Clinical trial results:
A Phase II Trial Testing Durvalumab Combined With Endocrine Therapy in Patients With ER+/Her2- Breast Cancer Eligible for Neoadjuvant Endocrine Therapy And Who Present CD8+ T Cell Infiltration After 4-6 Weeks Exposure to Immune-Attractant.

Summary

EudraCT number	2016-000764-42
Trial protocol	FR ES
Global end of trial date	28 July 2020

Results information

Result version number	v1 (current)
This version publication date	01 March 2022
First version publication date	01 March 2022

Trial information

Trial identification

Sponsor protocol code	UC-0140/1606

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02997995
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UNICANCER
Sponsor organisation address	101 rue de Tolbiac, Paris, France, 75013
Public contact	Nourredine AIT-RAHMOUNE, UNICANCER, 33 171936704, n.ait-rahmoune@unicancer.fr
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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	21 January 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of durvalumab combined with exemestane in patients with CD8+ T cells on pathological response at surgery after a lymphocyte attraction phase.

Protection of trial subjects:

In order to ensure the protection of the rights, safety and well-being of trial subjects, this clinical trial was conducted in accordance with the Declaration of Helsinki (1964) and subsequent amendments, ICH Good Clinical Practice Guidelines (CPMP/ICH/135/95), the European Directive (2001/20/CE) and the applicable local regulatory requirements and laws.
Furthermore, independent Ethics Committees in France, Sweden and Belgium reviewed and gave a favorable opinion to the study documents, including the initial protocol and all subsequent amendments, and all information and documents provided to subjects/patients.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 March 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	France: 52
Worldwide total number of subjects	61
EEA total number of subjects	61

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)	31
From 65 to 84 years	30
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Multicentric, open-label phase II trial testing an aromatase inhibitor in combination with durvalumab in ≥18 years old men or post-menopausal women eligible to neoadjuvant endocrine therapy for T2-4 ER+/HER2- breast cancer with CD8+T cell infiltration (>10% CD8+T cells in the tumour). patient recruitment: 02-Mar-2017 to 10-Apr-2020.

Pre-assignment

Screening details:

The study consisted of a screening phase of up to 30 days before treatment initiation to establish eligibility and document baseline measurements, a part 1 treatment phase (6-week), a part 2 treatment phase (28-day cycle; 6 months), a surgery and a long-term follow-up to monitor pathological complete response, CD8 infiltration, Ki67, and safety.

Pre-assignment period milestones

Number of subjects started	61
Intermediate milestone: Number of subjects	Part 1: Chemo-attractant: 61
Number of subjects completed	24

Pre-assignment subject non-completion reasons

Reason: Number of subjects	CD8+T cells infiltration lower than 10%: 31
Reason: Number of subjects	Adverse event, non-fatal: 3
Reason: Number of subjects	Protocol deviation: 3

Period 1

Period 1 title	Part 2 : Immunotherapy (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Tremelimumab

Arm description:

Part 1 used an open label, adaptive trial design of testing 4 to 6 weeks treatment with the immune attractants Tremelimumab plus Exemestane to increase CD8+T cell infiltration in the tumor site. Patients with >10% CD8+T cells in the tumor biopsy (3 weeks after Tremelimumab initiation) moved to the part 2 (core of the trial) of the study These patients received 6 months Exemestane plus Durvalumab before undergoing surgery.

Arm type	Experimental
Investigational medicinal product name	Durvalumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Durvalumab was administered, concomitant to Exemestane, as an IV infusion over approximately 60 minutes (±5 minutes) every 4 weeks.

Investigational medicinal product name	Tremelimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion

Routes of administration	Intravenous use

Dosage and administration details:

Tremelimumab was administered, concomitant to Exemestane (Section 9.4.1.2.1), as single IV infusion over approximately 60 minutes (±5 minutes).

Investigational medicinal product name	Exemestane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Exemestane was prescribed in the therapeutic indication of neoadjuvant therapy for hormone receptor positive disease in postmenopausal women. Thus, the posology was 25 mg/day per os (p.o.: oral) until the day prior surgery.

Number of subjects in period 1[1]	Tremelimumab
Started	24
Completed	20
Not completed	4
Adverse event, non-fatal	4

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Patients must have >10% CD8+T cell infiltration in the tumor site after Tremelimumab treatment (Part 1). 37 out of 61 patients treated with Tremelimumab were not included in part 2 of the study due to a CD8+T cells infiltration lower than 10% (n=31), adverse events (n=3), and non-compliance to treatment (n=3). Thus, only 24 patients were included in part 2. The Baseline period reported here correspond to the part 2.

Baseline characteristics

Reporting groups	
Reporting group title	Part 2 : Immunotherapy

Reporting group description: -

Reporting group values	Part 2 : Immunotherapy	Total	
Number of subjects	24	24	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	14	14	
From 65-84 years	10	10	
85 years and over	0	0	
Age continuous Units: years			
median	66		
inter-quartile range (Q1-Q3)	61 to 71	-	
Gender categorical Units: Subjects			
Female	24	24	
Male	0	0	
Tumor localization Units: Subjects			
Right Breast	10	10	
Left Breat	14	14	
Histological type Units: Subjects			
Lobular	7	7	
Invasive	11	11	
Canalar	3	3	
Mucinous	1	1	
Other	2	2	
Estrogen Allred score Units: Arbitrary			
median	8		
inter-quartile range (Q1-Q3)	8 to 8	-	
Progesterone Allred score Units: Arbitrary			
median	8		
inter-quartile range (Q1-Q3)	5 to 8	-	

End points

End points reporting groups

Reporting group title	Tremelimumab

Reporting group description:

Part 1 used an open label, adaptive trial design of testing 4 to 6 weeks treatment with the immune attractants Tremelimumab plus Exemestane to increase CD8+T cell infiltration in the tumor site. Patients with >10% CD8+T cells in the tumor biopsy (3 weeks after Tremelimumab initiation) moved to the part 2 (core of the trial) of the study These patients received 6 months Exemestane plus Durvalumab before undergoing surgery.

Primary: pathological Complete Response

End point title	pathological Complete Response[1]

End point description:

End point type	Primary

End point timeframe:

At surgery (7.5 months after inclusion)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The Simon’s optimal two-stage design was used for the part 2 of this study. In the first stage, if 2 or more pathological complete responses (pCR) were observed in 23 patients, the part 2 could move to stage 2, otherwise the study had to be stopped . Only 1 patient had pCR, thus the futility criterion was met and the study was stopped.

End point values	Tremelimumab			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: subject				
Yes	1			
No	21			
Missing	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in CD8+ T-cells infiltration over time

End point title	Changes in CD8+ T-cells infiltration over time

End point description:

End point type	Secondary

End point timeframe:

3 weeks from Tremelimumab treatment initiation

End point values	Tremelimumab			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: percent				
arithmetic mean (confidence interval 95%)	10.8 (6.8 to 14.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Changes un Ki67 expression over time

End point title	Changes un Ki67 expression over time

End point description:

End point type	Secondary

End point timeframe:

3 weeks from Tremelimumab treatment initiation

End point values	Tremelimumab			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: percent				
arithmetic mean (confidence interval 95%)	-6.0 (-8.8 to -3.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Measurements of Tumour Infiltrating Lymphocytes (TILs)

End point title	Measurements of Tumour Infiltrating Lymphocytes (TILs)

End point description:

End point type	Secondary

End point timeframe:

3 weeks from Tremelimumab treatment initiation

End point values	Tremelimumab			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: percent				
arithmetic mean (confidence interval 95%)	4.7 (0.7 to 8.6)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
24 months from inclusion	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	Tremelimumab

Reporting group description:

Part 1 used an open label, adaptive trial design of testing 4 to 6 weeks treatment with the immune attractants Tremelimumab plus Exemestane to increase CD8+T cell infiltration in the tumor site. Patients with >10% CD8+T cells in the tumor biopsy (3 weeks after Tremelimumab initiation) moved to the part 2 (core of the trial) of the study These patients received 6 months Exemestane plus Durvalumab before undergoing surgery.

Serious adverse events	Tremelimumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 24 (16.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Myocarditis			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic cytolysis			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Tremelimumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 24 (100.00%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	12 / 24 (50.00%)		
occurrences (all)	12		
Aspartate aminotransferase increased			
subjects affected / exposed	10 / 24 (41.67%)		
occurrences (all)	10		
Gamma-glutamyltransferase increased			
subjects affected / exposed	7 / 24 (29.17%)		
occurrences (all)	7		

Lactate dehydrogenase urine increased			
subjects affected / exposed	5 / 24 (20.83%)		
occurrences (all)	5		
alkaline phosphatase increased			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Potassium increased			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Serum amylase increased			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	4		
Serum lipase increased			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Thyroid-stimulating hormone decreased			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Thyroid-stimulating hormone increased			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	3		
Urea urine increased			
subjects affected / exposed	5 / 24 (20.83%)		
occurrences (all)	5		
Vascular disorders			
Hot flashes			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	3		
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
General disorders and administration site conditions			

Asthenia subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all)	3 / 24 (12.50%) 3 10 / 24 (41.67%) 10		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	 3 / 24 (12.50%) 3 23 / 24 (95.83%) 23 3 / 24 (12.50%) 3		
Skin and subcutaneous tissue disorders Psoriasis subjects affected / exposed occurrences (all)	 3 / 24 (12.50%) 3		
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	 6 / 24 (25.00%) 6		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	 4 / 24 (16.67%) 4		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	 2 / 24 (8.33%) 2		
Metabolism and nutrition disorders Hypercalcaemia subjects affected / exposed occurrences (all) Hyperglycaemia	 2 / 24 (8.33%) 2		

subjects affected / exposed	6 / 24 (25.00%)		
occurrences (all)	6		
Hypokalaemia			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	4		
Hypomagnesaemia			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 January 2018	A non-inclusion criterion has been added to exclude patients with previous malignancy within 5 years before inclusion in the study. Indeed, 5 years without recurrence is generally accepted as the minimum time to declare a person in remission. Basal cell carcinoma, squamous cell carcinoma of the skin and cervical carcinoma in situ, for which the cure rates are 100%, are not concerned by this measure.
14 May 2019	* An inclusion criterion has been reworded to make it clear that men can participate in this study. * To clarify the conditions for patient transition between the part 1 to part 2 of the study, the 3 inclusion criteria and 2 exclusion criteria related to patient safety which are to be reevaluated before inclusion in part 2 were specified in the study protocol. * A non-inclusion criterion was modified to exclude from Part 2 any patient who has experienced an adverse event of an immunological nature in Part 1. * Modification of the interim safety analysis section following the IDMC decision. The new version indicated that the inclusion of patients in the study was stopped on February 26th 2018 for the purpose of this analysis. On April 30th 2018, the IDMC decided that, according to the rules of the interim safety analysis, the study should continue.
02 July 2019	The inclusion criteria related to patient contraception has been modified in order to clarify the condition of contraception in men participating in the study
22 June 2020	The planned interim efficacy analysis was performed on 22 out of 24 patients included in the part 2 of the study. Results demonstrated that the study did not reach its primary objective thus, as planned in the protocol, the inclusion of new patients were definitively stopped

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.

Only 1 out of 4 cohorts of patients was tested in part 1 (immune attractant) of the study.

Concerning adverse events the "Occurrences all number" was not reported, thus, the number of patients is noted in this field.

Notes: