Clinical trial results:
Intensified methotrexate, vinblastine, doxorubicin and cisplatin (I-MVAC) with or without panitumumab as first-line treatment of advanced urothelial carcinoma in patients without H-Ras nor K-Ras mutations. Randomised phase II study.

Summary

EudraCT number	2009-011882-10
Trial protocol	FR
Global end of trial date	01 March 2018

Results information

Result version number	v1 (current)
This version publication date	14 October 2022
First version publication date	14 October 2022

Trial information

Trial identification

Sponsor protocol code	GETUG-AFU 19/0901

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02818725
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 1 71 93 67 04, 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	30 December 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the GETUG-AFU19 study was the evaluation of efficacy in terms of progression-free survival at 9 months of the combination of intensified methotrexate, vinblastine, doxorubicin and cisplatin (I-MVAC) with or without panitumumab as first-line treatment of advanced urothelial carcinoma in patients without H-Ras nor K-Ras mutations.

Protection of trial subjects:

In order to ensure the protection of the rights, safety and well-being of trial subjects, this study was conducted in accordance with the ethical principles that have their origins in the latest version of the Declaration of Helsinki (1964) and subsequent amendments, ICH Good Clinical Practice Guidelines (CPMP/ICH/135/95), the European Directive (2001/20/CE) on the conduct of clinical trials and subsequent texts (Eudralex Vol 10), and the applicable local regulatory requirements and laws (The Huriet Law N°88-1138 of the 20th December 1998 on the protection of persons taking part in biomedical research; The National Informatics and Freedoms Commission – Law N° 78-17 of the 6th January 1978 modified by the law N° 2004-801 of the 6th August 2004 concerning the protection of the person with regards to the use of personal data; Bioethical law N°2011-814 of the 8th July 2011).
Furthermore, independent Ethics Committees reviewed and gave favorable opinions to the study documents, including the initial protocol and all subsequent amendments, and all information and documents provided to subjects/patients.
Written informed consent was obtained from all patients prior to enrollment.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 September 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 97
Worldwide total number of subjects	97
EEA total number of subjects	97

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)	52
From 65 to 84 years	45
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The GETUG-AFU 19 was a multicentre, randomised phase II trial that evaluated the efficacy of intensified methotrexate, vinblastine, doxorubicin and cisplatin (I-MVAC) with or without panitumumab as first-line treatment of advanced urothelial carcinoma in patients without H-Ras nor K-Ras mutations.

Pre-assignment

Screening details:

The study consisted of a 28-day screening phase to establish patients' eligibility and document baseline measurements, a treatment phase (28-day cycle till disease progression - 6 cycles maximum), and a long-term follow-up to monitor the progression-free survival, the response rate, time to progression, overall survival, and toxicity.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	I-MVAC

Arm description:

Standard of care treatment. patients randomized in the I-MVAC arm received intravenous injection of methotrexate, vinblastine, doxorubicin, and cisplatin every two weeks until disease progression for a maximum of 6 cycles. Furthermore, patients received two subcutaneous injection of G-CSF at each cycle to decrease chemotherapy toxicity.

Arm type	Active comparator
Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Intravenous administration at a dose of 30mg/m² over 30 min in 100 ml of 5% glucose solution

Investigational medicinal product name	Vinblastine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate and solution for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Intravenous administration at a dose of 3 mg/m² over 15 min in 50 ml of 0.9% sodium chloride

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate and solution for solution for infusion, Powder for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Intravenous administration at a dose of 30 mg/m² over 30 min in 100 ml of 5% glucose solution

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Intravenous administration at a dose of 70 mg/m² over 2 hours in 250 ml of 0.9% sodium chloride, in between hyperhydration with 3 litres of 0.9% sodium chloride/24 hours, having started 24 hours before the cisplatin infusion and to be continued up to 24 hours after the end of the cisplatin infusion. Administration of magnesium to prevent magnesium loss might be performed

Arm title	I-MVAC plus panitumumab

Arm description:

Patients randomized in the I-MVAC plus panitumumab arm received intravenous injection of methotrexate, vinblastine, doxorubicin, cisplatin, and panitumumab every two weeks until disease progression for a maximum of 6 cycles. Furthermore, patients received two subcutaneous injection of G-CSF at each cycle to decrease chemotherapy toxicity.
After stopping treatment with I-MVAC, if panitumumab is well tolerated and in the absence of disease progression, panitumumab was continued alone as per the same regimen up to disease progression or the end of follow-up at 24 months.

Arm type	Experimental
Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Intravenous administration at a dose of 30mg/m² over 30 min in 100 ml of 5% glucose solution

Investigational medicinal product name	Vinblastine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate and solution for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Intravenous administration at a dose of 3 mg/m² over 15 min in 50 ml of 0.9% sodium chloride

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate and solution for solution for infusion, Powder for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Intravenous administration at a dose of 30 mg/m² over 30 min in 100 ml of 5% glucose solution

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Intravenous administration at a dose of 70 mg/m² over 2 hours in 250 ml of 0.9% sodium chloride, in between hyperhydration with 3 litres of 0.9% sodium chloride/24 hours, having started 24 hours before the cisplatin infusion and to be continued up to 24 hours after the end of the cisplatin infusion. Administration of magnesium to prevent magnesium loss might be performed

Investigational medicinal product name	Panitumumab
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Intravenous administration at a dose of 6 mg/kg over 1 hour in 100 ml of 0.9% sodium chloride solution, 1 hour after cisplatin

Number of subjects in period 1	I-MVAC	I-MVAC plus panitumumab
Started	33	64
Completed	25	38
Not completed	8	26
Patient decision	1	2
Physician decision	1	1
Disease progression	-	6
Adverse event, non-fatal	5	15
Death	-	1
Radiotherapy	1	-
Protocol deviation	-	1

Baseline characteristics

Reporting groups

Reporting group title	I-MVAC

Reporting group description:

Standard of care treatment. patients randomized in the I-MVAC arm received intravenous injection of methotrexate, vinblastine, doxorubicin, and cisplatin every two weeks until disease progression for a maximum of 6 cycles. Furthermore, patients received two subcutaneous injection of G-CSF at each cycle to decrease chemotherapy toxicity.

Reporting group title	I-MVAC plus panitumumab

Reporting group description:

Patients randomized in the I-MVAC plus panitumumab arm received intravenous injection of methotrexate, vinblastine, doxorubicin, cisplatin, and panitumumab every two weeks until disease progression for a maximum of 6 cycles. Furthermore, patients received two subcutaneous injection of G-CSF at each cycle to decrease chemotherapy toxicity.
After stopping treatment with I-MVAC, if panitumumab is well tolerated and in the absence of disease progression, panitumumab was continued alone as per the same regimen up to disease progression or the end of follow-up at 24 months.

Reporting group values	I-MVAC	I-MVAC plus panitumumab	Total
Number of subjects	33	64	97
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	65.4	63.8	
full range (min-max)	39.9 to 75.3	35.5 to 73.9	-
Gender categorical Units: Subjects			
Female	8	15	23
Male	25	49	74
ECOG PS Units: Subjects			
PS 0	13	25	38
PS 1	17	30	47
PS 2	0	1	1
Missing	3	8	11
Primary tumor Units: Subjects			
Upper urinary tract	6	15	21

Bladder	22	46	68
Both	5	3	8
Histological variant Units: Subjects			
Pure urothelial	27	56	83
Squamous	3	1	4
Glandular	0	1	1
Unknown	3	6	9
Disease stage Units: Subjects			
Locally advanced	4	6	10
Metastatic	29	58	87
Bajorin risk group Units: Subjects			
Favorable	7	15	22
Intermediate	23	40	63
Poor	0	1	1
Unknown	3	8	11

End points

End points reporting groups

Reporting group title	I-MVAC

Reporting group description:

Standard of care treatment. patients randomized in the I-MVAC arm received intravenous injection of methotrexate, vinblastine, doxorubicin, and cisplatin every two weeks until disease progression for a maximum of 6 cycles. Furthermore, patients received two subcutaneous injection of G-CSF at each cycle to decrease chemotherapy toxicity.

Reporting group title	I-MVAC plus panitumumab

Reporting group description:

Patients randomized in the I-MVAC plus panitumumab arm received intravenous injection of methotrexate, vinblastine, doxorubicin, cisplatin, and panitumumab every two weeks until disease progression for a maximum of 6 cycles. Furthermore, patients received two subcutaneous injection of G-CSF at each cycle to decrease chemotherapy toxicity.
After stopping treatment with I-MVAC, if panitumumab is well tolerated and in the absence of disease progression, panitumumab was continued alone as per the same regimen up to disease progression or the end of follow-up at 24 months.

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

Subject analysis set description:

All patients without major violations of eligibility criteria, and evaluable

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients that received at least administration of a study drugs (MVAC or panitumumab). The patients were analysed according to the actual treatment they received

Primary: 9-month progression-free survival

End point title	9-month progression-free survival[1]

End point description:

End point type	Primary

End point timeframe:

The primary endpoint PFS was evaluated at 9 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: For this study, no formal statistical analysis between arms was planned. The treatment would be considered to be active if at least 37 patients among 62 did not show tumour progression at 9 months. Only 10 out of 63 patients were alive without disease progression at 9 months in the arm I-MVAC plus panitumumab. Thus, the combination of I-MVAC and panitumumab as first-line treatment of advanced urothelial carcinoma in patients without H-Ras nor K-Ras mutations is not considered sufficiently active

End point values	I-MVAC	I-MVAC plus panitumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	63[2]		
Units: Patients				
No	22	53		
Yes	11	10		

Notes:

[2] - 1 patient died before treatment end was not analysed

Statistical analyses

No statistical analyses for this end point

Primary: Overall survival

End point title	Overall survival

End point description:

Survival rates will be estimated according to Kaplan-Meier. Patients alive at last follow-up news will be censored at the last visit date.

End point type	Primary

End point timeframe:

The event times for the analyse of OS were calculated from the date of randomisation to the date of death (up to 24 months)

End point values	I-MVAC	I-MVAC plus panitumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	63[3]		
Units: year				
median (confidence interval 95%)	20.2 (14.7 to 27.8)	12.5 (9.5 to 17.3)		

Notes:

[3] - 1 patient died before treatment end was not analysed

Statistical analyses

Statistical analysis title	OS analysis
Comparison groups	I-MVAC v I-MVAC plus panitumumab
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.024
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	3

Secondary: Objective response rate

End point title	Objective response rate

End point description:

Tumour evaluations were performed by chest-abdominal-pelvic CT scan and response to treatment were evaluated according to RECIST criteria v1.1.

End point type	Secondary

End point timeframe:

Tumor assessment were performed at baseline, every 6 weeks during and the treatment period (up to disease progression), then every 3 months for 2 years thereafter.

End point values	I-MVAC	I-MVAC plus panitumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	63[4]		
Units: Percent				
number (confidence interval 95%)	69.7 (51 to 84)	47.6 (35 to 61)		

Notes:

[4] - 1 patient died before treatment end was not analysed

Statistical analyses

No statistical analyses for this end point

Secondary: Time to progression

End point title	Time to progression

End point description:

Survival rates were estimated according to Kaplan-Meier. Patients alive at last follow-up news were censored at the date of last tumour assessment. Patients who died from causes other than disease progression were censored at the date of death. Patients who did not progress nor die were censored at the date of last tumour assessment, or at the date of a secondary treatment initiation in the case of absence of disease progression.

End point type	Secondary

End point timeframe:

The event times for the analysis of time to progression (TTP) were calculated from the date of randomisation to the date of progression (up to 24 months).

End point values	I-MVAC	I-MVAC plus panitumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	63[5]		
Units: month				
median (confidence interval 95%)	6.8 (6.3 to 10.0)	5.7 (4.6 to 6.4)		

Notes:

[5] - 1 patient died before treatment end was not analysed

Statistical analyses

Statistical analysis title	TTP analysis
Comparison groups	I-MVAC v I-MVAC plus panitumumab
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.028
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.05
upper limit	2.61

Post-hoc: Progression-free survival

End point title	Progression-free survival

End point description:

Tumour evaluations were performed by chest-abdominal-pelvic CT scan and response to treatment were evaluated according to RECIST criteria v1.1.

End point type	Post-hoc

End point timeframe:

Tumor assessment were performed every 6 weeks during and the treatment period (up to disease progression), then every 3 months for 2 years thereafter.

End point values	I-MVAC	I-MVAC plus panitumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	63[6]		
Units: month				
median (confidence interval 95%)	6.8 (6.3 to 9.2)	5.7 (4.6 to 6.4)		

Notes:

[6] - 1 patient died before treatment end was not analysed

Statistical analyses

Statistical analysis title	PFS analysis
Comparison groups	I-MVAC v I-MVAC plus panitumumab
Number of subjects included in analysis	96
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.038
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.01
upper limit	2.51

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From inclusion until 30 days after end of treatment (up to 2 years).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups	
Reporting group title	I-MVAC
Reporting group description: -	
Reporting group title	I-MVAC plus panitumumab
Reporting group description: -	

Serious adverse events	I-MVAC	I-MVAC plus panitumumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 33 (42.42%)	47 / 63 (74.60%)	
number of deaths (all causes)	20	50	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Meningeal carcinomatosis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Muscle neoplasm			
subjects affected / exposed	0 / 33 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer			
subjects affected / exposed	0 / 33 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Cerebrovascular accident			

subjects affected / exposed	0 / 33 (0.00%)	1 / 63 (1.59%)	
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	1 / 33 (3.03%)	4 / 63 (6.35%)	
occurrences causally related to treatment / all	0 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thromboembolic event			
subjects affected / exposed	0 / 33 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Nephrostomy			
subjects affected / exposed	0 / 33 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter occlusion			
subjects affected / exposed	1 / 33 (3.03%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	2 / 33 (6.06%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device malfunction			
subjects affected / exposed	0 / 33 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Disease progression			
subjects affected / exposed	0 / 33 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
General physical health deterioration			
subjects affected / exposed	2 / 33 (6.06%)	5 / 63 (7.94%)	
occurrences causally related to treatment / all	2 / 2	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumopathy			
subjects affected / exposed	1 / 33 (3.03%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Hallucination			
subjects affected / exposed	0 / 33 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Left ventricular ejection fraction decreased			
subjects affected / exposed	0 / 33 (0.00%)	1 / 63 (1.59%)	
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			
Drug administration error			
subjects affected / exposed	0 / 33 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 33 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Aphasia			
subjects affected / exposed	1 / 33 (3.03%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	0 / 33 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	0 / 33 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 33 (0.00%)	4 / 63 (6.35%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aplasia bone marrow			
subjects affected / exposed	0 / 33 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aplasia anaemia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bicytopenia			
subjects affected / exposed	0 / 33 (0.00%)	3 / 63 (4.76%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile aplasia			
subjects affected / exposed	2 / 33 (6.06%)	7 / 63 (11.11%)	
occurrences causally related to treatment / all	2 / 2	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	

Febrile neutropenia			
subjects affected / exposed	0 / 33 (0.00%)	2 / 63 (3.17%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 33 (3.03%)	4 / 63 (6.35%)	
occurrences causally related to treatment / all	1 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	2 / 33 (6.06%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 33 (3.03%)	2 / 63 (3.17%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 33 (3.03%)	2 / 63 (3.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 33 (3.03%)	2 / 63 (3.17%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 33 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Melaena			

subjects affected / exposed	1 / 33 (3.03%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucositis oral			
subjects affected / exposed	1 / 33 (3.03%)	4 / 63 (6.35%)	
occurrences causally related to treatment / all	1 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 33 (6.06%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Purpura			
subjects affected / exposed	0 / 33 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pustular skin eruption			
subjects affected / exposed	0 / 33 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute renal failure			
subjects affected / exposed	1 / 33 (3.03%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute renal insufficiency			
subjects affected / exposed	3 / 33 (9.09%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hematuria			
subjects affected / exposed	1 / 33 (3.03%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			

subjects affected / exposed	1 / 33 (3.03%)	4 / 63 (6.35%)	
occurrences causally related to treatment / all	1 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal insufficiency			
subjects affected / exposed	2 / 33 (6.06%)	5 / 63 (7.94%)	
occurrences causally related to treatment / all	2 / 2	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	0 / 33 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 33 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in spine			
subjects affected / exposed	1 / 33 (3.03%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Candida sepsis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter infection			
subjects affected / exposed	3 / 33 (9.09%)	4 / 63 (6.35%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatophytosis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Escherichia sepsis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella sepsis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panaritium			
subjects affected / exposed	0 / 33 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 33 (3.03%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 33 (0.00%)	2 / 63 (3.17%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septicaemia staphylococcal			
subjects affected / exposed	1 / 33 (3.03%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septicaemia			
subjects affected / exposed	1 / 33 (3.03%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcus epidermidis infection			
subjects affected / exposed	0 / 33 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary infection			

subjects affected / exposed	0 / 33 (0.00%)	2 / 63 (3.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 33 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	0 / 33 (0.00%)	1 / 63 (1.59%)	
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	I-MVAC	I-MVAC plus panitumumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 33 (100.00%)	63 / 63 (100.00%)	
Vascular disorders			
Left ventricular dysfunction			
subjects affected / exposed	0 / 33 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Thrombosis			
subjects affected / exposed	2 / 33 (6.06%)	5 / 63 (7.94%)	
occurrences (all)	2	5	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	29 / 33 (87.88%)	50 / 63 (79.37%)	
occurrences (all)	29	50	
Fever			
subjects affected / exposed	8 / 33 (24.24%)	16 / 63 (25.40%)	
occurrences (all)	8	16	
Weight			
subjects affected / exposed	17 / 33 (51.52%)	41 / 63 (65.08%)	
occurrences (all)	17	41	

Chills			
subjects affected / exposed	4 / 33 (12.12%)	1 / 63 (1.59%)	
occurrences (all)	4	1	
Oedema peripheral			
subjects affected / exposed	3 / 33 (9.09%)	3 / 63 (4.76%)	
occurrences (all)	3	3	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 33 (21.21%)	12 / 63 (19.05%)	
occurrences (all)	7	12	
Dyspnoea			
subjects affected / exposed	4 / 33 (12.12%)	11 / 63 (17.46%)	
occurrences (all)	4	11	
Thoracic pain			
subjects affected / exposed	4 / 33 (12.12%)	0 / 63 (0.00%)	
occurrences (all)	4	0	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 33 (3.03%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Peripheral neuropathy			
subjects affected / exposed	9 / 33 (27.27%)	10 / 63 (15.87%)	
occurrences (all)	9	10	
Insomnia			
subjects affected / exposed	1 / 33 (3.03%)	3 / 63 (4.76%)	
occurrences (all)	1	3	
Somnolence			
subjects affected / exposed	2 / 33 (6.06%)	1 / 63 (1.59%)	
occurrences (all)	2	1	
Blood and lymphatic system disorders			
Haemoglobin			
subjects affected / exposed	31 / 33 (93.94%)	62 / 63 (98.41%)	
occurrences (all)	31	62	
Neutrophil			

subjects affected / exposed	21 / 33 (63.64%)	36 / 63 (57.14%)	
occurrences (all)	21	36	
Febrile neutropenia			
subjects affected / exposed	2 / 33 (6.06%)	11 / 63 (17.46%)	
occurrences (all)	2	11	
Platelet			
subjects affected / exposed	25 / 33 (75.76%)	42 / 63 (66.67%)	
occurrences (all)	25	42	
Ear and labyrinth disorders			
Audition			
subjects affected / exposed	8 / 33 (24.24%)	6 / 63 (9.52%)	
occurrences (all)	8	6	
Eye disorders			
Visual impairment			
subjects affected / exposed	2 / 33 (6.06%)	2 / 63 (3.17%)	
occurrences (all)	2	2	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	12 / 33 (36.36%)	28 / 63 (44.44%)	
occurrences (all)	12	28	
Diarrhoea			
subjects affected / exposed	10 / 33 (30.30%)	27 / 63 (42.86%)	
occurrences (all)	10	27	
Nausea			
subjects affected / exposed	25 / 33 (75.76%)	46 / 63 (73.02%)	
occurrences (all)	25	46	
Stomatitis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	14 / 33 (42.42%)	27 / 63 (42.86%)	
occurrences (all)	14	27	
Mucositis			
subjects affected / exposed	11 / 33 (33.33%)	41 / 63 (65.08%)	
occurrences (all)	11	41	
Abdominal pain			

subjects affected / exposed	6 / 33 (18.18%)	8 / 63 (12.70%)	
occurrences (all)	6	8	
Hepatobiliary disorders			
Bilirubin			
subjects affected / exposed	4 / 33 (12.12%)	6 / 63 (9.52%)	
occurrences (all)	4	6	
Alkaline phosphatase			
subjects affected / exposed	11 / 33 (33.33%)	30 / 63 (47.62%)	
occurrences (all)	11	30	
Alanine aminotransferase			
subjects affected / exposed	6 / 33 (18.18%)	15 / 63 (23.81%)	
occurrences (all)	6	15	
Aspartate aminotransferase			
subjects affected / exposed	6 / 33 (18.18%)	10 / 63 (15.87%)	
occurrences (all)	6	10	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	12 / 33 (36.36%)	20 / 63 (31.75%)	
occurrences (all)	12	20	
Desquamation			
subjects affected / exposed	0 / 33 (0.00%)	6 / 63 (9.52%)	
occurrences (all)	0	6	
Dry skin			
subjects affected / exposed	2 / 33 (6.06%)	20 / 63 (31.75%)	
occurrences (all)	2	20	
Erythema			
subjects affected / exposed	0 / 33 (0.00%)	20 / 63 (31.75%)	
occurrences (all)	0	20	
Hand-foot syndrome			
subjects affected / exposed	0 / 33 (0.00%)	7 / 63 (11.11%)	
occurrences (all)	0	7	
Rash			
subjects affected / exposed	0 / 33 (0.00%)	37 / 63 (58.73%)	
occurrences (all)	0	37	
Skin fissures			

subjects affected / exposed	0 / 33 (0.00%)	8 / 63 (12.70%)	
occurrences (all)	0	8	
Renal and urinary disorders			
Creatine			
subjects affected / exposed	13 / 33 (39.39%)	27 / 63 (42.86%)	
occurrences (all)	13	27	
Haematuria			
subjects affected / exposed	4 / 33 (12.12%)	14 / 63 (22.22%)	
occurrences (all)	4	14	
Proteinuria			
subjects affected / exposed	1 / 33 (3.03%)	2 / 63 (3.17%)	
occurrences (all)	1	2	
Infections and infestations			
Infection with neutropenia			
subjects affected / exposed	3 / 33 (9.09%)	3 / 63 (4.76%)	
occurrences (all)	3	3	
Infection without neutropenia			
subjects affected / exposed	6 / 33 (18.18%)	12 / 63 (19.05%)	
occurrences (all)	6	12	
Paronychia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 63 (1.59%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	12 / 33 (36.36%)	38 / 63 (60.32%)	
occurrences (all)	12	38	
Hypomagnesaemia			
subjects affected / exposed	12 / 33 (36.36%)	31 / 63 (49.21%)	
occurrences (all)	12	31	
Hypocalcaemia			
subjects affected / exposed	9 / 33 (27.27%)	33 / 63 (52.38%)	
occurrences (all)	9	33	
Hypokalaemia			
subjects affected / exposed	10 / 33 (30.30%)	23 / 63 (36.51%)	
occurrences (all)	10	23	
Dehydration			

subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	3 / 63 (4.76%) 3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 July 2011	* In order not to exclude patients with bone metastases due to alkaline phosphatases exceeding the limits mentioned in the protocol, the inclusion criterion #10 was added so that patients with bone metastases and ALP < grade 3 according to CTC-AE v 4 were eligible. * Approximately 30% of patients with urothelial cancer for whom prostate cancer is diagnosed during histopathological analysis of the cystectomy specimen. In order not to exclude patients with low-risk prostate cancer, and therefore without impact on the survival prognosis of these patients who also have urothelial cancer, the inclusion criterion #2 was reworded to specify the eligibility of these patients in this protocol.
22 May 2012	Patients with brain metastasis require special management, particularly radiotherapy, which is not compatible with the chemotherapy proposed in the protocol. Thus, the non-inclusion criterion #2 was modified to include this parameter and the inclusion criterion #4 reworded.
11 September 2012	The inclusion period was extended by 2 years to allow inclusion of the last 50 patients.
15 July 2014	* Initially, the protocol planned to register 107 patients and randomize 93, with a rate of 20% of patients not eligible for randomization and analysis. However, it has been observed that about 30% of the registered patients were not randomized (screening failure, death before randomization, deterioration of the general state before randomization, etc.) and that 15% of the randomized patients could not be taken into account in the analysis (absence of measurable lesions and/or untreated patients). Thus, the population to be screened was increased to 135 registered patients to reach 93 evaluable patients. * Given the need to increase the number of patients to be registered and given the average inclusion rate (3 patients/month), the inclusion period was extended by 8 months.
26 March 2015	* The inclusion period was extended by 8 months to allow inclusion of the last patients. * The calculation of the number of patients to be registered necessary to reach the objective of 93 analyzable patients was incorrect. Indeed, the estimated percentage of non-analyzable patients being 45% (30% of patients not randomizedand 15% of patients randomized but not evaluable), the required number of patients to be registrered was 170 patients and not 135 as specified in the amendment approved on 15-Jul-2014 .

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.

For adverse events, the "total number of occurrences" was not reported, so the number of patients is noted in this field.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/33753043