Clinical trial results:
A single arm Phase I-II multicenter trial with avelumab plus autologous dendritic cell vaccine in pre-treated mismatch repair-proficient (MSS) metastatic colorectal cancer patients.

Summary

EudraCT number	2016-003838-24
Trial protocol	ES
Global end of trial date	15 September 2020

Results information

Result version number	v1 (current)
This version publication date	10 March 2023
First version publication date	10 March 2023
Summary attachment (see zip file)	ICH3 CSR AVEVAC (AVEVAC_Clinical_Study_Report_rev_clean.pdf)

Trial information

Trial identification

Sponsor protocol code	GEMCAD-1602

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03152565
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GEMCAD
Sponsor organisation address	C/ Balmes 243 5º 1º, Barcelona, Spain, 08006
Public contact	Pau Doñate, MFAR Clinical Research, investigacion@mfar.net
Scientific contact	Pau Doñate, MFAR Clinical Research, investigacion@mfar.net

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	26 January 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 September 2020
Global end of trial reached?	Yes
Global end of trial date	15 September 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Phase I: To determine the recommended phase II dose (RP2D) of avelumab in combination with ADC vaccine in previously treated MSS CRC patients who have progressed at least to 2 chemotherapy lines. Phase II: To increase the percentage (from 20% to 40%) of pre-treated MSS mCRC patients free of progression at 6 months.

Protection of trial subjects:

The protocol and the patient information sheet as weel as the informed consent contain all measures needed to reduce and mitigate risks for trial subjects

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 March 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 19
Worldwide total number of subjects	19
EEA total number of subjects	19

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)	10
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

28 patients were screened

Pre-assignment period milestones

Number of subjects started	28[1]
Number of subjects completed	19

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Not elegible patient: 8
Reason: Number of subjects	Apheresis not feasible: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 28 patients were screened in the pre-assignment period. Only 19 comply eligibility and were enrolled in the study and allocated to receive the study treatment

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Avelumab plus dendritic cell vaccine

Arm description:

Avelumab biweekly intravenous during a maximum of 12 months and biweekly 10x106 ADC vaccine (intradermal) for five doses (days 1, 14, 28, 42 and 56) followed by a maximum of 6 doses every 6 months.

Arm type	Experimental
Investigational medicinal product name	Avelumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Avelumab will be administered intravenously at a dose of 10 mg per kilogram of body weight, every 14 days until disease progression or unacceptable toxicity.

Investigational medicinal product name	Dendritic cell vaccine (autologous)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

10x106 ADC vaccine (intradermal) for five doses (days 1, 14, 28, 42 and 56) followed by a maximum of 6 doses every 6 months

Number of subjects in period 1	Avelumab plus dendritic cell vaccine
Started	19
Completed	19

Baseline characteristics

Reporting groups

Reporting group title	Overall study

Reporting group description: -

Reporting group values	Overall study	Total	
Number of subjects	19	19	
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)	10	10	
From 65-84 years	9	9	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	9	9	
Male	10	10	
IMMETCOLS			
Number of patients that consume competitively inhibitors of HMG-CoA reductase, an enzyme that limits the rate of cholesterol biosynthesis, and inhibits cholesterol synthesis in the liver.			
Units: Subjects			
Yes	5	5	
No	10	10	
Not evaluable	4	4	
GEP			
Number of patients with expression of Granulin epithelin precursor (GEP), which is reported to function as a growth factor stimulating proliferation and migration, and conferring chemoresistance in many cancer types.			
Units: Subjects			
Yes	5	5	
No	10	10	
Not evaluable	4	4	
LDH			
Measure Description: Number of patients with lactate dehydrogenase (LDH) blood levels in the normal (<234) or higher (>234) range.			
Units: Subjects			
Values < 234	11	11	
Values > 234	8	8	
Local diagnosis			
Number of patients stratified according to the local region of the primary tumor			
Units: Subjects			
Rectum	6	6	

Sigma	13	13	
Local tumor surgery			
Number of patients that had their primary tumor surgically removed			
Units: Subjects			
Yes	13	13	
No	6	6	
Previous treatment lines			
Number of patients classified by the number of previous treatment lines they had received atinclusion. The patients were clustered in 1-2 previous lines or more than 2 previous lines			
Units: Subjects			
Previous lines ≤2	3	3	
Previous lines >2	16	16	
Genotype			
Number of patients with mutations in typical candidate genes for colorectal cancer			
Units: Subjects			
All native	5	5	
KRAS mutant	13	13	
BRAF mutant	1	1	
ECOG			
Number of patients stratified by their East Cooperative Oncology Group (EGOG) performance status (PS). The ECOG PS measures the performance and independence of patients to develop activities of daily living. The score ranges from 0 (fully functional) to 5 (exitus)			
Units: Subjects			
Score 0	13	13	
Score 1	6	6	
Number of affected organs Units: Subjects			
1 organ	4	4	
>1 organ	15	15	
Neo/adjuvant chemotherapy			
Number of patients thar received a neo/adjuvant chemotherapy regimen			
Units: Subjects			
Yes	2	2	
No	17	17	
Tumor stage at diagnosis			
Tumor stage measures the level of spread of cancer. Stage 0: This is called cancer in situ. Stage I: The cancer has grown through the mucosa and has invaded the muscular layer of the colon or rectum. Stage II: The cancer has grown through the wall of the colon or rectum but has not spread to nearby tissue or to the nearby lymph nodes. Stage III: The cancer has grown through the inner lining or into the muscle layers of the intestine. It has spread. Stage IV: The cancer has spread to distant part of the body.			
Units: Subjects			
Stage II	1	1	
Stage III	2	2	
Stage IV	16	16	

End points

End points reporting groups

Reporting group title	Avelumab plus dendritic cell vaccine

Reporting group description:

Avelumab biweekly intravenous during a maximum of 12 months and biweekly 10x106 ADC vaccine (intradermal) for five doses (days 1, 14, 28, 42 and 56) followed by a maximum of 6 doses every 6 months.

Primary: Dose of Avelumab in Combination With Autologous Dendritic Cells

End point title	Dose of Avelumab in Combination With Autologous Dendritic Cells[1]

End point description:

End point type	Primary

End point timeframe:

18 months

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: This is a phase I/II trial with a single arm, non randomized, open-label design. There were no control or comparison arms contemplated by the study design. Thus, statistical comparisons are not applicable

End point values	Avelumab plus dendritic cell vaccine			
Subject group type	Reporting group			
Number of subjects analysed	6[2]			
Units: miligram / kilogram				
number (not applicable)	10			

Notes:

[2] - Only those patients in the dose escalation phase

Statistical analyses

No statistical analyses for this end point

Primary: Progression free survival (PFS) rate

End point title	Progression free survival (PFS) rate[3]

End point description:

Percentage of patients without progression of disease at 6 months

End point type	Primary

End point timeframe:

6 months

Notes:

[3] - 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: This is a phase I/II trial with a single arm, non randomized, open-label design. There were no control or comparison arms contemplated by the study design. Thus, statistical comparisons are not applicable

End point values	Avelumab plus dendritic cell vaccine			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Patients				
Progression-free patients	0			
Progression	19			

Statistical analyses

No statistical analyses for this end point

Primary: Progression free survival

End point title	Progression free survival[4]

End point description:

Estimation by kaplan meier of the median PFS. The PFS is defined as time from treatment start until radiological progression disease according to RECIST criteria

End point type	Primary

End point timeframe:

Throughout the study period, average 12 months

Notes:

[4] - 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: This is a phase I/II trial with a single arm, non randomized, open-label design. There were no control or comparison arms contemplated by the study design. Thus, statistical comparisons are not applicable

End point values	Avelumab plus dendritic cell vaccine			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Months				
median (full range (min-max))	3.1 (2.1 to 5.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: KRAS mutational status

End point title	KRAS mutational status

End point description:

KRAS mutation status at baseline and during treatment.

End point type	Secondary

End point timeframe:

18 months

End point values	Avelumab plus dendritic cell vaccine			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Patients				
Native	6			
Mutant	13			
Not evaluable	0			

Statistical analyses

No statistical analyses for this end point

Secondary: NRAS mutational status

End point title	NRAS mutational status

End point description:

NRAS mutation status at baseline and during treatment.

End point type	Secondary

End point timeframe:

18 months

End point values	Avelumab plus dendritic cell vaccine			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Patients				
Native	17			
Mutated	0			
Not evaluable	2			

Statistical analyses

No statistical analyses for this end point

Secondary: BRAF mutational status

End point title	BRAF mutational status

End point description:

BRAF mutation status at baseline and during treatment.

End point type	Secondary

End point timeframe:

18 months

End point values	Avelumab plus dendritic cell vaccine			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Patients				
Native	16			
Mutated	1			
Not evaluable	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Median value of overall survival estimated by kaplan meier. Defined as time from treatment start to death from any cause

End point type	Secondary

End point timeframe:

Throughout the study period, average 12 months

End point values	Avelumab plus dendritic cell vaccine			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Months				
median (full range (min-max))	12.1 (3.2 to 22.9)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Throughout the study period, up to 24 months	
Assessment type	Systematic

Dictionary used	
Dictionary name	NCI CTCAE
Dictionary version	4.0

Reporting groups	
Reporting group title	Avelumab plus dendritic cell vaccine

Reporting group description:

Avelumab biweekly intravenous during a maximum of 12 months and biweekly 10x106 ADC vaccine (intradermal) for five doses (days 1, 14, 28, 42 and 56) followed by a maximum of 6 doses every 6 months.

Serious adverse events	Avelumab plus dendritic cell vaccine		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 19 (42.11%)		
number of deaths (all causes)	18		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
Clinical deterioration			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Fever			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute injury			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Muscle weakness left-sided			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Port-a-cath infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Avelumab plus dendritic cell vaccine		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 19 (100.00%)		
General disorders and administration site conditions			
Cough			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	11 / 19 (57.89%)		
occurrences (all)	11		
Fever			
subjects affected / exposed	5 / 19 (26.32%)		
occurrences (all)	5		
Infected cyst			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Chills			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Night sweats			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Pelvic pain			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Perineal pain			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
chest wall pain			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Pneumonitis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Memory impairment			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Mood disorder due to a general medical condition			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Investigations			
Hypocalcaemia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
ALT increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
AST increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
LDH increased			
subjects affected / exposed	4 / 19 (21.05%)		
occurrences (all)	4		
bilirrubin increased			

subjects affected / exposed occurrences (all) creatinine increased subjects affected / exposed occurrences (all) low hematocrit subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1 1 / 19 (5.26%) 1 1 / 19 (5.26%) 1		
Nervous system disorders peripheral neuropathy subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	 3 / 19 (15.79%) 3 1 / 19 (5.26%) 1 1 / 19 (5.26%) 1		
Blood and lymphatic system disorders Erythema subjects affected / exposed occurrences (all) platelet cound decrease subjects affected / exposed occurrences (all)	 1 / 19 (5.26%) 1 1 / 19 (5.26%) 1		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	 1 / 19 (5.26%) 1		
Eye disorders decline of vision subjects affected / exposed occurrences (all)	 1 / 19 (5.26%) 1		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	 4 / 19 (21.05%) 4		

Constipation				
subjects affected / exposed	4 / 19 (21.05%)			
occurrences (all)	4			
Diarrhoea				
subjects affected / exposed	3 / 19 (15.79%)			
occurrences (all)	3			
Flank pain				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Intestinal obstruction				
subjects affected / exposed	2 / 19 (10.53%)			
occurrences (all)	2			
Small intestinal obstruction				
subjects affected / exposed	2 / 19 (10.53%)			
occurrences (all)	2			
Vomiting				
subjects affected / exposed	3 / 19 (15.79%)			
occurrences (all)	3			
anal pain				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Dysphagia				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Mucositis oral				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Nausea				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
rectal hemorrage				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			
Toothache				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences (all)	1			

flu like symptoms subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Hepatobiliary disorders Hepatic pain subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Skin and subcutaneous tissue disorders Urticaria subjects affected / exposed occurrences (all) Skin toxicity subjects affected / exposed occurrences (all) bollous dermatitis subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all)	 1 / 19 (5.26%) 1 1 / 19 (5.26%) 1 1 / 19 (5.26%) 1 1 / 19 (5.26%) 1 2 / 19 (10.53%) 2		
Renal and urinary disorders hematuria subjects affected / exposed occurrences (all)	 1 / 19 (5.26%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Bone pain	 2 / 19 (10.53%) 2 4 / 19 (21.05%) 4		

subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
tendinitis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Infections and infestations			
upper respiratory infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Tooth infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
ALK increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Anorexia and bulimia syndrome			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	3		
hyperglycaemia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Hypothyroidism			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 July 2019	changes in elegibility criteria

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.

The study was ended prematurely due to lack of efficacy

Notes: