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Sponsor

Novartis

Generic Drug Name

Capmatinib (INC280) and spartalizumab (PDR001)

Trial Indication(s)

Advanced non-small cell lung cancer (NSCLC)

Protocol Number

CINC280J12201

Protocol Title

A double-blind, placebo controlled, randomized, phase II study evaluating the efficacy and safety of capmatinib (INC280) and spartalizumab (PDR001) combination therapy versus capmatinib and placebo as first line treatment for locally advanced or metastatic non-small cell lung cancer patients with MET exon 14 skipping mutations

Clinical Trial Phase

Phase 2

Phase of Drug Development

Capmatinib (phase 4) and spartalizumab (phase 3)

Study Start/End Dates

Study Start Date: August 19, 2020 (Actual)
Primary Completion Date: December 14, 2022 (Actual)
Study Completion Date: January 26, 2023 (Actual)

Reason for Termination

The study enrollment was halted on 28-Jul-2021 per sponsor's decision. The enrollment halt decision was due to safety concerns with the combination treatment of capmatinib and spartalizumab during the safety run-in part of the study (Part 1). Subjects who received capmatinib plus spartalizumab in Part 1 of this study showed higher occurrence rates of serious adverse events (SAEs) and adverse events (AEs), leading to dose interruption and/or discontinuation of both study drugs when compared to data generated from capmatinib single agent studies.

Study Design/Methodology

This was a two-part, multicenter, phase II study to evaluate the efficacy and safety of capmatinib in combination with spartalizumab in treatment naive subjects with epidermal growth factor receptor (EGFR) wildtype (wt), anaplastic lymphoma kinase (ALK) rearrangement negative advanced non-small cell lung carcinoma (NSCLC), harboring METΔex14 mutations.

The study consisted of a single arm open label run-in part (Part 1) followed by a double-blind, placebo controlled, randomized part (Part 2). The run-in part (Part 1) was conducted to determine the anti-tumor activity and safety of capmatinib in combination with spartalizumab. Upon review of safety data and confirmation of anti-tumor activity in Part 1, the randomized part (Part 2) was planned to be initiated to compare the efficacy and safety of capmatinib plus spartalizumab to capmatinib plus placebo.

The study enrollment was halted on 28-Jul-2021 per sponsor's decision. The enrollment halt decision was based on lack of tolerability observed in capmatinib and spartalizumab combination treatment in the run-in part (Part 1) of the trial.

Following the study enrollment halt during Part 1 (Run in Part), Part 2 was not initiated.

Immediately following the enrollment halt:

- All ongoing subjects were discontinued from spartalizumab treatment and continue to receive single agent capmatinib, given the proven tolerability and efficacy of capmatinib monotherapy in this study indication.
- Enrolled subjects who had not started study treatment were to receive capmatinib single agent treatment from the start

Centers

15 centers in 9 countries: Belgium(1), France(3), Germany(4), Korea, Republic of(1), Spain(2), Canada(1), Japan(1), United States(1), Italy(1)

Objectives:

The primary objectives of the trial were:

- Run-in part: To evaluate the anti-tumor activity of capmatinib in combination with spartalizumab
- Randomized part: To compare the efficacy of capmatinib in combination with spartalizumab versus capmatinib plus placebo

The secondary objectives of the trial were:

- Run-in part:
  - To assess safety and tolerability of capmatinib in combination with spartalizumab
  - To further evaluate the anti-tumor activity of capmatinib in combination with spartalizumab
  - To evaluate the pharmacokinetics (PK) of capmatinib and spartalizumab
- Randomized part:
  - To compare overall survival of subjects randomized to capmatinib in combination with spartalizumab versus those to capmatinib plus placebo group
  - To assess safety and tolerability of capmatinib in combination with spartalizumab versus capmatinib plus placebo
  - To further evaluate the anti-tumor activity of capmatinib in combination with spartalizumab versus capmatinib plus placebo

- To evaluate patient reported outcomes of capmatinib in combination with spartalizumab versus capmatinib plus placebo
- To evaluate the PK of capmatinib and spartalizumab
- To evaluate the prevalence and incidence of immunogenicity of spartalizumab in combination with capmatinib

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

For this study, the investigational drugs were capmatinib and spartalizumab. The study treatment is defined as capmatinib plus spartalizumab. All subjects in run-in part (Part 1) were to be treated with capmatinib 400 mg orally as tablets twice daily in combination with spartalizumab 400 mg intravenously every 28 days. A complete cycle of treatment is defined as 28 days of continuous capmatinib treatment and an infusion of spartalizumab every 28 days.

After the enrollment halt, all ongoing subjects were discontinued from spartalizumab treatment and continued to receive single agent capmatinib 400 mg orally twice daily. Enrolled subjects who had not started study treatment at the time of enrollment halt received capmatinib single agent treatment from the start.

Subjects were treated until they experienced unacceptable toxicity, disease progression per RECIST 1.1 as determined by Investigator assessment (with or without confirmation by BIRC), and/or treatment is discontinued at the discretion of the Investigator or the subject. Subjects were permitted to continue study treatment beyond disease progression per RECIST 1.1 as determined by Investigator.

Statistical Methods

Analysis of the primary endpoint

The primary objective of the run-in part was to evaluate the anti-tumor activity of capmatinib in combination with spartalizumab, as measured by Overall Response Rate (ORR) by Investigator assessment according to Response Evaluation Criteria In Solid Tumors (RECIST v1.1).

ORR is defined as the proportion of subjects with confirmed Best Overall Response (BOR) of Complete Response (CR) or Partial response (PR) according to RECIST v1.1. ORR by investigator assessment was calculated based on the data from the Full Analysis Set (FAS) and the corresponding 95% confidence interval (CI) based on the exact binomial distribution was presented. The FAS comprised all subjects to whom study treatment had been assigned and who received at least one dose of study treatment (i.e. at least one dose of any component of the study treatment that is capmatinib or spartalizumab (including incomplete infusion)).

Analysis of the secondary endpoint

Efficacy: The secondary efficacy endpoints of the run-in part were Disease Control Rate (DCR) and Progression-Free Survival (PFS) by investigator assessment as per RECIST v1.1.

DCR is defined as the proportion of subjects with a confirmed BOR of CR or PR or stable disease (SD) according to RECIST v1.1. DCR was calculated based on the data from the FAS and the corresponding 95% confidence intervals based on the exact binomial distribution was presented.

PFS was defined as the time from the date of start of treatment to the date of the first documented progression according to RECIST 1.1, or death due to any cause. If a subject had no progression or death, the subject was censored at the date of last adequate tumor assessment. PFS was summarized using the Kaplan-Meier (KM) method, based on FAS. Median PFS, with corresponding 95% CI was presented.

Safety and tolerability: For all safety analysis, the safety set was used. The safety set was identical to the FAS. Adverse events (AEs) were summarized by primary system organ class (SOC) and preferred term (PT) using MedDRA version 25.1 coding.

Tolerability was assessed by summarizing the number of patients with dose interruptions and dose reductions. Dose intensity was also summarized.

Pharmacokinetics:

Pharmacokinetics (PK) parameters summary statistics were based on the capmatinib full pharmacokinetic analysis set (INC-FPAS) and spartalizumab full pharmacokinetic analysis set (PDR-FPAS). The INC-FPAS included all INC-PAS subjects who provided a capmatinib evaluable PK profile on Cycle 3 Day 1 (only applicable to participants with extensive PK sampling).

The PK parameters were determined by non-compartmental methods. Drug concentrations below the lower limit of quantification (LLOQ) were treated as zero for PK parameter calculations.

Missing data was not imputed and was treated as missing.

Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion Criteria:

- Histologically confirmed locally advanced or metastatic NSCLC which is EGFR wild-type, ALK rearrangement negative and METΔex14 mutated
- No prior systemic therapy for advanced/metastatic disease (neo-adjuvant/adjuvant treatment completed > 12 months before relapse are permitted)
- Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1
- Measurable disease as per RECIST 1.1
- Known PD-L1 tumor expression status (applicable to Randomized part 2 only)

Key Exclusion Criteria:

- Prior treatment with a PD-1/PD-L1 inhibitor, MET inhibitor or HGF inhibitor
- Presence of symptomatic CNS metastases or requiring local CNS-directed therapy (radiotherapy or surgery), or increasing doses of corticosteroids 2 weeks prior to study entry
- Impaired cardiac function or clinically significant cardiac disease

- Presence or history of interstitial lung disease, non-infectious pneumonitis or interstitial pneumonitis, including clinically significant radiation pneumonitis
- History of allogenic bone marrow or solid organ transplant
- Radiotherapy to lung fields ≤ 4 weeks or to any other anatomic site ≤ 2 weeks prior to start of study treatment (palliative radiotherapy for bone lesions is allowed)

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Participant Flow Table

Overall Study

	Run-in part: Capmatinib 400 mg BID + Spartalizumab 400 mg Q4W	Randomized part: Capmatinib 400 mg BID + Spartalizumab 400 mg Q4W	Randomized part: Capmatinib 400 mg BID + Placebo	Total
Arm/Group Description	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab 400 mg intravenously every 28 days (Q4W) in the run-in part.	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab 400 mg intravenously every 28 days (Q4W) in the randomized part.	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab matching placebo intravenously every 28 days (Q4W) in the randomized part.	
Started	31	0	0	31
Treated with capmatinib + spartalizumab	28	0	0	28
Treated with capmatinib only	3	0	0	3
Completed	0	0	0	0
Not Completed	31	0	0	31
Adverse Event	7	0	0	7
Transfer to another clinical study or to other alternative treatment option	8	0	0	8
Death	1	0	0	1
Physician Decision	2	0	0	2
Progressive disease	10	0	0	10
Subject decision	3	0	0	3

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Baseline Characteristics

	Run-in part: Capmatinib 400 mg BID + Spartalizumab 400 mg Q4W	Randomized part: Capmatinib 400 mg BID + Spartalizumab 400 mg Q4W	Randomized part: Capmatinib 400 mg BID + Placebo	Total
Arm/Group Description	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab 400 mg intravenously every 28 days (Q4W) in the run-in part.	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab 400 mg intravenously every 28 days (Q4W) in the randomized part.	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab matching placebo intravenously every 28 days (Q4W) in the randomized part.	
Number of Participants [units: participants]	31	0	0	31
Baseline Analysis Population Description	All patients to whom study treatment had been assigned and who received at least one dose of study treatment (i.e. at least one dose of any component of the study treatment that is capmatinib or spartalizumab). The randomized part of the study was not initiated.			
Age Continuous (units: years) Analysis Population Type: Participants Mean ± Standard Deviation				
	71.6±9.50			71.6±9.50
Sex: Female, Male (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)				
Female	16			16
Male	15			15
Race/Ethnicity, Customized (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)				
White	23			23

Black or African American	1	1
Asian	6	6
Unknown	1	1

Primary Outcome Result(s)

Run-in part: Overall Response Rate (ORR) by investigator assessment as per RECIST 1.1

Description	Tumor response was based on local investigator assessment as per Response Evaluation Criteria In Solid Tumors (RECIST) v1.1. ORR per RECIST v1.1 is defined as the percentage of participants with a best overall response of Complete Response (CR) or Partial Response (PR). 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 approximately 2 years and 4 months
Analysis Population Description	All patients to whom study treatment had been assigned and who received at least one dose of study treatment (i.e. at least one dose of any component of the study treatment that is capmatinib or spartalizumab) in the single arm run-in part. Patients were analyzed according to the treatment they were assigned to.

	Run-in part: Capmatinib 400 mg BID + Spartalizumab 400 mg Q4W
Arm/Group Description	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab 400 mg intravenously every 28 days (Q4W) in the run-in part.
Number of Participants Analyzed [units: participants]	31
Run-in part: Overall Response Rate (ORR) by investigator assessment as per RECIST 1.1 (units: percentage of participants)	**Number (95% Confidence Interval)**
	35.5 (19.2 to 54.6)

Randomized part: Progression-Free Survival (PFS) by BIRC as per RECIST 1.1

Description	PFS is defined as the time from the date of start of treatment to the date of the first documented progression or death due to any cause. Tumor response based on blinded independent review committee (BIRC) assessment per RECIST v1.1.
Time Frame	Up to 6 years
Analysis Population Description	All patients to whom study treatment had been assigned and who received at least one dose of study treatment in the randomized part. The randomized part of the study was not initiated and data was not collected.

	Randomized part: Capmatinib 400 mg BID + Spartalizumab 400 mg Q4W	Randomized part: Capmatinib 400 mg BID + Placebo
Arm/Group Description	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab 400 mg intravenously every 28 days (Q4W) in the randomized part.	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab matching placebo intravenously every 28 days (Q4W) in the randomized part.
Number of Participants Analyzed [units: participants]	0	0
Randomized part: Progression-Free Survival (PFS) by BIRC as per RECIST 1.1 (units:)	**()**	**()**

Secondary Outcome Result(s)

Run-in part: Number of participants with dose reductions and dose interruptions of capmatinib

Description	Number of participants with at least one dose reduction of capmatinib and number of participants with at least one dose interruption of capmatinib.
Time Frame	From first dose of capmatinib to last dose, up to 2.4 years

Analysis Population Description	All patients to whom study treatment had been assigned and who received at least one dose of capmatinib in the single arm run-in part. Patients were analyzed according to the treatment they were assigned to.

	Run-in part: Capmatinib 400 mg BID + Spartalizumab 400 mg Q4W
Arm/Group Description	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab 400 mg intravenously every 28 days (Q4W) in the run-in part.
Number of Participants Analyzed [units: participants]	31
Run-in part: Number of participants with dose reductions and dose interruptions of capmatinib (units: participants)	**Count of Participants (Percentage)**
At least one dose reduction	19 (61.29%)
At least one dose interruption	20 (64.52%)

Run-in part: Number of participants with dose reductions and dose interruptions of spartalizumab

Description	Number of participants with at least one dose reduction of spartalizumab and number of participants with at least one dose interruption of spartalizumab. Dose reductions were not allowed for spartalizumab.
Time Frame	From first dose of spartalizumab to last dose, up to 0.9 years
Analysis Population Description	All patients to whom study treatment had been assigned and who received at least one dose of spartalizumab in the single arm run-in part. Patients were analyzed according to the treatment they were assigned to.

	Run-in part: Capmatinib 400 mg BID + Spartalizumab 400 mg Q4W
Arm/Group Description	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab 400 mg intravenously every 28 days (Q4W) in the run-in part.

Number of Participants Analyzed [units: participants]	28
Run-in part: Number of participants with dose reductions and dose interruptions of spartalizumab (units: participants)	**Count of Participants (Percentage)**
At least one dose reduction	0 (%)
At least one dose interruption	7 (25%)

Run-in part: Dose intensity of capmatinib

Description	Dose intensity of capmatinib was calculated as actual cumulative dose in milligrams divided by duration of exposure in days.
Time Frame	From first dose of capmatinib to last dose, up to 2.4 years
Analysis Population Description	All patients to whom study treatment had been assigned and who received at least one dose of capmatinib in the single arm run-in part. Patients were analyzed according to the treatment they were assigned to.

	Run-in part: Capmatinib 400 mg BID + Spartalizumab 400 mg Q4W
Arm/Group Description	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab 400 mg intravenously every 28 days (Q4W) in the run-in part.
Number of Participants Analyzed [units: participants]	31
Run-in part: Dose intensity of capmatinib (units: mg/day)	**Mean ± Standard Deviation**
	595.9 ± 173.6

Run-in part: Dose intensity of spartalizumab

Description	Dose intensity of spartalizumab was calculated as actual cumulative dose in milligrams divided by duration of exposure in days and then multiplied by the duration of one cycle (28 days).

Time Frame	From first dose of spartalizumab to last dose, up to 0.9 years
Analysis Population Description	All patients to whom study treatment had been assigned and who received at least one dose of spartalizumab in the single arm run-in part. Patients were analyzed according to the treatment they were assigned to.

	Run-in part: Capmatinib 400 mg BID + Spartalizumab 400 mg Q4W
Arm/Group Description	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab 400 mg intravenously every 28 days (Q4W) in the run-in part.
Number of Participants Analyzed [units: participants]	28
Run-in part: Dose intensity of spartalizumab (units: mg/cycle)	**Mean ± Standard Deviation**
	365.6 ± 51.5

Run-in part: Disease Control Rate (DCR) by investigator assessment as per RECIST 1.1

Description	DCR is defined as the percentage of participants with a best overall response of Complete Response (CR), Partial Response (PR), Stable Disease (SD), and non-CR/non-progressive disease (for subjects without target lesions). Tumor response was based on local investigator assessment per RECIST v1.1. 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 approximately 2 years and 4 months
Analysis Population Description	All patients to whom study treatment had been assigned and who received at least one dose of study treatment (i.e. at least one dose of any component of the study treatment that is capmatinib or spartalizumab) in the single arm run-in part. Patients were analyzed according to the treatment they were assigned to.

	Run-in part: Capmatinib 400 mg BID + Spartalizumab 400 mg Q4W

Arm/Group Description	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab 400 mg intravenously every 28 days (Q4W) in the run-in part.
Number of Participants Analyzed [units: participants]	31
Run-in part: Disease Control Rate (DCR) by investigator assessment as per RECIST 1.1 (units: percentage of participants)	**Number (95% Confidence Interval)**
	77.4 (58.9 to 90.4)

Run-in part: Progression-Free Survival (PFS) by investigator assessment as per RECIST 1.1

Description	PFS is defined as the time from the date of start of treatment to the date of the first documented progression or death due to any cause. If a patient did not have an event, PFS was censored at the date of the last adequate tumor assessment. Tumor response was based on investigator assessment per RECIST v1.1. Progression is defined using RECIST v1.1 as at least 20% increase in the sum of diameters of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition, the sum must also demonstrate an absolute increase of at least 5 mm. PFS was analyzed using Kaplan-Meier estimates.
Time Frame	Up to approximately 2 years and 5 months
Analysis Population Description	All patients to whom study treatment had been assigned and who received at least one dose of study treatment (i.e. at least one dose of any component of the study treatment that is capmatinib or spartalizumab) in the single arm run-in part. Patients were analyzed according to the treatment they were assigned to.

	Run-in part: Capmatinib 400 mg BID + Spartalizumab 400 mg Q4W
Arm/Group Description	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab 400 mg intravenously every 28 days (Q4W) in the run-in part.
Number of Participants Analyzed [units: participants]	31
Run-in part: Progression-Free Survival (PFS) by investigator assessment as per RECIST 1.1 (units: months)	**Median (95% Confidence Interval)**
	16.5 (7.4 to NA)[1]

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

Run-in part: 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 3 Day 1. The duration of one cycle was 28 days.
Analysis Population Description	Patients in the capmatinib full pharmacokinetic analysis set (INC-FPAS) with an available value for the outcome measure. INC-FPAS consists of all patients who had an extensive PK sampling and provided a capmatinib evaluable PK profile on Cycle 3 Day 1.

	Run-in part: Capmatinib 400 mg BID + Spartalizumab 400 mg Q4W
Arm/Group Description	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab 400 mg intravenously every 28 days (Q4W) in the run-in part.
Number of Participants Analyzed [units: participants]	7
Run-in part: Maximum observed plasma concentration (Cmax) of capmatinib (units: ng/mL)	**Geometric Mean (Geometric Coefficient of Variation)**
	2730 (74.3%)

Run-in part: 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 3 Day 1. The duration of one cycle was 28 days.
Analysis Population Description	Patients in the capmatinib full pharmacokinetic analysis set (INC-FPAS) with an available value for the outcome measure. INC-FPAS consists of all patients who had an extensive PK sampling and provided a capmatinib evaluable PK profile on Cycle 3 Day 1.

	Run-in part: Capmatinib 400 mg BID + Spartalizumab 400 mg Q4W
Arm/Group Description	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab 400 mg intravenously every 28 days (Q4W) in the run-in part.
Number of Participants Analyzed [units: participants]	7
Run-in part: Time to reach maximum plasma concentration (Tmax) of capmatinib (units: hours)	**Median (Full Range)**
	1.75 (1.00 to 3.92)

Run-in part: Area under the plasma concentration-time curve from time zero to the end of a dosing interval (AUCtau) of capmatinib

Description	PK parameters were calculated based on capmatinib plasma concentrations by using non-compartmental methods. The linear trapezoidal method was used for AUCtau calculation. A dosing interval (tau) is defined as 12 hours. The portion of area under the curve between 8 hours and 12 hours post-dose was calculated by extrapolation based on terminal elimination slop.
Time Frame	pre-dose and 1, 2, 4 and 8 hours after morning dose on Cycle 3 Day 1. The duration of one cycle was 28 days.
Analysis Population Description	Patients in the capmatinib full pharmacokinetic analysis set (INC-FPAS) with an available value for the outcome measure. INC-FPAS consists of all patients who had an extensive PK sampling and provided a capmatinib evaluable PK profile on Cycle 3 Day 1.

	Run-in part: Capmatinib 400 mg BID + Spartalizumab 400 mg Q4W
Arm/Group Description	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab 400 mg intravenously every 28 days (Q4W) in the run-in part.
Number of Participants Analyzed [units: participants]	3
Run-in part: Area under the plasma concentration-time curve from time zero to the end of a dosing interval (AUCtau) of capmatinib (units: hr*ng/mL)	**Geometric Mean (Geometric Coefficient of Variation)**
	12900 (96.1%)

Run-in part: 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 3 Day 1. The duration of one cycle was 28 days.
Analysis Population Description	Patients in the capmatinib full pharmacokinetic analysis set (INC-FPAS) with an available value for the outcome measure. INC-FPAS consists of all patients who had an extensive PK sampling and provided a capmatinib evaluable PK profile on Cycle 3 Day 1.

	Run-in part: Capmatinib 400 mg BID + Spartalizumab 400 mg Q4W
Arm/Group Description	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab 400 mg intravenously every 28 days (Q4W) in the run-in part.
Number of Participants Analyzed [units: participants]	7
Run-in part: 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)**
	10000 (61.8%)

Run-in part: Maximum observed serum concentration (Cmax) of spartalizumab

Description	Pharmacokinetic (PK) parameters were calculated based on spartalizumab serum concentrations by using non-compartmental methods. Cmax is defined as the maximum (peak) observed serum concentration following a dose.
Time Frame	pre-infusion and 1, 72, 168, 336 and 672 hours after completion of the spartalizumab infusion on Cycle 3 Day 1. The duration of the infusion was approximately 30 minutes. The duration of one cycle was 28 days.
Analysis Population Description	Patients in the spartalizumab full pharmacokinetic analysis set (PDR-FPAS) with an available value for the outcome measure. PDR-FPAS consists of all patients who had an extensive PK sampling and provided a spartalizumab evaluable PK profile on Cycle 3.

	Run-in part: Capmatinib 400 mg BID + Spartalizumab 400 mg Q4W
Arm/Group Description	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab 400 mg intravenously every 28 days (Q4W) in the run-in part.
Number of Participants Analyzed [units: participants]	9
Run-in part: Maximum observed serum concentration (Cmax) of spartalizumab (units: µg/mL)	**Geometric Mean (Geometric Coefficient of Variation)**
	135 (28.4%)

Run-in part: Time to reach maximum serum concentration (Tmax) of spartalizumab

Description	PK parameters were calculated based on spartalizumab serum concentrations by using non-compartmental methods. Tmax is defined as the time to reach maximum (peak) serum concentration following a dose. Actual recorded sampling times were considered for the calculations.
Time Frame	pre-infusion and 1, 72, 168, 336 and 672 hours after completion of the spartalizumab infusion on Cycle 3 Day 1. The duration of the infusion was approximately 30 minutes. The duration of one cycle was 28 days.
Analysis Population Description	Patients in the spartalizumab full pharmacokinetic analysis set (PDR-FPAS) with an available value for the outcome measure. PDR-FPAS consists of all patients who had an extensive PK sampling and provided a spartalizumab evaluable PK profile on Cycle 3.

	Run-in part: Capmatinib 400 mg BID + Spartalizumab 400 mg Q4W
Arm/Group Description	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab 400 mg intravenously every 28 days (Q4W) in the run-in part.
Number of Participants Analyzed [units: participants]	9
Run-in part: Time to reach maximum serum concentration (Tmax) of spartalizumab (units: hours)	**Median (Full Range)**
	1.67 (0.917 to 164)

Run-in part: Area under the serum concentration-time curve from time zero to the end of a dosing interval (AUCtau) of spartalizumab

Description	PK parameters were calculated based on spartalizumab serum concentrations by using non-compartmental methods. The linear trapezoidal method was used for AUCtau calculation. A dosing interval (tau) is defined as 28 days.
Time Frame	pre-infusion and 1, 72, 168, 336 and 672 hours after completion of the spartalizumab infusion on Cycle 3 Day 1. The duration of the infusion was approximately 30 minutes. The duration of one cycle was 28 days.
Analysis Population Description	Patients in the spartalizumab full pharmacokinetic analysis set (PDR-FPAS) with an available value for the outcome measure. PDR-FPAS consists of all patients who had an extensive PK sampling and provided a spartalizumab evaluable PK profile on Cycle 3.

	Run-in part: Capmatinib 400 mg BID + Spartalizumab 400 mg Q4W
Arm/Group Description	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab 400 mg intravenously every 28 days (Q4W) in the run-in part.
Number of Participants Analyzed [units: participants]	8
Run-in part: Area under the serum concentration-time curve from time zero to the end of a dosing interval (AUCtau) of spartalizumab (units: hr*µg/mL)	**Geometric Mean (Geometric Coefficient of Variation)**
	49700 (47.8%)

Run-in part: Area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration (AUClast) of spartalizumab

Description	PK parameters were calculated based on spartalizumab serum concentrations by using non-compartmental methods. The linear trapezoidal method was used for AUClast calculation.
Time Frame	pre-infusion and 1, 72, 168, 336 and 672 hours after completion of the spartalizumab infusion on Cycle 3 Day 1. The duration of the infusion was approximately 30 minutes. The duration of one cycle was 28 days.
Analysis Population Description	Patients in the spartalizumab full pharmacokinetic analysis set (PDR-FPAS) with an available value for the outcome measure. PDR-FPAS consists of all patients who had an extensive PK sampling and provided a spartalizumab evaluable PK profile on Cycle 3.

	Run-in part: Capmatinib 400 mg BID + Spartalizumab 400 mg Q4W
Arm/Group Description	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab 400 mg intravenously every 28 days (Q4W) in the run-in part.
Number of Participants Analyzed [units: participants]	9
Run-in part: Area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration (AUClast) of spartalizumab (units: hr*µg/mL)	**Geometric Mean (Geometric Coefficient of Variation)**
	52900 (64.6%)

Randomized part: Overall Survival (OS)

Description	OS is defined as the time from date of start of treatment to date of death due to any cause.
Time Frame	Up to 12 years
Analysis Population Description	All patients to whom study treatment had been assigned and who received at least one dose of study treatment in the randomized part. The randomized part of the study was not initiated and data was not collected.

	Randomized part: Capmatinib 400 mg BID + Spartalizumab 400 mg Q4W	Randomized part: Capmatinib 400 mg BID + Placebo
Arm/Group Description	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab 400 mg intravenously every 28 days (Q4W) in the randomized part.	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab matching placebo intravenously every 28 days (Q4W) in the randomized part.
Number of Participants Analyzed [units: participants]	0	0
Randomized part: Overall Survival (OS) (units:)	**()**	**()**

Randomized part: Number of participants with dose reductions and dose interruptions of capmatinib and spartalizumab

Description	Number of participants with at least one dose reduction of capmatinib and spartalizumab and number of participants with at least one dose interruption of capmatinib and spartalizumab.
Time Frame	Up to 6 years
Analysis Population Description	All patients to whom study treatment had been assigned and who received at least one dose of study treatment in the randomized part. The randomized part of the study was not initiated and data was not collected.

	Randomized part: Capmatinib 400 mg BID + Spartalizumab 400 mg Q4W	Randomized part: Capmatinib 400 mg BID + Placebo
Arm/Group Description	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab 400 mg intravenously every 28 days (Q4W) in the randomized part.	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab matching placebo intravenously every 28 days (Q4W) in the randomized part.
Number of Participants Analyzed [units: participants]	0	0
Randomized part: Number of participants with dose reductions and dose interruptions of capmatinib and spartalizumab (units:)	**()**	**()**

Randomized part: Dose intensity of capmatinib and spartalizumab

Description	Dose intensity is defined as the ratio of actual cumulative dose and duration of exposure.
Time Frame	Up to 6 years
Analysis Population Description	All patients to whom study treatment had been assigned and who received at least one dose of study treatment in the randomized part. The randomized part of the study was not initiated and data was not collected.

	Randomized part: Capmatinib 400 mg BID + Spartalizumab 400 mg Q4W	Randomized part: Capmatinib 400 mg BID + Placebo
Arm/Group Description	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab 400 mg intravenously every 28 days (Q4W) in the randomized part.	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab matching placebo intravenously every 28 days (Q4W) in the randomized part.
Number of Participants Analyzed [units: participants]	0	0
Randomized part: Dose intensity of capmatinib and spartalizumab (units:)	()	()

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

Description	PFS is defined as the time from the date of start of treatment to the date of the first documented progression or death due to any cause. Tumor response based on investigator assessment per RECIST v1.1.
Time Frame	Up to 6 years
Analysis Population Description	All patients to whom study treatment had been assigned and who received at least one dose of study treatment in the randomized part. The randomized part of the study was not initiated and data was not collected.

	Randomized part: Capmatinib 400 mg BID + Spartalizumab 400 mg Q4W	Randomized part: Capmatinib 400 mg BID + Placebo
Arm/Group Description	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab 400 mg intravenously every 28 days (Q4W) in the randomized part.	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab matching placebo intravenously every 28 days (Q4W) in the randomized part.
Number of Participants Analyzed [units: participants]	0	0
Randomized part: Progression-Free Survival (PFS) by investigator assessment as per RECIST 1.1 (units:)	()	()

Randomized part: Disease Control Rate (DCR) by BIRC and investigator assessment as per RECIST 1.1

Description	DCR is defined as the percentage of participants with a best overall response of Complete Response (CR), Partial Response (PR), Stable Disease (SD), and non-CR/non-progressive disease (for subjects without target lesions). Tumor response based on BIRC and local investigator assessment per RECIST v1.1.
Time Frame	Up to 6 years
Analysis Population Description	All patients to whom study treatment had been assigned and who received at least one dose of study treatment in the randomized part. The randomized part of the study was not initiated and data was not collected.

	Randomized part: Capmatinib 400 mg BID + Spartalizumab 400 mg Q4W	**Randomized part: Capmatinib 400 mg BID + Placebo**
Arm/Group Description	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab 400 mg intravenously every 28 days (Q4W) in the randomized part.	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab matching placebo intravenously every 28 days (Q4W) in the randomized part.
Number of Participants Analyzed [units: participants]	0	0
Randomized part: Disease Control Rate (DCR) by BIRC and investigator assessment as per RECIST 1.1 (units:)	**()**	**()**

Randomized part: Overall Response Rate (ORR) by BIRC and investigator assessment as per RECIST 1.1

Description	ORR is defined as the percentage of participants with a best overall response of Complete Response (CR) and Partial Response (PR). Tumor response based on BIRC and local investigator assessment per RECIST v1.1.
Time Frame	Up to 6 years
Analysis Population Description	All patients to whom study treatment had been assigned and who received at least one dose of study treatment in the randomized part. The randomized part of the study was not initiated and data was not collected.

	Randomized part: Capmatinib 400 mg BID + Spartalizumab 400 mg Q4W	Randomized part: Capmatinib 400 mg BID + Placebo
Arm/Group Description	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab 400 mg intravenously every 28 days (Q4W) in the randomized part.	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab matching placebo intravenously every 28 days (Q4W) in the randomized part.
Number of Participants Analyzed [units: participants]	0	0
Randomized part: Overall Response Rate (ORR) by BIRC and investigator assessment as per RECIST 1.1 (units:)	()	()

Randomized part: Duration of Response (DOR) by BIRC and investigator assessment as per RECIST 1.1

Description	DOR is defined as the time from the date of first documented response (CR or PR) to the first documented progression per RECIST 1.1 or death due to any cause.
Time Frame	Up to 6 years
Analysis Population Description	All patients to whom study treatment had been assigned and who received at least one dose of study treatment in the randomized part. The randomized part of the study was not initiated and data was not collected.

	Randomized part: Capmatinib 400 mg BID + Spartalizumab 400 mg Q4W	Randomized part: Capmatinib 400 mg BID + Placebo
Arm/Group Description	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab 400 mg intravenously every 28 days (Q4W) in the randomized part.	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab matching placebo intravenously every 28 days (Q4W) in the randomized part.
Number of Participants Analyzed [units: participants]	0	0
Randomized part: Duration of Response (DOR) by BIRC and investigator assessment as per RECIST 1.1 (units:)	()	()

Randomized part: Time to response (TTR) by BIRC and investigator assessment as per RECIST 1.1

Description	TTR is defined as the time from the date of start of treatment to the first documented response of either CR or PR, which must be subsequently confirmed, according to RECIST 1.1.
Time Frame	Up to 6 years
Analysis Population Description	All patients to whom study treatment had been assigned and who received at least one dose of study treatment in the randomized part. The randomized part of the study was not initiated and data was not collected.

	Randomized part: Capmatinib 400 mg BID + Spartalizumab 400 mg Q4W	Randomized part: Capmatinib 400 mg BID + Placebo
Arm/Group Description	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab 400 mg intravenously every 28 days (Q4W) in the randomized part.	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab matching placebo intravenously every 28 days (Q4W) in the randomized part.
Number of Participants Analyzed [units: participants]	0	0
Randomized part: Time to response (TTR) by BIRC and investigator assessment as per RECIST 1.1 (units:)	**()**	**()**

Randomized part: Change from baseline in EORTC QLQ-C30

Description	The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) contains 30 items and is composed of both multi-item scales and single-item measures. These include 5 functional scales (physical, role, emotional, cognitive, and social functioning), 3 symptom scales (fatigue, nausea/vomiting, and pain), 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial impact) and a global health status/QoL scale. All scales and single-item measures range in score from 0 to 100. For the functional and the global QoL scales, a higher score indicates better health. For the symptom scales, a higher score indicates more symptom burden. The QLQ-C30 summary score (0-100) is calculated as the mean of 13 of the 15 QLQ-C30 scale and item scores (excluding global QoL and financial impact), with a higher score indicating a better health-related QoL.
Time Frame	Up to 6 years

Analysis Population Description	All patients to whom study treatment had been assigned and who received at least one dose of study treatment in the randomized part. The randomized part of the study was not initiated and data was not collected.

	Randomized part: Capmatinib 400 mg BID + Spartalizumab 400 mg Q4W	Randomized part: Capmatinib 400 mg BID + Placebo
Arm/Group Description	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab 400 mg intravenously every 28 days (Q4W) in the randomized part.	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab matching placebo intravenously every 28 days (Q4W) in the randomized part.
Number of Participants Analyzed [units: participants]	0	0
Randomized part: Change from baseline in EORTC QLQ-C30 (units:)	**()**	**()**

Randomized part: Change from baseline in EORTC QLQ-LC13

Description	EORTC QLQ-LC13 is used in conjunction with the EORTC QLQ-C30 and provides information on an additional 13 items specifically related to lung cancer. The five domains of the LC13 include pain, dyspnea, coughing and hemoptysis, and are based on their presence over the past week. All but the pain domain are scored on a 4 point Likert scale ranging from “not at all” to “very much”. Pain score is based on its presence, hence yes or no. Scores are averaged and transformed to 0 to 100. A higher score indicates a higher presence of symptoms.
Time Frame	Up to 6 years
Analysis Population Description	All patients to whom study treatment had been assigned and who received at least one dose of study treatment in the randomized part. The randomized part of the study was not initiated and data was not collected.

	Randomized part: Capmatinib 400 mg BID + Spartalizumab 400 mg Q4W	Randomized part: Capmatinib 400 mg BID + Placebo
Arm/Group Description	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab 400 mg intravenously every 28 days (Q4W) in the randomized part.	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab matching placebo intravenously every 28 days (Q4W) in the randomized part.

Number of Participants Analyzed [units: participants]	0	0
Randomized part: Change from baseline in EORTC QLQ-LC13 (units:)	**()**	**()**

Randomized part: Change from baseline in EQ-5D-5L

Description	The EQ-5D-5L is a standardized measure of health utility that provides a single index value for one's health status. The EQ-5D-5L contains one item for each of five dimensions of health-related quality of life (HRQOL) (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Response options for each item vary from having no problems to extreme problems. Subject responses to the five dimensions of HRQOL reflect a specific health state that corresponds to a population preference weight for that state on a continuous scale of 0 (death) to 1 (perfect health). A visual analog scale (ranging from 0 to 100) is also included to capture subject's rating of their overall health status. Higher scores of the EQ-5D-5L represent better health states.
Time Frame	Up to 6 years
Analysis Population Description	All patients to whom study treatment had been assigned and who received at least one dose of study treatment in the randomized part. The randomized part of the study was not initiated and data was not collected.

	Randomized part: Capmatinib 400 mg BID + Spartalizumab 400 mg Q4W	**Randomized part: Capmatinib 400 mg BID + Placebo**
Arm/Group Description	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab 400 mg intravenously every 28 days (Q4W) in the randomized part.	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab matching placebo intravenously every 28 days (Q4W) in the randomized part.
Number of Participants Analyzed [units: participants]	0	0
Randomized part: Change from baseline in EQ-5D-5L (units:)	**()**	**()**

Randomized part: Time to definitive 10 points deterioration symptom scores for pain in chest, coughing and dyspnea per QLQ-LC13 questionnaire

Description	EORTC QLQ-LC13 is used in conjunction with the EORTC QLQ-C30 and provides information on an additional 13 items specifically related to lung cancer. The five domains of the LC13 include pain in chest, dyspnea, coughing and hemoptysis, and are based on their presence over the past week. All but the pain domain are scored on a 4 point Likert scale ranging from “not at all” to “very much”. Pain score is based on its presence, hence yes or no. Scores are averaged and transformed to 0 to 100. A higher score indicates a higher presence of symptoms. The time to definitive 10 points deterioration is defined as the time from the date of randomization to the date of event, which is defined as at least 10 points relative to baseline worsening of the corresponding scale score or death due to any cause.
Time Frame	Up to 6 years
Analysis Population Description	All patients to whom study treatment had been assigned and who received at least one dose of study treatment in the randomized part. The randomized part of the study was not initiated and data was not collected.

	Randomized part: Capmatinib 400 mg BID + Spartalizumab 400 mg Q4W	Randomized part: Capmatinib 400 mg BID + Placebo
Arm/Group Description	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab 400 mg intravenously every 28 days (Q4W) in the randomized part.	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab matching placebo intravenously every 28 days (Q4W) in the randomized part.
Number of Participants Analyzed [units: participants]	0	0
Randomized part: Time to definitive 10 points deterioration symptom scores for pain in chest, coughing and dyspnea per QLQ-LC13 questionnaire (units:)	**()**	**()**

Randomized part: Time to definitive deterioration in global health status/QoL, shortness of breath and pain per EORTC QLQ-C30

Description	The EORTC QLQ-C30 contains 30 items and is composed of both multi-item scales and single-item measures. These include 5 functional scales (physical, role, emotional, cognitive, and social functioning), 3 symptom scales (fatigue, nausea/vomiting, and pain), 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial impact) and a global health status/QoL scale. All scales and single-item measures range in score from 0 to 100. For the functional and the global QoL scales, a higher score indicates better health. For the

	symptom scales, a higher score indicates more symptom burden. The time to definitive 10 points deterioration is defined as the time from the date of randomization to the date of event, which is defined as at least 10 points relative to baseline worsening of the corresponding scale score or death due to any cause.
Time Frame	Up to 6 years
Analysis Population Description	All patients to whom study treatment had been assigned and who received at least one dose of study treatment in the randomized part. The randomized part of the study was not initiated and data was not collected.

	Randomized part: Capmatinib 400 mg BID + Spartalizumab 400 mg Q4W	**Randomized part: Capmatinib 400 mg BID + Placebo**
Arm/Group Description	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab 400 mg intravenously every 28 days (Q4W) in the randomized part.	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab matching placebo intravenously every 28 days (Q4W) in the randomized part.
Number of Participants Analyzed [units: participants]	0	0
Randomized part: Time to definitive deterioration in global health status/QoL, shortness of breath and pain per EORTC QLQ-C30 (units:)	**()**	**()**

Randomized part: Maximum observed concentration (Cmax) of capmatinib and spartalizumab

Description	Pharmacokinetic (PK) parameters calculated based on capmatinib and spartalizumab concentrations in plasma and serum, respectively, by using non-compartmental methods. Cmax is defined as the maximum (peak) observed concentration following a dose.
Time Frame	Up to 6 years
Analysis Population Description	All patients to whom study treatment had been assigned and who received at least one dose of study treatment in the randomized part. The randomized part of the study was not initiated and data was not collected.

	Randomized part: Capmatinib 400 mg BID + Spartalizumab 400 mg Q4W	**Randomized part: Capmatinib 400 mg BID + Placebo**

Arm/Group Description	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab 400 mg intravenously every 28 days (Q4W) in the randomized part.	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab matching placebo intravenously every 28 days (Q4W) in the randomized part.
Number of Participants Analyzed [units: participants]	0	0
Randomized part: Maximum observed concentration (Cmax) of capmatinib and spartalizumab (units:)	**()**	**()**

Randomized part: Time to reach maximum concentration (Tmax) of capmatinib and spartalizumab

Description	Pharmacokinetic (PK) parameters calculated based on capmatinib and spartalizumab concentrations in plasma and serum, respectively, by using non-compartmental methods. Tmax is defined as the time to reach maximum (peak) concentration following a dose.
Time Frame	Up to 6 years
Analysis Population Description	All patients to whom study treatment had been assigned and who received at least one dose of study treatment in the randomized part. The randomized part of the study was not initiated and data was not collected.

	Randomized part: Capmatinib 400 mg BID + Spartalizumab 400 mg Q4W	**Randomized part: Capmatinib 400 mg BID + Placebo**
Arm/Group Description	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab 400 mg intravenously every 28 days (Q4W) in the randomized part.	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab matching placebo intravenously every 28 days (Q4W) in the randomized part.
Number of Participants Analyzed [units: participants]	0	0
Randomized part: Time to reach maximum concentration (Tmax) of capmatinib and spartalizumab (units:)	**()**	**()**

Randomized part: Area under the concentration-time curve from time zero to the end of a dosing interval (AUCtau) of capmatinib and spartalizumab

Description	Pharmacokinetic (PK) parameters calculated based on capmatinib and spartalizumab concentrations in plasma and serum, respectively, by using non-compartmental methods.
Time Frame	Up to 6 years
Analysis Population Description	All patients to whom study treatment had been assigned and who received at least one dose of study treatment in the randomized part. The randomized part of the study was not initiated and data was not collected.

	Randomized part: Capmatinib 400 mg BID + Spartalizumab 400 mg Q4W	**Randomized part: Capmatinib 400 mg BID + Placebo**
Arm/Group Description	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab 400 mg intravenously every 28 days (Q4W) in the randomized part.	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab matching placebo intravenously every 28 days (Q4W) in the randomized part.
Number of Participants Analyzed [units: participants]	0	0
Randomized part: Area under the concentration-time curve from time zero to the end of a dosing interval (AUCtau) of capmatinib and spartalizumab (units:)	**()**	**()**

Randomized part: Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (AUClast) of capmatinib and spartalizumab

Description	Pharmacokinetic (PK) parameters calculated based on capmatinib and spartalizumab concentrations in plasma and serum, respectively, by using non-compartmental methods.
Time Frame	Up to 6 years
Analysis Population Description	All patients to whom study treatment had been assigned and who received at least one dose of study treatment in the randomized part. The randomized part of the study was not initiated and data was not collected.

	Randomized part: Capmatinib 400 mg BID + Spartalizumab 400 mg Q4W	Randomized part: Capmatinib 400 mg BID + Placebo
Arm/Group Description	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab 400 mg intravenously every 28 days (Q4W) in the randomized part.	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab matching placebo intravenously every 28 days (Q4W) in the randomized part.
Number of Participants Analyzed [units: participants]	0	0
Randomized part: Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (AUClast) of capmatinib and spartalizumab (units:)	**()**	**()**

Randomized part: Number of participants with anti-spartalizumab antibodies

Description	Immunogenicity (IG) evaluated in serum samples. The assay to quantify and assess the IG was a validated homogeneous enzyme-linked immunosorbent assay (ELISA).
Time Frame	Baseline (pre-dose), up to 6 years
Analysis Population Description	All patients to whom study treatment had been assigned and who received at least one dose of study treatment in the randomized part. The randomized part of the study was not initiated and data was not collected.

	Randomized part: Capmatinib 400 mg BID + Spartalizumab 400 mg Q4W	Randomized part: Capmatinib 400 mg BID + Placebo
Arm/Group Description	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab 400 mg intravenously every 28 days (Q4W) in the randomized part.	Capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab matching placebo intravenously every 28 days (Q4W) in the randomized part.
Number of Participants Analyzed [units: participants]	0	0
Randomized part: Number of participants with anti-spartalizumab antibodies (units:)	**()**	**()**

Safety Results

Time Frame	Adverse events were collected from first dose of spartalizumab+capmatinib (or capmatinib single agent for enrolled patients who had not started study treatment at the time of spartalizumab discontinuation) to 150 days after last dose of spartalizumab or 30 days after last dose of capmatinib, whichever was longer, up to approximately 2 years and 5 months.
Additional Description	Patients were analyzed according to the treatment they actually received.
Source Vocabulary for Table Default	MedDRA (25.0)
Collection Approach for Table Default	Systematic Assessment

All-Cause Mortality

	Run-in part: Capmatinib 400mg BID + Spartalizumab 400mg Q4W (Prior discontinuing spartalizumab) N = 28	**Run-in part: Capmatinib 400mg BID + Spartalizumab 400mg Q4W (After discontinuing spartalizumab) N = 28**	**Run-in part: Capmatinib 400mg BID only N = 3**
Arm/Group Description	Capmatinib 400 mg BID in combination with spartalizumab 400 mg Q4W before the discontinuation of spartalizumab	Capmatinib 400 mg BID in combination with spartalizumab 400 mg Q4W after the discontinuation of spartalizumab	Immediately following the discontinuation of spartalizumab (and enrollment halt), enrolled subjects who had not started study treatment

			received capmatinib single agent treatment from the start
Total Number Affected	4	0	0
Total Number At Risk	28	28	3

Serious Adverse Events

Time Frame	Adverse events were collected from first dose of spartalizumab+capmatinib (or capmatinib single agent for enrolled patients who had not started study treatment at the time of spartalizumab discontinuation) to 150 days after last dose of spartalizumab or 30 days after last dose of capmatinib, whichever was longer, up to approximately 2 years and 5 months.
Additional Description	Patients were analyzed according to the treatment they actually received.
Source Vocabulary for Table Default	MedDRA (25.0)
Collection Approach for Table Default	Systematic Assessment

	Run-in part: Capmatinib 400mg BID + Spartalizumab 400mg Q4W (Prior discontinuing spartalizumab) N = 28	**Run-in part: Capmatinib 400mg BID + Spartalizumab 400mg Q4W (After discontinuing spartalizumab) N = 28**	**Run-in part: Capmatinib 400mg BID only N = 3**
Arm/Group Description	Capmatinib 400 mg BID in combination with spartalizumab 400 mg Q4W before the discontinuation of spartalizumab	Capmatinib 400 mg BID in combination with spartalizumab 400 mg Q4W after the discontinuation of spartalizumab	Immediately following the discontinuation of spartalizumab (and enrollment halt), enrolled subjects who had not started study treatment

			received capmatinib single agent treatment from the start
Total # Affected by any Serious Adverse Event	11	8	1
Total # at Risk by any Serious Adverse Event	28	28	3
Gastrointestinal disorders			
Pancreatitis	0 (0.00%)	1 (3.57%)	0 (0.00%)
General disorders and administration site conditions			
General physical health deterioration	1 (3.57%)	0 (0.00%)	1 (33.33%)
Medical device site haemorrhage	0 (0.00%)	1 (3.57%)	0 (0.00%)
Oedema	0 (0.00%)	1 (3.57%)	0 (0.00%)
Oedema peripheral	0 (0.00%)	0 (0.00%)	1 (33.33%)
Pyrexia	0 (0.00%)	0 (0.00%)	1 (33.33%)
Hepatobiliary disorders			
Drug-induced liver injury	1 (3.57%)	0 (0.00%)	0 (0.00%)
Hepatic function abnormal	1 (3.57%)	0 (0.00%)	0 (0.00%)
Hepatitis	0 (0.00%)	1 (3.57%)	0 (0.00%)
Hepatotoxicity	0 (0.00%)	1 (3.57%)	0 (0.00%)
Infections and infestations			
Clostridium colitis	0 (0.00%)	1 (3.57%)	0 (0.00%)
Gastroenteritis rotavirus	1 (3.57%)	0 (0.00%)	0 (0.00%)
Osteomyelitis	1 (3.57%)	0 (0.00%)	0 (0.00%)
Pneumonia	1 (3.57%)	0 (0.00%)	1 (33.33%)
Respiratory tract infection	1 (3.57%)	0 (0.00%)	1 (33.33%)
Streptococcal infection	0 (0.00%)	0 (0.00%)	1 (33.33%)

Injury, poisoning and procedural complications			
Infusion related reaction	0 (0.00%)	1 (3.57%)	0 (0.00%)
Joint dislocation	0 (0.00%)	1 (3.57%)	0 (0.00%)
Investigations			
Alanine aminotransferase increased	1 (3.57%)	1 (3.57%)	0 (0.00%)
Aspartate aminotransferase increased	1 (3.57%)	0 (0.00%)	0 (0.00%)
Metabolism and nutrition disorders			
Hyponatraemia	0 (0.00%)	1 (3.57%)	0 (0.00%)
Nervous system disorders			
Brain oedema	1 (3.57%)	0 (0.00%)	0 (0.00%)
Encephalopathy	1 (3.57%)	0 (0.00%)	0 (0.00%)
Renal and urinary disorders			
Acute kidney injury	1 (3.57%)	0 (0.00%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure	0 (0.00%)	1 (3.57%)	0 (0.00%)
Pleural effusion	1 (3.57%)	0 (0.00%)	0 (0.00%)
Pleurisy	1 (3.57%)	0 (0.00%)	0 (0.00%)
Skin and subcutaneous tissue disorders			
Rash maculo-papular	1 (3.57%)	0 (0.00%)	0 (0.00%)
Vascular disorders			
Inferior vena cava syndrome	0 (0.00%)	1 (3.57%)	0 (0.00%)

Other (Not Including Serious) Adverse Events

Time Frame	Adverse events were collected from first dose of spartalizumab+capmatinib (or capmatinib single agent for enrolled patients who had not started study treatment at the time of spartalizumab discontinuation) to 150 days after last dose of spartalizumab or 30 days after last dose of capmatinib, whichever was longer, up to approximately 2 years and 5 months.
Additional Description	Patients were analyzed according to the treatment they actually received.
Source Vocabulary for Table Default	MedDRA (25.0)
Collection Approach for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	Run-in part: Capmatinib 400mg BID + Spartalizumab 400mg Q4W (Prior discontinuing spartalizumab) N = 28	**Run-in part: Capmatinib 400mg BID + Spartalizumab 400mg Q4W (After discontinuing spartalizumab) N = 28**	**Run-in part: Capmatinib 400mg BID only N = 3**
Arm/Group Description	Capmatinib 400 mg BID in combination with spartalizumab 400 mg Q4W before the discontinuation of spartalizumab	Capmatinib 400 mg BID in combination with spartalizumab 400 mg Q4W after the discontinuation of spartalizumab	Immediately following the discontinuation of spartalizumab (and enrollment halt), enrolled subjects who had not started study treatment received capmatinib single agent treatment from the start

Total # Affected by any Other Adverse Event	25	18	3
Total # at Risk by any Other Adverse Event	28	28	3
Blood and lymphatic system disorders			
Anaemia	1 (3.57%)	3 (10.71%)	0 (0.00%)
Thrombocytopenia	2 (7.14%)	1 (3.57%)	1 (33.33%)
Eye disorders			
Periorbital oedema	0 (0.00%)	0 (0.00%)	1 (33.33%)
Gastrointestinal disorders			
Constipation	8 (28.57%)	1 (3.57%)	2 (66.67%)
Diarrhoea	0 (0.00%)	5 (17.86%)	1 (33.33%)
Dry mouth	0 (0.00%)	2 (7.14%)	0 (0.00%)
Gastritis	2 (7.14%)	2 (7.14%)	0 (0.00%)
Gastrooesophageal reflux disease	1 (3.57%)	1 (3.57%)	1 (33.33%)
Nausea	9 (32.14%)	2 (7.14%)	1 (33.33%)
Stomatitis	2 (7.14%)	1 (3.57%)	0 (0.00%)
Vomiting	5 (17.86%)	0 (0.00%)	0 (0.00%)
General disorders and administration site conditions			
Asthenia	1 (3.57%)	1 (3.57%)	1 (33.33%)
Chest pain	2 (7.14%)	1 (3.57%)	1 (33.33%)
Face oedema	3 (10.71%)	0 (0.00%)	0 (0.00%)
Fatigue	3 (10.71%)	3 (10.71%)	1 (33.33%)
Oedema	1 (3.57%)	4 (14.29%)	0 (0.00%)
Oedema peripheral	11 (39.29%)	15 (53.57%)	3 (100.00%)
Pyrexia	0 (0.00%)	0 (0.00%)	1 (33.33%)

Swelling	0 (0.00%)	0 (0.00%)	1 (33.33%)
Infections and infestations			
Beta haemolytic streptococcal infection	0 (0.00%)	0 (0.00%)	1 (33.33%)
COVID-19	0 (0.00%)	0 (0.00%)	2 (66.67%)
Gastroenteritis	0 (0.00%)	2 (7.14%)	0 (0.00%)
Nasopharyngitis	0 (0.00%)	3 (10.71%)	1 (33.33%)
Respiratory tract infection	1 (3.57%)	0 (0.00%)	1 (33.33%)
Upper respiratory tract infection	0 (0.00%)	0 (0.00%)	2 (66.67%)
Investigations			
Alanine aminotransferase increased	8 (28.57%)	6 (21.43%)	1 (33.33%)
Amylase increased	3 (10.71%)	4 (14.29%)	0 (0.00%)
Aspartate aminotransferase increased	9 (32.14%)	6 (21.43%)	1 (33.33%)
Blood alkaline phosphatase increased	1 (3.57%)	1 (3.57%)	1 (33.33%)
Blood bilirubin increased	2 (7.14%)	2 (7.14%)	1 (33.33%)
Blood creatine phosphokinase increased	1 (3.57%)	4 (14.29%)	0 (0.00%)
Blood creatinine increased	10 (35.71%)	11 (39.29%)	2 (66.67%)
Blood lactate dehydrogenase increased	2 (7.14%)	0 (0.00%)	0 (0.00%)
Gamma-glutamyltransferase increased	2 (7.14%)	1 (3.57%)	1 (33.33%)
Lipase increased	3 (10.71%)	5 (17.86%)	1 (33.33%)
Lymphocyte count decreased	0 (0.00%)	2 (7.14%)	0 (0.00%)
Neutrophil count decreased	0 (0.00%)	0 (0.00%)	1 (33.33%)
Platelet count decreased	2 (7.14%)	0 (0.00%)	0 (0.00%)
Weight decreased	3 (10.71%)	0 (0.00%)	1 (33.33%)
Weight increased	2 (7.14%)	4 (14.29%)	1 (33.33%)

Metabolism and nutrition disorders			
Decreased appetite	4 (14.29%)	2 (7.14%)	1 (33.33%)
Hyperkalaemia	2 (7.14%)	0 (0.00%)	0 (0.00%)
Hypoalbuminaemia	1 (3.57%)	5 (17.86%)	2 (66.67%)
Hypokalaemia	0 (0.00%)	3 (10.71%)	1 (33.33%)
Hyponatraemia	1 (3.57%)	3 (10.71%)	0 (0.00%)
Hypophosphataemia	0 (0.00%)	1 (3.57%)	1 (33.33%)
Musculoskeletal and connective tissue disorders			
Arthralgia	3 (10.71%)	2 (7.14%)	0 (0.00%)
Back pain	2 (7.14%)	2 (7.14%)	1 (33.33%)
Muscle spasms	2 (7.14%)	1 (3.57%)	0 (0.00%)
Pain in extremity	1 (3.57%)	4 (14.29%)	0 (0.00%)
Nervous system disorders			
Dizziness	3 (10.71%)	0 (0.00%)	1 (33.33%)
Headache	3 (10.71%)	2 (7.14%)	1 (33.33%)
Psychiatric disorders			
Confusional state	2 (7.14%)	0 (0.00%)	0 (0.00%)
Insomnia	1 (3.57%)	2 (7.14%)	0 (0.00%)
Reproductive system and breast disorders			
Scrotal oedema	0 (0.00%)	0 (0.00%)	1 (33.33%)
Respiratory, thoracic and mediastinal disorders			
Asphyxia	0 (0.00%)	0 (0.00%)	1 (33.33%)
Cough	0 (0.00%)	3 (10.71%)	1 (33.33%)

Dyspnoea	1 (3.57%)	4 (14.29%)	2 (66.67%)
Pleural effusion	2 (7.14%)	1 (3.57%)	0 (0.00%)
Pneumonitis	0 (0.00%)	2 (7.14%)	0 (0.00%)
Skin and subcutaneous tissue disorders			
Alopecia	2 (7.14%)	1 (3.57%)	0 (0.00%)
Dermatitis acneiform	0 (0.00%)	2 (7.14%)	0 (0.00%)
Pruritus	2 (7.14%)	1 (3.57%)	0 (0.00%)
Rash	2 (7.14%)	1 (3.57%)	0 (0.00%)
Rash maculo-papular	4 (14.29%)	1 (3.57%)	1 (33.33%)
Vascular disorders			
Hypertension	0 (0.00%)	0 (0.00%)	1 (33.33%)
Hypotension	0 (0.00%)	2 (7.14%)	1 (33.33%)
Orthostatic hypotension	0 (0.00%)	0 (0.00%)	1 (33.33%)

Conclusion:

The combination treatment of capmatinib and spartalizumab in advanced METΔex14 NSCLC subjects, with no prior systemic therapy for advanced disease, was poorly tolerated by the study subjects and resulted in high rates of SAEs and high rates of treatment related AEs leading to study treatment discontinuation as compared with capmatinib monotherapy studies. These safety findings had shifted the benefit/risk ratio in favor of capmatinib monotherapy in the study subjects. The results of the PK analysis were not suggestive of PK interaction between capmatinib and spartalizumab and therefore did not appear to be a contributing factor to the safety findings.

With limited sample size and duration of treatment, modest ORR was seen with capmatinib and spartalizumab combination in this study. The observed ORR was inferior to the published ORR of capmatinib monotherapy in first line setting. Frequent

dose reduction and/or interruption of study treatment due to treatment related AEs may be a contributing factor to the observed ORR in this study.

The modest clinical activity along with the observed safety concerns and unfavorable risk/benefit profile of capmatinib in combination with spartalizumab does not support further exploration of this combination.

Single agent mesenchymal epithelial transition (MET) inhibitor remains the preferred therapeutic option for METΔex14 advanced NSCLC subjects with no prior systemic therapy for advanced disease.

Date of Clinical Trial Report

23-Oct-2023