.96%)	3 (12.00%)

Headache	3 (5.88%)	1 (1.96%)	3 (12.00%)
Hypoaesthesia	0 (0.00%)	0 (0.00%)	3 (12.00%)
Paraesthesia	1 (1.96%)	1 (1.96%)	4 (16.00%)
Peripheral sensory neuropathy	0 (0.00%)	1 (1.96%)	2 (8.00%)
Psychiatric disorders			
Insomnia	4 (7.84%)	3 (5.88%)	4 (16.00%)
Respiratory, thoracic and mediastinal disorders			
Cough	2 (3.92%)	3 (5.88%)	4 (16.00%)
Dyspnoea	5 (9.80%)	5 (9.80%)	3 (12.00%)
Haemoptysis	1 (1.96%)	1 (1.96%)	2 (8.00%)
Nasal congestion	0 (0.00%)	0 (0.00%)	2 (8.00%)
Pneumonitis	0 (0.00%)	1 (1.96%)	2 (8.00%)
Productive cough	0 (0.00%)	0 (0.00%)	3 (12.00%)
Skin and subcutaneous tissue disorders			
Alopecia	0 (0.00%)	0 (0.00%)	2 (8.00%)
Dermatitis acneiform	0 (0.00%)	0 (0.00%)	2 (8.00%)
Dry skin	1 (1.96%)	2 (3.92%)	2 (8.00%)
Ecchymosis	0 (0.00%)	0 (0.00%)	2 (8.00%)
Erythema	0 (0.00%)	0 (0.00%)	2 (8.00%)
Pruritus	5 (9.80%)	7 (13.73%)	8 (32.00%)
Rash	5 (9.80%)	5 (9.80%)	3 (12.00%)

Rash maculo-papular	0 (0.00%)	0 (0.00%)	2 (8.00%)
Vascular disorders			
Hypertension	1 (1.96%)	0 (0.00%)	6 (24.00%)

Conclusion:

The addition of the MET inhibitor capmatinib was expected to induce positive immunomodulation effect and enhance the antitumor activity of pembrolizumab. However, the combination treatment of capmatinib and pembrolizumab in this study was associated with higher rates of SAEs and higher rates of AEs leading to study treatment dose adjustments/interruptions and/or treatment discontinuation compared to pembrolizumab alone. This led to the decision by the Sponsor to halt study recruitment.

Given that capmatinib was discontinued prematurely in subjects in the investigational arm, the initially planned Bayesian analysis for PFS was not performed and no statistical comparison was made between the 2 treatment arms. Modest ORR was seen with the capmatinib and pembrolizumab combination. Frequent dose reduction and/or interruption of study treatment due to AEs may have impacted the ORR results negatively.

In conclusion, the lack of any signal suggesting improved efficacy with the addition of capmatinib to pembrolizumab, along with the observed safety concern and the unfavorable benefit/risk profile of capmatinib in combination with pembrolizumab does not support further exploration of this combination.

Date of Clinical Trial Report

13-Nov-2023 (v1.0, original version) and 19-Dec-2023 (v2.0, amendment)