



Clinical trial results:

The ROME trial from histology to target: the road to personalize target therapy and immunotherapy

Summary

EudraCT number	2018-002190-21
Trial protocol	IT
Global end of trial date	06 September 2024

Results information

Result version number	v1 (current)
This version publication date	14 September 2025
First version publication date	14 September 2025

Trial information

Trial identification

Sponsor protocol code	MAR-BAS-18-005
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04591431
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Fondazione per la Medicina Personalizzata
Sponsor organisation address	Viale Regina Margherita, 302, ROMA, Italy, 00198
Public contact	Clinical Trial Unit, Fondazione per la Medicina Personalizzata, 39 3208630311, silvia.violetti@clinicaltrialsfmp.it
Scientific contact	Clinical Trial Unit, Fondazione per la Medicina Personalizzata, 39 06 83977939, silvia.violetti@clinicaltrialsfmp.it

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 January 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 September 2024
Global end of trial reached?	Yes
Global end of trial date	06 September 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of our study is to evaluate the efficacy analyses (meant as overall response rate ORR) of TT vs SoC. The main efficacy analyses were conducted on the modified ITT population composed by 400 patients. The safety data regard the SAFETY population which consisted in the patients exposed to the study treatments, i.e. the randomized patients who assumed one dose of treatment at least. The SAFETY population was composed by 362 patients

Protection of trial subjects:

On 29/11/2022, the Data Monitoring Board met in accordance with the clinical protocol, having reached 20% enrolment of randomised patients. The database data was locked on 31 October 2022 and patients data were extracted. After reviewing the data, DSUR and other documentation, the Board did not identify any safety issues related to the treatments assigned to patients or any futility of the study. It therefore recommended the continuation of the study.

Background therapy:

Since these were cancer patients with various conditions treated in different hospitals, the concomitant drugs assigned were those used in clinical practice at the various hospitals.

Evidence for comparator:

Recent studies have shown that targeted agents are superior to standard non-targeted treatments. Therefore, the ROME study could contribute to the evaluation of the impact of personalised therapies in different types of tumours based on the patient's genomic profile vs Standard of Care treatments. This approach could be extended to all other cancer histologies in which the second or third line of treatment has not well defined, has unsatisfactory clinical outcomes or is lack of well-defined therapeutic targets.

Actual start date of recruitment	13 October 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 400
Worldwide total number of subjects	400
EEA total number of subjects	400

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	250
From 65 to 84 years	149
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Eligible participants were adult patients with advanced solid tumors, ECOG performance status 0–1, and measurable disease per RECIST/iRECIST. Molecular profiling was required prior to randomization based on inclusion and exclusion criteria.

Pre-assignment

Screening details:

Patients with progressive disease of breast cancer, metastatic gastro-intestinal tumors, non small cell lung cancer (NSCLC) or others. Patients should have completed or failed at least 1 line of treatment and no more than 2. Patients who are candidates to potentially curative surgery or other locoregional treatment are excluded

Pre-assignment period milestones

Number of subjects started	400
Number of subjects completed	400

Period 1

Period 1 title	TREATMENT PHASE (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	ARM A: SoC

Arm description:

Patients will be treated with standard therapy according the current version of the AIOM guidelines for their type of cancer. At the first PD the patient switched to the Tailored Treatment defined by Molecular Tumor Board at the time of randomization. The patient stayed in the study until the occurrence of a second PD or 18 months after randomization.

Arm type	Active comparator
Investigational medicinal product name	Oncological Standard of Care Treatment
Investigational medicinal product code	
Other name	All the oncological treatments according to the current version of the AIOM guidelines
Pharmaceutical forms	Coated tablet, Concentrate and solvent for intravesical solution, Concentrate and solvent for solution for infusion, Concentrate and solvent for solution for injection/infusion, Injection/infusion, Capsule
Routes of administration	Cutaneous use, Infusion , Instillation , Oral use, Other use

Dosage and administration details:

Farmaceutical forms and route of administration were performed according to the relevant clinical practice

Arm title	ARM B: TT
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Arm description:

TAILORED THERAPY according to the genomic profile. Patients were treated with target therapy and/or immunotherapy according to their genomic profile evidenced by the liquid and tissue profiling. Patients were treated with one or more drugs of the following list, if a safe combination is available in a phase II trial already conducted.

At the first PD, patient switched to SoC until the occurrence of a second PD or 18 months after randomization

Arm type	Experimental
Investigational medicinal product name	Erlotinib
Investigational medicinal product code	
Other name	Tarceva
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details: 150/100 mg/die according to the tumor type	
Investigational medicinal product name	TRASTUZUMAB
Investigational medicinal product code	
Other name	Herceptin
Pharmaceutical forms	Solution for infusion in administration system
Routes of administration	Infusion
Dosage and administration details: 8-4mg/kg/week according to the tumor type. the maintenance dose reduced to 6-2mg/kg/week respectively	
Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	
Other name	Perjeta
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion
Dosage and administration details: 8 mg/kg/week followed by 6 mg/kg /3 weeks for maintenance	
Investigational medicinal product name	Trastuzumab Emtansine
Investigational medicinal product code	
Other name	Kadcyla
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Infusion
Dosage and administration details: 3,6 mg/kg/3 weeks	
Investigational medicinal product name	Vemurafenib
Investigational medicinal product code	
Other name	Zelboraf
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details: 960 mg bid	
Investigational medicinal product name	Cobimetinib
Investigational medicinal product code	
Other name	Cotellic
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details: 60 mg/die	
Investigational medicinal product name	Alectinib
Investigational medicinal product code	
Other name	Alecensa
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:	
600 mg bid	
Investigational medicinal product name	Vismogedib
Investigational medicinal product code	
Other name	Erivedge
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details:	
150 mg die	
Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	
Other name	Tecentriq
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion
Dosage and administration details:	
• 840 mg every two weeks • 1200 mg every three weeks • 1680 mg every four weeks.	
Investigational medicinal product name	Ipatasertib
Investigational medicinal product code	RO5532961
Other name	GDC-0068, G-035608
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
400 mg/die scalable down to 200 mg/die according to safety condition	
Investigational medicinal product name	Entrectinib
Investigational medicinal product code	
Other name	Rozlytrek
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details:	
600 mg die scalable down to 200 mg according to safety condition	
Investigational medicinal product name	Everolimus
Investigational medicinal product code	
Other name	Afinitor
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
10 mg once a day	
Investigational medicinal product name	Palbociclib
Investigational medicinal product code	
Other name	Ibrance
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details:	
125 mg once daily	
Investigational medicinal product name	Lapatinib
Investigational medicinal product code	
Other name	Tyverb
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:	
1250 mg die	
Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	
Other name	Yervoy
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion
Dosage and administration details:	
3 mg/kg every 3 weeks	
Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	Opdivo
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion
Dosage and administration details:	
240 mg every 2 weeks or 480 mg every 4 weeks	
Investigational medicinal product name	Brigatinib
Investigational medicinal product code	
Other name	Alunbrig
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
90 mg orally once daily for the first 7 days; when tolerated, increased to 180 mg orally once daily.	
Investigational medicinal product name	Ponatinib
Investigational medicinal product code	
Other name	Iclusig
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
45 mg die scalable down to 15 mg die according to safety condition	
Investigational medicinal product name	Itacitinib
Investigational medicinal product code	INCB039110
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
600 mg/die scalable down to 200 mg according to safety condition	
Investigational medicinal product name	Pemigatinib
Investigational medicinal product code	INCB054828
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
13.5 mg orally once daily	
Investigational medicinal product name	Alpelisib
Investigational medicinal product code	
Other name	Pigray
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
300 mg once a day scalable down to 200 mg according to safety condition	

Investigational medicinal product name	Tepotinib
Investigational medicinal product code	
Other name	TEPMETKO
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
500 mg one a day scalable down to 250 mg once a day according to safety condition	
Investigational medicinal product name	Pralsetinib
Investigational medicinal product code	
Other name	Gavreto
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details:	
400 mg/die scalable down to 100 mg/die according to safety condition	
Investigational medicinal product name	Talazoparib
Investigational medicinal product code	
Other name	Talzenna
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details:	
1 mg once daily, scalable down to 0.25 mg/die according to safety condition	
Investigational medicinal product name	Selpercatinib
Investigational medicinal product code	
Other name	Retevmo
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details:	
• Less than 50 kg: 120 mg/bid scalable down to 40 mg/bid according to safety condition • 50 kg or greater: 160 mg/bid scalable down to 40 mg/bid according to safety condition	

Number of subjects in period 1	ARM A: SoC	ARM B: TT
Started	200	200
Completed	33	41
Not completed	167	159
Adverse event, serious fatal	38	36
Consent withdrawn by subject	10	6
Adverse event, non-fatal	20	28
Lost to follow-up	5	2
Physical deterioration, other deaths	64	65
Protocol deviation	30	22

Baseline characteristics

Reporting groups

Reporting group title	ARM A: SoC
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Reporting group description:

Patients will be treated with standard therapy according the current version of the AIOM guidelines for their type of cancer. At the first PD the patient switched to the Tailored Treatment defined by Molecular Tumor Board at the time of randomization. The patient stayed in the study until the occurrence of a second PD or 18 months after randomization.

Reporting group title	ARM B: TT
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Reporting group description:

TAILORED THERAPY according to the genomic profile. Patients were treated with target therapy and/or immunotherapy according to their genomic profile evidenced by the liquid and tissue profiling. Patients were treated with one or more drugs of the following list, if a safe combination is available in a phase II trial already conducted.

At the first PD, patient switched to SoC until the occurrence of a second PD or 18 months after randomization

Reporting group values	ARM A: SoC	ARM B: TT	Total
Number of subjects	200	200	400
Age categorical			
age 18-64; age 65-84; >84			
Units: Subjects			
Adults (18-64 years)	132	118	250
From 65-84 years	68	81	149
85 years and over	0	1	1
Age continuous			
Age at the time of the signed of the Informed Consent			
Units: years			
arithmetic mean	59.3	60.4	
standard deviation	± 11.7	± 11.7	-
Gender categorical			
Male and Female			
Units: Subjects			
Female	100	108	208
Male	100	92	192
Genetic Profile			
A molecular profile of the cancer was evaluated on tumor tissue biopsy and on ctDNA on 1794 patients. After FO evaluations patients with actionable mutations, not previously identified with other methods, for which approved drugs according to histotype were available, were excluded. Once identified molecular abnormalities (not only those that were disease-specific), that could be modulated with target or immunotherapeutic intervention available within the present study, patients were randomized into Arm A or B to receive therapy			
Units: Subjects			
A Stratum-Breast	20	20	40
B Stratum_Gastric	55	54	109
C Stratum_NSCLC	15	16	31
C Stratum_Other	110	110	220

Subject analysis sets

Subject analysis set title	Baseline characteristics
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The following baseline characteristics of all the randomized patients were analyzed:
Age, Gender, Hospitalization, Race, ECOG PS, Medical and Oncological History, Prior and Concomitant Medication, Hiv, Hbv, Hcv tests

Subject analysis set title	Efficacy analysis
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The following endpoints were analyzed on the mITT population:
ORR, OS, PFS, TTTF, TTNT.

Moreover, exploratory analyses on MSI-H, hTMB, BRAF mutations, and HER2 alterations groups were analysed with the same analyses, i.e. ORR, OS, PFS, TTTF and TTNT.

Subject analysis set title	Safety Analysis
Subject analysis set type	Safety analysis

Subject analysis set description:

The following safety analyses were performed on the safety population exposed to treatment:
AEs, Laboratory Data, Vital Signs

Reporting group values	Baseline characteristics	Efficacy analysis	Safety Analysis
Number of subjects	400	400	362
Age categorical			
age 18-64; age 65-84; >84			
Units: Subjects			
Adults (18-64 years)	250	250	225
From 65-84 years	49	49	136
85 years and over	1	1	1
Age continuous			
Age at the time of the signed of the Informed Consent			
Units: years			
arithmetic mean	59.8	59.8	59.9
standard deviation	± 11.7	± 11.7	± 11.8
Gender categorical			
Male and Female			
Units: Subjects			
Female	208	208	188
Male	192	192	174
Genetic Profile			
A molecular profile of the cancer was evaluated on tumor tissue biopsy and on ctDNA on 1794 patients. After FO evaluations patients with actionable mutations, not previously identified with other methods, for which approved drugs according to histotype were available, were excluded. Once identified molecular abnormalities (not only those that were disease-specific), that could be modulated with target or immunotherapeutic intervention available within the present study, patients were randomized into Arm A or B to receive therapy			
Units: Subjects			
A Stratum-Breast	40	40	37
B Stratum_Gastric	109	109	97
C Stratum_NSCLC	31	31	26
C Stratum_Other	220	220	202

End points

End points reporting groups

Reporting group title	ARM A: SoC
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Reporting group description:

Patients will be treated with standard therapy according the current version of the AIOM guidelines for their type of cancer. At the first PD the patient switched to the Tailored Treatment defined by Molecular Tumor Board at the time of randomization. The patient stayed in the study until the occurrence of a second PD or 18 months after randomization.

Reporting group title	ARM B: TT
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Reporting group description:

TAILORED THERAPY according to the genomic profile. Patients were treated with target therapy and/or immunotherapy according to their genomic profile evidenced by the liquid and tissue profiling.

Patients were treated with one or more drugs of the following list, if a safe combination is available in a phase II trial already conducted.

At the first PD, patient switched to SoC until the occurrence of a second PD or 18 months after randomization

Subject analysis set title	Baseline characteristics
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

The following baseline characteristics of all the randomized patients were analyzed:

Age, Gender, Hospitalization, Race, ECOG PS, Medical and Oncological History, Prior and Concomitant Medication, Hiv, Hbv, Hcv tests

Subject analysis set title	Efficacy analysis
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

The following endpoints were analyzed on the mITT population:

ORR, OS, PFS, TTTF, TTNT.

Moreover, exploratory analyses on MSI-H, hTMB, BRAF mutations, and HER2 alterations groups were analysed with the same analyses, i.e. ORR, OS, PFS, TTTF and TTNT.

Subject analysis set title	Safety Analysis
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Subject analysis set type	Safety analysis
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Subject analysis set description:

The following safety analyses were performed on the safety population exposed to treatment:

AEs, Laboratory Data, Vital Signs

Primary: OVERALL RESPONSE RATE by Arm

End point title	OVERALL RESPONSE RATE by Arm
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End point description:

Overall Response Rate (ORR) defined as the proportion of patients with a complete response (CR) or partial response (PR)

End point type	Primary
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End point timeframe:

OVERALL RESPONSE RATE (ORR) on the entire treatment period

End point values	ARM A: SoC	ARM B: TT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200	200		
Units: %				
number (not applicable)	10	17.5		

Statistical analyses

Statistical analysis title	Overall Response Rate
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Statistical analysis description:

The results of the primary endpoint are included in the post-text Table 14.2.1a of the CSR. The table includes the analysis on the mITT, ITT and PP populations. All the raw data are included in post-text Listing 16.2.2 of the CSR. The Overall Response Rate (ORR) is defined as the proportion of patients with a complete response (CR) or partial response (PR), across the four predefined tumor strata in the mITT population.

Comparison groups	ARM A: SoC v ARM B: TT
Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0285 ^[1]
Method	Cochran-Mantel-Haenszel

Notes:

[1] - The ORR was significantly higher in the Tailored Therapy group compared to the Standard of Care group, with a Cochran-Mantel-Haenszel p-value of 0.0285, suggesting a potential benefit of molecularly guided treatment strategies.

Secondary: Progression Free Survival

End point title	Progression Free Survival
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End point description:

PFS was evaluated in the modified Intention-to-Treat (mITT) population and is summarized in post-text Table 12.2.3a of the CSR and the corresponding Kaplan-Meier curve.

Patients receiving Tailored Therapy (TT) experienced a longer mean PFS of 7.75 months (Standard Error [SE]: 0.61) compared to 4.60 months (SE: 0.36) in the Standard of Care (SoC) arm.

Median PFS was also extended in the TT group, at 3.45 months (95% Confidence Interval [CI]: 3.03 to 4.84), versus 2.80 months (95% CI: 2.53 to 3.19) in the SoC group.

The hazard ratio (HR) for progression or death was 0.66 (95% CI: 0.53 to 0.82), indicating a statistically significant 34% reduction in the risk of progression or death for patients treated with TT compared to SoC.

The 9-month PFS rate was 27.8% (95% CI: 21.4 to 34.2) in the TT arm versus 13.4% (95% CI: 8.4 to 18.5) in the SoC arm, while the 12-month PFS rate was 22.0% (95% CI: 16.0 to 28.0) versus 8.3% (95% CI: 4.2 to 12.5), respectively.

End point type	Secondary
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End point timeframe:

PFS during the entire course of the study

End point values	ARM A: SoC	ARM B: TT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200	200		
Units: month				
median (confidence interval 95%)	2.8 (2.53 to 3.19)	3.45 (3.03 to 4.84)		

Statistical analyses

Statistical analysis title	PROGRESSION FREE SURVIVAL
Statistical analysis description:	
These results demonstrate a clear and clinically meaningful improvement in PFS with Tailored Therapy over Standard of Care, supporting the efficacy of biomarker-guided treatment strategies in this patient population.	
Comparison groups	ARM B: TT v ARM A: SoC
Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	0.82

Secondary: OVERALL SURVIVAL

End point title	OVERALL SURVIVAL
End point description:	
OS defined as the time from randomization to death from any cause. Data for patients with no record of death were censored at the last date they were known to be alive.	
End point type	Secondary
End point timeframe:	
OS during the entire course of the study	

End point values	ARM A: SoC	ARM B: TT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200	200		
Units: months				
median (confidence interval 95%)	7.86 (5.43 to 10.0)	9.11 (6.78 to 11.02)		

Statistical analyses

Statistical analysis title	Overall Survival
Statistical analysis description: No relevant differences were observed between the two arms	
Comparison groups	ARM A: SoC v ARM B: TT
Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.19

Secondary: Time to Treatment Failure

End point title	Time to Treatment Failure
End point description: Time to Treatment Failure (TTTF) is defined as the time from randomization or first dose of study treatment until the date of permanent treatment discontinuation for any reason, including disease progression, adverse events, death, or withdrawal from study.	
End point type	Secondary
End point timeframe: TTTF during the entire course of the study	

End point values	ARM A: SoC	ARM B: TT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200	200		
Units: months				
median (confidence interval 95%)	2.76 (2.53 to 3.06)	3.49 (3.06 to 4.86)		

Statistical analyses

Statistical analysis title	TTTF
Statistical analysis description: Pts in the Tailored Therapy (TT) arm showed a longer median TTF of 3.49 months (95% Confidence Interval [CI]: 3.06 to 4.87) compared to 2.76 months (95% CI: 2.53 to 3.06) in the Standard of Care (SoC) arm. The hazard ratio (HR) for treatment failure was 0.64 (95% CI: 0.51 to 0.79), demonstrating a 36% reduction in the risk of treatment discontinuation for any reason in the TT arm versus SoC.	
Comparison groups	ARM A: SoC v ARM B: TT

Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	0.79

Secondary: Time to Next Treatment

End point title	Time to Next Treatment
End point description:	
Time to Next Treatment (TTNT) is defined as the time interval from the date of randomization or first dose of study treatment to the date of initiation of subsequent anticancer therapy after discontinuation of the study treatment, whichever occurs first.	
End point type	Secondary
End point timeframe:	
TTNT during the entire course of the study	

End point values	ARM A: SoC	ARM B: TT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200	200		
Units: months				
median (confidence interval 95%)	3.45 (2.99 to 3.75)	5.03 (3.91 to 6.32)		

Statistical analyses

Statistical analysis title	Time to Next Treatment
Statistical analysis description:	
The median TTNT was extended in the TT group at 5.03 months (95% Confidence Interval [CI]: 3.91 to 6.32), versus 3.45 months (95% CI: 2.99 to 3.75) in the SoC group.	
The hazard ratio (HR) for initiation of next treatment was 0.58 (95% CI: 0.46 to 0.73), indicating a statistically significant 42% reduction in the risk of starting subsequent therapy for patients treated with TT compared to SoC.	
Comparison groups	ARM A: SoC v ARM B: TT
Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.58

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	0.73

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events occurring between the date of informed consent signature and 3 months after last drug administration were collected

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.1
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Reporting groups

Reporting group title	Arm A: SoC
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Reporting group description:

All adverse events were collected by the SoC arm in the safety population.

Reporting group title	Arm B: TT
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Reporting group description:

All adverse events were collected by the TT arm in the safety population.

Serious adverse events	Arm A: SoC	Arm B: TT	
Total subjects affected by serious adverse events			
subjects affected / exposed	76 / 179 (42.46%)	62 / 183 (33.88%)	
number of deaths (all causes)	110	113	
number of deaths resulting from adverse events	42	39	
Vascular disorders			
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 179 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemorrhage intracranial			
subjects affected / exposed	1 / 179 (0.56%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Ischaemia			
subjects affected / exposed	0 / 179 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Surgical and medical procedures			

Hospitalisation			
subjects affected / exposed	0 / 179 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	13 / 179 (7.26%)	11 / 183 (6.01%)	
occurrences causally related to treatment / all	1 / 13	1 / 11	
deaths causally related to treatment / all	1 / 13	1 / 10	
General physical health deterioration			
subjects affected / exposed	12 / 179 (6.70%)	10 / 183 (5.46%)	
occurrences causally related to treatment / all	0 / 12	1 / 10	
deaths causally related to treatment / all	0 / 12	1 / 9	
Hyperpyrexia			
subjects affected / exposed	0 / 179 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 179 (0.00%)	2 / 183 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyrexia			
subjects affected / exposed	4 / 179 (2.23%)	3 / 183 (1.64%)	
occurrences causally related to treatment / all	1 / 4	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 179 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea			

subjects affected / exposed	1 / 179 (0.56%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Interstitial lung disease			
subjects affected / exposed	2 / 179 (1.12%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 179 (0.56%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 179 (1.12%)	2 / 183 (1.09%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 179 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 179 (1.12%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	1 / 179 (0.56%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device occlusion			
subjects affected / exposed	0 / 179 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Blood Bilirubin increased subjects affected / exposed	4 / 179 (2.23%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Blood creatinine increased subjects affected / exposed	1 / 179 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased subjects affected / exposed	1 / 179 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SARS-CoV-2 test positive subjects affected / exposed	0 / 179 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Transaminases increased subjects affected / exposed	0 / 179 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Osteoradionecrosis subjects affected / exposed	0 / 179 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal cuff dehiscence subjects affected / exposed	1 / 179 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation subjects affected / exposed	1 / 179 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac arrest			
subjects affected / exposed	1 / 179 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocarditis			
subjects affected / exposed	1 / 179 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain oedema			
subjects affected / exposed	2 / 179 (1.12%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 179 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			
subjects affected / exposed	1 / 179 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	1 / 179 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	1 / 179 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	0 / 179 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Encephalopathy			

subjects affected / exposed	0 / 179 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Epilepsy			
subjects affected / exposed	1 / 179 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	1 / 179 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	0 / 179 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 179 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 179 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 179 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 179 (1.12%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Melanaemia			

subjects affected / exposed	1 / 179 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 179 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 179 (1.68%)	2 / 183 (1.09%)	
occurrences causally related to treatment / all	0 / 3	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ascites			
subjects affected / exposed	1 / 179 (0.56%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 179 (1.12%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Dysphagia			
subjects affected / exposed	0 / 179 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric perforation			
subjects affected / exposed	1 / 179 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 179 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			

subjects affected / exposed	1 / 179 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	1 / 179 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 179 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intra-abdominal haemorrhage			
subjects affected / exposed	0 / 179 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Large intestinal obstruction			
subjects affected / exposed	1 / 179 (0.56%)	2 / 183 (1.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 179 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sialoadenitis			
subjects affected / exposed	1 / 179 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 179 (0.56%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stenosis			

subjects affected / exposed	0 / 179 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	0 / 179 (0.00%)	3 / 183 (1.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 179 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 179 (0.00%)	3 / 183 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Hepatitis			
subjects affected / exposed	1 / 179 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 179 (0.56%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypertransaminasaemia			
subjects affected / exposed	0 / 179 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 179 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	0 / 179 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oliguria			
subjects affected / exposed	0 / 179 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 179 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	0 / 179 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 179 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 179 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genitourinary tract infection			
subjects affected / exposed	1 / 179 (0.56%)	3 / 183 (1.64%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin abscess			
subjects affected / exposed	1 / 179 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infection			
subjects affected / exposed	0 / 179 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis bacterial			
subjects affected / exposed	1 / 179 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia fungal			
subjects affected / exposed	1 / 179 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	8 / 179 (4.47%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 8	1 / 1	
deaths causally related to treatment / all	0 / 3	1 / 1	
Systemic infection			
subjects affected / exposed	1 / 179 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperammonaemia			
subjects affected / exposed	0 / 179 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 179 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 179 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			

subjects affected / exposed	1 / 179 (0.56%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Arm A: SoC	Arm B: TT	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	147 / 179 (82.12%)	161 / 183 (87.98%)	
Investigations			
SARS-CoV-2 test positive			
subjects affected / exposed	8 / 179 (4.47%)	10 / 183 (5.46%)	
occurrences (all)	9	10	
Nervous system disorders			
Headache			
subjects affected / exposed	12 / 179 (6.70%)	10 / 183 (5.46%)	
occurrences (all)	15	12	
Paraesthesia			
subjects affected / exposed	12 / 179 (6.70%)	8 / 183 (4.37%)	
occurrences (all)	12	10	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	32 / 179 (17.88%)	27 / 183 (14.75%)	
occurrences (all)	59	37	
Neutropenia			
subjects affected / exposed	24 / 179 (13.41%)	13 / 183 (7.10%)	
occurrences (all)	72	25	
Thrombocytopenia			
subjects affected / exposed	13 / 179 (7.26%)	14 / 183 (7.65%)	
occurrences (all)	16	21	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	57 / 179 (31.84%)	49 / 183 (26.78%)	
occurrences (all)	84	68	
Fatigue			

subjects affected / exposed	20 / 179 (11.17%)	15 / 183 (8.20%)	
occurrences (all)	24	19	
Mucosal inflammation			
subjects affected / exposed	23 / 179 (12.85%)	14 / 183 (7.65%)	
occurrences (all)	32	18	
Oedema peripheral			
subjects affected / exposed	9 / 179 (5.03%)	9 / 183 (4.92%)	
occurrences (all)	10	9	
Pain			
subjects affected / exposed	17 / 179 (9.50%)	16 / 183 (8.74%)	
occurrences (all)	20	17	
Pyrexia			
subjects affected / exposed	25 / 179 (13.97%)	30 / 183 (16.39%)	
occurrences (all)	36	43	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	14 / 179 (7.82%)	19 / 183 (10.38%)	
occurrences (all)	18	20	
Diarrhoea			
subjects affected / exposed	48 / 179 (26.82%)	72 / 183 (39.34%)	
occurrences (all)	78	129	
Vomiting			
subjects affected / exposed	19 / 179 (10.61%)	19 / 183 (10.38%)	
occurrences (all)	26	21	
Abdominal pain			
subjects affected / exposed	18 / 179 (10.06%)	16 / 183 (8.74%)	
occurrences (all)	20	17	
Nausea			
subjects affected / exposed	43 / 179 (24.02%)	29 / 183 (15.85%)	
occurrences (all)	74	41	
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	14 / 179 (7.82%)	10 / 183 (5.46%)	
occurrences (all)	18	18	
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	14 / 179 (7.82%) 22	15 / 183 (8.20%) 16	
Dyspnoea subjects affected / exposed occurrences (all)	13 / 179 (7.26%) 16	8 / 183 (4.37%) 9	
Skin and subcutaneous tissue disorders			
Pruritus subjects affected / exposed occurrences (all)	6 / 179 (3.35%) 6	19 / 183 (10.38%) 24	
Rash subjects affected / exposed occurrences (all)	16 / 179 (8.94%) 23	14 / 183 (7.65%) 18	
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	8 / 179 (4.47%) 10	11 / 183 (6.01%) 17	
Back pain subjects affected / exposed occurrences (all)	7 / 179 (3.91%) 7	13 / 183 (7.10%) 14	
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	23 / 179 (12.85%) 27	21 / 183 (11.48%) 23	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 December 2020	The request for a substantial amendment concerns the complete IMPD for the drug entrectinib. The drug supplier, ROCHE, has sent a new Cross Reference Letter indicating the study (Protocol GO40728 – EudraCT 2015-003385-84) to be referenced for this study (Protocol MAR-BAS-18-005 - EudraCT 2018-002190-21). ROCHE has stated that study Protocol GO40728 – EudraCT 2015-003385-84 has already been authorized by AIFA.
30 August 2022	1. Addition of 5 new IMPs (alpelisib, tepotinib, pralsetinib, talazoparib, selpercatinib) 2. Modification of inclusion criteria no. 5 and no. 8 and modification of exclusion criteria no. 3 3. Modification regarding the use of the drug entrectinib 4. Modification of the timing of sample collection for nanostring analysis and immuno-monitoring 5. Replacement of the centralised laboratory for tissue genomic evaluation 6. Addition of new centralised laboratory for immune-monitoring analysis 7. Additional supply for entrectinib and atezolizumab 8. Update to list of participating centres 9. Update of insurance certificate 10. New company name of the Depo-pack import site 11. Name change of production site: Clinigen Clinical Supplies Management GmbH 12. Update of PI Coordinator's affiliation
20 April 2023	The amendment concerns the availability in the study of an additional supply of the medicinal product ipilimumab, which will be available in 50 mg/10 ml vials in addition to that already present in the CTA (200 mg/40 ml).
14 February 2024	The amendment concerns the availability in the study of an additional supply of the medicine pemigatinib, which will be available in bottles of 14 tablets of 4.5 mg in addition to that already supplied by Incyte (60 tablets of 4.5 mg).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Difficulties due to COVID during the study.

Notes: