



Clinical trial results:

EORTC ILOC study: Phase II of immunotherapy plus local tumor ablation (RFA or stereotactic radiotherapy) in patients with colorectal cancer liver metastases

Summary

EudraCT number	2017-001375-22
Trial protocol	DE AT SE NL
Global end of trial date	22 February 2022

Results information

Result version number	v1 (current)
This version publication date	04 March 2023
First version publication date	04 March 2023

Trial information

Trial identification

Sponsor protocol code	1560-GITCG
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03101475
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	European Organisation for the Research and Treatment of Cancer (EORTC)
Sponsor organisation address	Avenue Emmanuel Mounier 83/11, Brussels, Belgium, 1200
Public contact	Clinical Operations Department/RAU, European Organisation for the Research and Treatment of Cancer (EORTC), +32 27741023, regulatory@eortc.org
Scientific contact	Clinical Operations Department/RAU, European Organisation for the Research and Treatment of Cancer (EORTC), +32 27741023, regulatory@eortc.org

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 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 February 2022
Global end of trial reached?	Yes
Global end of trial date	22 February 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this proof of concept study will be to investigate whether the combined use of local tumor ablation/radiation plus immunomodulating drugs may induce a significant immune response in patient with incurable liver metastases from colorectal cancer (CRC) (+/- limited extrahepatic disease) being stable or in partial response after a course of first- or second-line therapy.

The primary objective of the study is to show an overall response rate of lesions not treated by ablation/radiotherapy including the extrahepatic lesions (according to iRECIST criteria) higher than 10%. With the continuation of first line systemic treatment, no further responses are expected.

In order to be able to study the impact of the local technique on the final results (secondary objective), patients will be enrolled in two cohorts according whether they will be treated by RFA or with SBRT.

Protection of trial subjects:

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (available on the World Medical Association web site (<http://www.wma.net>)) and/or the laws and regulations of the country, whichever provides the greatest protection of the patient. The protocol has been written, and the study was conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP, available online at https://www.ema.europa.eu/documents/scientific-guideline/ich-e6-r1-guideline-good-clinical-practice_en.pdf). The protocol was approved by the competent ethics committee(s) as required by the applicable national legislation.

Background therapy:

This is a single-arm study testing an experimental treatment and without a control arm. Standard of care in this setting is systemic treatment with chemotherapy.

Evidence for comparator:

Patients with unresectable metastatic CRC show a median OS of 30 months when treated with different lines of systemic treatment. However, when stable disease is obtained during first line treatment the chances of response after prolonged treatment or second line treatment are low, 5% and 15% respectively. In the COIN study randomizing treatment interruption after 3 months fluoropyrimidine/oxaliplatin vs continuous treatment, the overall response in the continuation arm was 46%, and the overall response for intermittent therapy 49% indicating that longer treatment (as in the continuation arm) does not increase the response rate (Adam RA, Meade AM, Seymour MT et al. Intermittent versus continuous oxaliplatin and fluoropyrimidine combination chemotherapy for first-line treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. *Lancet Oncol.* 2011; 12:642-53). In the FIRE-3 trial comparing FOLFIRI/cetuximab vs FOLFIRI/bevacizumab, most tumor shrinkage occurred during the first 12 weeks, without a major further shrinkage after 12 weeks (Stintzing S, Modest DP, von Weikersthal LF, et al. Independent radiological evaluation of objective response, early tumour shrinkage, and depth of response in FIRE-3 (AIO KRK-0306) in the final RAS evaluable population (abstract LBA11). *Ann Oncol.* 2014;25).

Actual start date of recruitment	26 March 2019
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	Netherlands: 9
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Switzerland: 9
Worldwide total number of subjects	23
EEA total number of subjects	14

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
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)	17
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between 26/03/2019 and 01/03/2021, 23 patients with non-resectable liver predominant metastases from colorectal cancer and at least stable disease following 3-6 months first-line or second line chemotherapy were recruited in 4 countries (France, Netherlands, Sweden, Switzerland).

Pre-assignment

Screening details:

There is no pre-assignment period. After verification of eligibility criteria, patients were enrolled.

Period 1

Period 1 title	From registration (Overall Trial) (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	RFA with durvalumab and tremelimumab

Arm description:

RFA plus combined immunotherapy (tremelimumab and durvalumab) followed by maintenance therapy with durvalumab.

Arm type	Experimental
Investigational medicinal product name	Imfini
Investigational medicinal product code	L01XC28
Other name	Durvalumab
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

There should be a maximum 8 weeks between receipt of the last dose of anti-cancer therapy and the first dose of study drugs. RFA must be performed within 8 to 14 days after start of immunotherapy. Combination durvalumab and tremelimumab will be administered for 4 cycles maximum of 4 weeks each (combined immunotherapy tremelimumab 75 mg and durvalumab 1500 mg for 4 cycles). Thereafter the treatment will continue as maintenance therapy with durvalumab alone (durvalumab 1500 mg every 4 weeks up to week 48). Subjects who have a dose interruption of less than 30 days due to toxicity in the first 12 months of treatment may resume treatment and complete the 12-month treatment period. Treatment (durvalumab) should be administered for a maximum of 12 months (maximum of 13 doses, last infusion on week 48). Subjects who have a dose interruption of less than 30 days due to toxicity in the first 12 months of treatment may resume treatment and complete the 12-month treatment period.

Investigational medicinal product name	Imjudo
Investigational medicinal product code	L01FX20
Other name	Tremelimumab
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

There should be a maximum 8 weeks between receipt of the last dose of anti-cancer therapy and the first dose of study drugs. RFA must be performed within 8 to 14 days after start of immunotherapy. Combination durvalumab and tremelimumab will be administered for 4 cycles maximum of 4 weeks each (combined immunotherapy tremelimumab 75 mg and durvalumab 1500 mg for 4 cycles). Thereafter the treatment will continue as maintenance therapy with durvalumab alone (durvalumab 1500 mg every 4 weeks up to week 48). Subjects who have a dose interruption of less than 30 days due to toxicity in the first 12 months of treatment may resume treatment and complete the 12-month treatment period. Treatment (durvalumab) should be administered for a maximum of 12 months (maximum of 13 doses, last infusion on week 48). Subjects who have a dose interruption of less than 30 days due to toxicity in the first 12 months of treatment may resume treatment and complete the 12-month treatment period.

Arm title	SBRT with durvalumab and tremelimumab
Arm description: SBRT plus combined immunotherapy (tremelimumab and durvalumab) followed by maintenance therapy with durvalumab.	
Arm type	Experimental
Investigational medicinal product name	Imfini
Investigational medicinal product code	L01XC28
Other name	Durvalumab
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

There should be a maximum 8 weeks between receipt of the last dose of anti-cancer therapy and the first dose of study drugs. SBRT must start within 8 to 14 days after start of immunotherapy. SBRT to the PTV will be delivered in 3 fractions of 10 Gy over 1 week, preferably every other day, to a total of 30 Gy (BED10 60 Gy). Combination durvalumab and tremelimumab will be administered for 4 cycles maximum of 4 weeks each (combined immunotherapy tremelimumab 75 mg and durvalumab 1500 mg for 4 cycles). Thereafter the treatment will continue as maintenance therapy with durvalumab alone (durvalumab 1500 mg every 4 weeks up to week 48). Treatment (durvalumab) should be administered for a maximum of 12 months (maximum of 13 doses, last infusion on week 48). Subjects who have a dose interruption of less than 30 days due to toxicity in the first 12 months of treatment may resume treatment and complete the 12-month treatment period.

Investigational medicinal product name	Imjudo
Investigational medicinal product code	L01FX20
Other name	Tremelimumab
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

There should be a maximum 8 weeks between receipt of the last dose of anti-cancer therapy and the first dose of study drugs. SBRT must start within 8 to 14 days after start of immunotherapy. SBRT to the PTV will be delivered in 3 fractions of 10 Gy over 1 week, preferably every other day, to a total of 30 Gy (BED10 60 Gy). Combination durvalumab and tremelimumab will be administered for 4 cycles maximum of 4 weeks each (combined immunotherapy tremelimumab 75 mg and durvalumab 1500 mg for 4 cycles). Thereafter the treatment will continue as maintenance therapy with durvalumab alone (durvalumab 1500 mg every 4 weeks up to week 48). Treatment (durvalumab) should be administered for a maximum of 12 months (maximum of 13 doses, last infusion on week 48). Subjects who have a dose interruption of less than 30 days due to toxicity in the first 12 months of treatment may resume treatment and complete the 12-month treatment period.

Number of subjects in period 1	RFA with durvalumab and tremelimumab	SBRT with durvalumab and tremelimumab
Started	14	9
Completed	12	8
Not completed	2	1
Consent withdrawn by subject	2	-
Physician decision	-	1

Baseline characteristics

Reporting groups

Reporting group title	RFA with durvalumab and tremelimumab
Reporting group description: RFA plus combined immunotherapy (tremelimumab and durvalumab) followed by maintenance therapy with durvalumab.	
Reporting group title	SBRT with durvalumab and tremelimumab
Reporting group description: SBRT plus combined immunotherapy (tremelimumab and durvalumab) followed by maintenance therapy with durvalumab.	

Reporting group values	RFA with durvalumab and tremelimumab	SBRT with durvalumab and tremelimumab	Total
Number of subjects	14	9	23
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	10	7	17
From 65-84 years	4	2	6
85 years and over	0	0	0
Age continuous Units: years			
median	59.5	57.0	-
full range (min-max)	45.0 to 74.0	43.0 to 77.0	-
Gender categorical Units: Subjects			
Female	4	2	6
Male	10	7	17
WHO performance status Units: Subjects			
Normal Activity	11	6	17
Symptomatic and ambulatory	3	3	6
Site of primary tumor Units: Subjects			
Ascending colon	1	3	4
Transverse colon	1	0	1
Left flexure	0	1	1
Sigmoid colon	5	2	7
Right colon	1	0	1
Left colon	1	0	1
Rectosigmoid	1	0	1
Rectum	4	3	7

Clinical T stage			
Units: Subjects			
T2	1	0	1
T3	6	3	9
T4	3	2	5
Tx	1	3	4
Unknown	1	1	2
Missing	2	0	2
Clinical N stage			
Units: Subjects			
N0	1	0	1
N1	4	0	4
N2	2	6	8
Nx	5	1	6
Unknown	0	1	1
Missing	2	1	3
Clinical M stage			
Units: Subjects			
M1	12	8	20
Unknown	0	1	1
Missing	2	0	2
pT status			
Units: Subjects			
pT3a	1	0	1
pT3b	0	1	1
pT3	2	1	3
pT4a	1	1	2
pT4b	1	0	1
pTx	1	2	3
Unknown	3	1	4
Missing	5	3	8
pN status			
Units: Subjects			
pN1a	1	0	1
pN1b	1	0	1
pN2a	1	3	4
pNx	3	2	5
Missing	8	4	12
pM status			
Units: Subjects			
pM1a	3	0	3
pM1b	0	1	1
pM1c	1	0	1
pM1	2	1	3
pMx	0	2	2
Unknown	3	2	5
Missing	5	3	8
Any prior chemotherapy or other anticancer treatment			
Units: Subjects			
Yes	14	9	23
In which setting has this prior systemic			

treatment been administered Units: Subjects			
Neoadjuvant therapy for Primary CRC	1	0	1
First-line therapy	13	9	22
Has the patient progressed after this treatment Units: Subjects			
No	14	9	23
Patient's best response to this last prior systemic treatment Units: Subjects			
PR	9	7	16
SD	5	2	7
Did the patient undergo prior systemic surgery (primary or metastases) Units: Subjects			
No	12	7	19
Yes	2	2	4
Surgery performed to Units: Subjects			
Primary tumor	2	2	4
Not applicable	12	7	19
Any prior chemotherapy or other anticancer treatment Units: Subjects			
Yes	14	9	23
Was any prior anticancer radiotherapy administered Units: Subjects			
No	13	9	22
Yes	1	0	1
If yes, Site of prior anticancer radiotherapy Units: Subjects			
Other site: rectum	1	0	1
no prior anticancer radiotherapy	13	9	22
Any extra hepatic disease Units: Subjects			
No	4	5	9
Yes, limited (including up to 2 extra)	10	4	14
If any extra hepatic disease, dimension of the LARGEST extrahepatic lesion Units: Subjects			
less or equal to 5 cm	10	4	14
no extra hepatic disease	4	5	9
Liver metastases amenable to RFA or SBRT at completion of last prior systemic treatment Units: Subjects			
Yes	14	9	23
IF RFA: allowing a total ablated volume of at least 25cm ³ and a max advised volume of 120cm ³			

Units: Subjects			
Yes	14	0	14
no RFA	0	9	9
IF SBRT: allowing a total ablated vol. of at least 25cm ³ and max of 40cm ³ with max 2 lesions treated			
Units: Subjects			
Yes	0	9	9
no SBRT	14	0	14
Measurable disease according to RECIST v.1.1			
Units: Subjects			
Yes	14	9	23
Hilar liver lesions close to central bile ducts to be treated by RFA			
Units: Subjects			
No	14	9	23
At least two measurable liver lesions to REMAIN UNTREATED locally			
Units: Subjects			
Yes	14	9	23
Patient with liver metastases from CRC, curative treatment is not possibly resection and or RFA/SBRT			
Units: Subjects			
Yes	14	9	23
Time from baseline imaging to registration (days)			
Units: days			
median	17.5	17.0	
full range (min-max)	4.0 to 30.0	0.0 to 23.0	-
Time elapsed from last histological diagnosis of the primary tumor (CRC) to registration (weeks)			
Units: weeks			
median	24.1	31.9	
full range (min-max)	1.6 to 40.0	21.0 to 41.1	-
Time elapsed from first diagnosis of metastatic disease to registration (weeks)			
Units: weeks			
median	28.9	32.3	
full range (min-max)	21.6 to 40.0	23.1 to 40.9	-

End points

End points reporting groups

Reporting group title	RFA with durvalumab and tremelimumab
Reporting group description: RFA plus combined immunotherapy (tremelimumab and durvalumab) followed by maintenance therapy with durvalumab.	
Reporting group title	SBRT with durvalumab and tremelimumab
Reporting group description: SBRT plus combined immunotherapy (tremelimumab and durvalumab) followed by maintenance therapy with durvalumab.	
Subject analysis set title	Per protocol population
Subject analysis set type	Per protocol
Subject analysis set description: Per protocol population: All patients who are eligible, have at least started their immunotherapy treatment with tremelimumab and durvalumab, underwent local treatment with RFA or SBRT and have their imaging assessment at baseline and their first post-baseline assessment available.	

Primary: Best overall immune response rate of lesions not treated by ablation/radiotherapy including the extrahepatic lesions according to iRECIST (with response confirmation)

End point title	Best overall immune response rate of lesions not treated by ablation/radiotherapy including the extrahepatic lesions according to iRECIST (with response confirmation)
End point description: The primary endpoint iBOR (iCR+iPR), documented by iRECIST, is analyzed in the per protocol population as follow: the primary endpoint is binomial, i.e., each patient either has a response or not. The number of responding patients will be counted and decision rule will be applied according to a two-stage Simon design as described in statistical analysis.	
End point type	Primary
End point timeframe: The response evaluation is based on the whole period from the start of study treatment until confirmed progression according to iRECIST (iCPD) or the start of further anticancer treatment or 1 year maximum after start of study treatment.	

End point values	RFA with durvalumab and tremelimumab	SBRT with durvalumab and tremelimumab	Per protocol population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	12	8	20	
Units: Number of patients				
iCR+iPR	0	0	0	
iSD	5	4	9	
iCPD/iUPD	7	4	11	
Not evaluable	0	0	0	

Statistical analyses

Statistical analysis title	Primary analysis
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Statistical analysis description:

The reference probability p_0 was chosen at 10% in the statistical design because a response rate of 10% in the experimental arm will be judged too low to justify this combined approach. On the contrary, a response rate of 25% will be judged very promising. The null hypothesis that the true response rate is 10% ($H_0: p_0=10\%$) will be tested against the one-sided alternative that true response rate is 25% ($H_1: p_1=25\%$), using a one-sided type I error of 5%.

Comparison groups	RFA with durvalumab and tremelimumab v SBRT with durvalumab and tremelimumab
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other ^[1]
P-value	= 0.8784 ^[2]
Method	Exact binomial

Notes:

[1] - This study was designed as a single arm, pooling the two cohorts into one single arm. 21 patients should be accrued. If there are 2 or fewer responses, the study should be stopped. Otherwise, 45 additional patients should be accrued for a total of 66. The null hypothesis of a 10% response rate should be rejected if 11 or more responses are observed in 66 patients. After 20 patients in the protocol population and 23 enrolled, no response rate was seen and the recruitment was prematurely closed.

[2] - This is the exact one-sided p-value for the test to reject a 10% response rate in the per protocol population (20 patients).

Secondary: Progression free survival according to iRECIST

End point title	Progression free survival according to iRECIST
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End point description:

Progression free survival (iPFS) according to iRECIST is computed from the date of registration to the date of first progression according to the iRECIST criteria or death, whatever comes first. Patients alive and free of progression prior to the analysis cut-off date are censored at the date of the most recent assessment. The date used for calculation of iPFS is the first date that progression criteria are met (i.e. the date of iUPD) providing that iCPD is confirmed at the next assessment. If iUPD occurs, but is disregarded because of later iSD, iPR or iCR, that iUPD date is not used as the progression event date. In case the progression was not confirmed by imaging but there was lack of clinical benefit/clinical progression/start of new antitumoral treatment, it was considered as an event for iPFS and the date iUPD is used as the date of the event.

End point type	Secondary
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End point timeframe:

Tumor assessments should be performed every 8 weeks (± 1 week) until week 48 relative to the date the treatment started and then every 12 weeks (± 1 week) until confirmed progression according to iRECIST.

End point values	RFA with durvalumab and tremelimumab	SBRT with durvalumab and tremelimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	8		
Units: Months				
median (confidence interval 95%)				
Event(Progression or death)	2.2 (1.7 to 3.9)	2.8 (1.4 to 3.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival according to RECIST criteria (version 1.1)

End point title	Progression free survival according to RECIST criteria (version 1.1)
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End point description:

Progression Free Survival (PFS) according to RECIST is computed from the date of registration to the date of first progression according to the RECIST criteria (version 1.1) or death, whatever comes first. Patients alive and free of progression prior to the analysis cut-off date are censored at the date of the most recent assessment. The date used for calculation of progression free survival (PFS) according to RECIST is defined as the first day when the RECIST (version 1.1) criteria for PD are met.

End point type	Secondary
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End point timeframe:

Tumor assessments had been performed every 8 weeks (\pm 1 week) until week 48 relative to the date the treatment started and then every 12 weeks (\pm 1 week) until confirmed progression according to iRECIST.

End point values	RFA with durvalumab and tremelimumab	SBRT with durvalumab and tremelimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	8		
Units: Months				
median (confidence interval 95%)				
Event (progression or death)	2.2 (1.7 to 3.9)	2.8 (1.4 to 3.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival
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End point description:

Overall survival is computed from the date of registration to the date of death. Patients still alive at the analysis cut-off date are censored at the last date known to be alive.

End point type	Secondary
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End point timeframe:

After end of treatment, patients had been followed for survival every 2 months till month 12 after registration and then every 6 months till minimum month 30 after registration or death. The median follow-up duration is 17.1 months (95% CI:12.5-22.0).

End point values	RFA with durvalumab and tremelimumab	SBRT with durvalumab and tremelimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	8		
Units: Death				
Event (death)	7	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response (including extrahepatic lesions)

End point title	Best Overall Response (including extrahepatic lesions)
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End point description:

Best overall response rate according to RECIST v1.1 is computed as the rate of CR+PR in the per protocol population.

End point type	Secondary
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End point timeframe:

All patients have their BEST OVERALL RESPONSE (BOR) according to RECIST 1.1 from the start of study treatment until progression or the start of further anticancer therapy or maximum 1 year after the start of study treatment whatever comes first.

End point values	RFA with durvalumab and tremelimumab	SBRT with durvalumab and tremelimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	8		
Units: Number of patients				
CR+PR	0	0		
Stable disease (SD)	5	4		
Progressive disease (PD)	7	4		
Not evaluable	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were collected at baseline, during treatment and until 90 days post last dose of immunotherapy. All AEs had to be followed until resolution or stabilization. SAEs/AESIs related to study treatment had to be reported until month 30 minimum or death.

Adverse event reporting additional description:

CRF for AEs contains pre-specified items + additional boxes for all "other" AEs.

AEs are evaluated using CTC grading, SAEs using MedDra. Non-SAEs have not been collected specifically, all AEs will be reported in non-SAE section.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	SBRT(stereotactic radiotherapy)
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Reporting group description: -

Reporting group title	RFA(radiofrequency ablation)
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Reporting group description: -

Serious adverse events	SBRT(stereotactic radiotherapy)	RFA(radiofrequency ablation)	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 8 (12.50%)	2 / 13 (15.38%)	
number of deaths (all causes)	4	7	
number of deaths resulting from adverse events	0	0	
Hepatobiliary disorders			
HEPATITIS			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 8 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
IMMUNE-MEDIATED LUNG DISEASE			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 8 (12.50%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

URINARY TRACT INFECTION			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 8 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	SBRT(stereotactic radiotherapy)	RFA(radiofrequency ablation)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)	9 / 13 (69.23%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
OVARIAN CYST			
alternative dictionary used: CTCAE 3.5			
subjects affected / exposed	1 / 8 (12.50%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
FLUSHING			
alternative dictionary used: CTCAE 3.5			
subjects affected / exposed	0 / 8 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
FATIGUE			
alternative dictionary used: CTCAE 3.5			
subjects affected / exposed	2 / 8 (25.00%)	4 / 13 (30.77%)	
occurrences (all)	2	6	
INFUSION RELATED REACTION			
alternative dictionary used: CTCAE 3.5			
subjects affected / exposed	0 / 8 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
FEVER			
alternative dictionary used: CTCAE 3.5			
subjects affected / exposed	2 / 8 (25.00%)	3 / 13 (23.08%)	
occurrences (all)	2	4	
PAIN			

alternative dictionary used: CTCAE 3.5 subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 13 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders PNEUMONITIS alternative dictionary used: CTCAE 3.5 subjects affected / exposed occurrences (all) DYSYPNEA alternative dictionary used: CTCAE 3.5 subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1 1 / 8 (12.50%) 1	0 / 13 (0.00%) 0 0 / 13 (0.00%) 0	
Psychiatric disorders DEPRESSION alternative dictionary used: CTCAE 3.5 subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 13 (0.00%) 0	
Investigations ALANINE AMINOTRANSFERASE INCREASED alternative dictionary used: CTCAE 3.5 subjects affected / exposed occurrences (all) GGT INCREASED alternative dictionary used: CTCAE 3.5 subjects affected / exposed occurrences (all) BLOOD BILIRUBIN INCREASED alternative dictionary used: CTCAE 3.5 subjects affected / exposed occurrences (all) ASPARTATE AMINOTRANSFERASE INCREASED alternative dictionary used: CTCAE 3.5 subjects affected / exposed occurrences (all)	3 / 8 (37.50%) 4 3 / 8 (37.50%) 5 0 / 8 (0.00%) 0 2 / 8 (25.00%) 3	1 / 13 (7.69%) 1 4 / 13 (30.77%) 6 2 / 13 (15.38%) 2 4 / 13 (30.77%) 7	

ALKALINE PHOSPHATASE INCREASED			
alternative dictionary used: CTCAE 3.5			
subjects affected / exposed	2 / 8 (25.00%)	4 / 13 (30.77%)	
occurrences (all)	3	6	
LIPASE INCREASED			
alternative dictionary used: CTCAE 3.5			
subjects affected / exposed	1 / 8 (12.50%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
SERUM AMYLASE INCREASED			
alternative dictionary used: CTCAE 3.5			
subjects affected / exposed	0 / 8 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	2	
PLATELET COUNT DECREASED			
alternative dictionary used: CTCAE 3.5			
subjects affected / exposed	2 / 8 (25.00%)	1 / 13 (7.69%)	
occurrences (all)	2	1	
NEUTROPHIL COUNT DECREASED			
alternative dictionary used: CTCAE 3.5			
subjects affected / exposed	1 / 8 (12.50%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
LYMPHOCYTE COUNT DECREASED			
alternative dictionary used: CTCAE 3.5			
subjects affected / exposed	1 / 8 (12.50%)	1 / 13 (7.69%)	
occurrences (all)	2	1	
WEIGHT LOSS			
alternative dictionary used: CTCAE 3.5			
subjects affected / exposed	2 / 8 (25.00%)	2 / 13 (15.38%)	
occurrences (all)	2	2	
WHITE BLOOD CELL DECREASED			
alternative dictionary used: CTCAE 3.5			
subjects affected / exposed	0 / 8 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			

PROLAPSE OF INTESTINAL STOMA alternative dictionary used: CTCAE 3.5 subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 13 (0.00%) 0	
Nervous system disorders PERIPHERAL SENSORY NEUROPATHY alternative dictionary used: CTCAE 3.5 subjects affected / exposed occurrences (all) PARESTHESIA alternative dictionary used: CTCAE 3.5 subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0 1 / 8 (12.50%) 1	1 / 13 (7.69%) 1 0 / 13 (0.00%) 0	
Blood and lymphatic system disorders ANEMIA alternative dictionary used: CTCAE 3.5 subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	2 / 13 (15.38%) 2	
Gastrointestinal disorders COLITIS alternative dictionary used: CTCAE 3.5 subjects affected / exposed occurrences (all) CONSTIPATION alternative dictionary used: CTCAE 3.5 subjects affected / exposed occurrences (all) ABDOMINAL PAIN alternative dictionary used: CTCAE 3.5 subjects affected / exposed occurrences (all) DIARRHEA alternative dictionary used: CTCAE 3.5 subjects affected / exposed occurrences (all) MUCOSITIS ORAL	0 / 8 (0.00%) 0 0 / 8 (0.00%) 0 1 / 8 (12.50%) 1 1 / 8 (12.50%) 1	1 / 13 (7.69%) 1 3 / 13 (23.08%) 3 1 / 13 (7.69%) 2 3 / 13 (23.08%) 3	

<p>alternative dictionary used: CTCAE 3.5</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 8 (0.00%)</p> <p>0</p>	<p>1 / 13 (7.69%)</p> <p>3</p>	
<p>RECTAL HEMORRHAGE</p> <p>alternative dictionary used: CTCAE 3.5</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 8 (0.00%)</p> <p>0</p>	<p>1 / 13 (7.69%)</p> <p>1</p>	
<p>PROCTITIS</p> <p>alternative dictionary used: CTCAE 3.5</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 8 (25.00%)</p> <p>2</p>	<p>0 / 13 (0.00%)</p> <p>0</p>	
<p>Hepatobiliary disorders</p> <p>HEPATITIS VIRAL</p> <p>alternative dictionary used: CTCAE 3.5</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 8 (0.00%)</p> <p>0</p>	<p>1 / 13 (7.69%)</p> <p>1</p>	
<p>Skin and subcutaneous tissue disorders</p> <p>RASH MACULO-PAPULAR</p> <p>alternative dictionary used: CTCAE 3.5</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 8 (12.50%)</p> <p>1</p>	<p>0 / 13 (0.00%)</p> <p>0</p>	
<p>Renal and urinary disorders</p> <p>PROTEINURIA</p> <p>alternative dictionary used: CTCAE 3.5</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 8 (0.00%)</p> <p>0</p>	<p>1 / 13 (7.69%)</p> <p>1</p>	
<p>Musculoskeletal and connective tissue disorders</p> <p>ARTHRALGIA</p> <p>alternative dictionary used: CTCAE 3.5</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>ARTHRITIS</p> <p>alternative dictionary used: CTCAE 3.5</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 8 (0.00%)</p> <p>0</p> <p>1 / 8 (12.50%)</p> <p>2</p>	<p>1 / 13 (7.69%)</p> <p>1</p> <p>0 / 13 (0.00%)</p> <p>0</p>	

PAIN IN EXTREMITY alternative dictionary used: CTCAE 3.5 subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	3 / 13 (23.08%) 3	
Infections and infestations MUCOSAL INFECTION alternative dictionary used: CTCAE 3.5 subjects affected / exposed occurrences (all) URINARY TRACT INFECTION alternative dictionary used: CTCAE 3.5 subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0 1 / 8 (12.50%) 1	1 / 13 (7.69%) 1 2 / 13 (15.38%) 2	
Metabolism and nutrition disorders ANOREXIA alternative dictionary used: CTCAE 3.5 subjects affected / exposed occurrences (all) HYPOALBUMINEMIA alternative dictionary used: CTCAE 3.5 subjects affected / exposed occurrences (all) HYPOKALEMIA alternative dictionary used: CTCAE 3.5 subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0	0 / 13 (0.00%) 0 2 / 13 (15.38%) 2 1 / 13 (7.69%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 August 2017	<p>Global Amendment number 1:</p> <p>Modifications to the current protocol from version 1.0 dated on 09JUNE2017 to version 1.1 09AUG2017.</p> <p>Description of the amendment: Further to recommendation of Investigator's brochure (IB), the follow up for adverse events after treatment discontinuation has been prolonged to 120 or 180 days depending on treatment received by the patient at the time of discontinuation.</p> <p>This is an administrative amendment.</p>
08 December 2017	<p>Global Amendment number 2:</p> <p>Modifications to the current protocol from version 1.1 dated on 09AUG2017 to version 2.0 dated on 08DEC2017.</p> <p>Description of the amendment: Safety information and language related to durvalumab and tremelimumab have been updated in the protocol and PIS/IC following the release of a new edition of the IBs (Durvalumab Edition 12, 03 November 2017, Tremelimumab Edition 8, 02 November 2017).</p> <p>This is a scientific amendment.</p>
01 June 2018	<p>Global Amendment number 3:</p> <p>Modifications to the current protocol from version 2.0 dated on 08DEC2017 to version 3.0 dated on 01JUN2018.</p> <p>Description of the amendment: The protocol and PIS/IC have been amended to take into account request from competent authorities to:</p> <ul style="list-style-type: none">-in the exclusion criteria section: more examples of autoimmune or inflammatory disorders excluded are listed-refer to the CTFG guidelines for the contraception methods and pregnancy testing, added as appendix J,-increase the frequency of the thyroid function testing i.e. every cycle instead of every 2 cycles (q4 weeks)-clarification on the period of collection and reporting of AEs-correction in appendix H on toxicity management guidelines for durvalumab and tremelimumab and addition of precise guidance in case Stevens-Johnson syndrome or toxic epidermal necrolysis is observed. <p>This is a scientific amendment.</p>
30 March 2020	<p>Global Amendment number 4:</p> <p>Modifications to the current protocol from version 3.0 dated on 01JUN2018 to version 4.0 dated on 30MAR2020.</p> <p>Description of the amendment:</p> <ul style="list-style-type: none">-Second line treatment was allowed-To relax eligibility criteria by allowing pts treated with more than one line-To clarify that the assumption on no further improvement does not change-To relax eligibility criteria by allowing patients treated with more than one line and to allow more time between end of previous treatment and start of new treatment-Change of time point to allow a broader time window between baseline scan and start of treatment. <p>This is a scientific amendment.</p>

23 April 2020	<p>Global Amendment number 5:</p> <p>Modifications to the current protocol from version 4.0 dated on 30MAR2020 to version 5.0 dated on 23APR2020.</p> <p>Description of the amendment:</p> <ul style="list-style-type: none"> -Data for tremelimumab in combination with durvalumab are presented in the IB for durvalumab -For information regarding the combination of durvalumab and tremelimumab, the reader is referred to reference safety information in the current durvalumab IB". <p>Given that in this study we never administer tremelimumab in monotherapy, the RSI table related to treme monotherapy was not needed for reporting and we did not refer to it in the next reporting period.</p> <p>This is a scientific amendment.</p>
10 December 2020	<p>Global Amendment number 6:</p> <p>Modifications to the current protocol from version 5.0 dated on 23APR2020 to version 6.0 dated on 10DEC2020.</p> <p>Description of the amendment:</p> <ul style="list-style-type: none"> -Clarification -eligibility criterion was modified in previous amendment but this part had not been changed and was inconsistent with the rest -To link the screening tests to registration and not to start of treatment -Clarification about timing of pregnancy test -Updated toxicity management guidelines according to new version released by AZ on 14 October 2020 <p>This is a scientific amendment.</p>

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.

None reported

Notes: