Clinical trial results:
Phase II Study of Paclitaxel and TAK-228 in metastatic urothelial carcinoma (UC) and the impact of PI3K-mTOR pathway genomic alterations

Summary

EudraCT number	2017-004486-27
Trial protocol	ES
Global end of trial date	15 April 2021

Results information

Result version number	v1 (current)
This version publication date	06 April 2022
First version publication date	06 April 2022

Trial information

Trial identification

Sponsor protocol code	X31005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03745911
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Associació Per a la Recerca Oncològica (APRO)
Sponsor organisation address	Calle Vilarrúbias, 20 , SABADELL / Barcelona, Spain, 08202
Public contact	Joaquim Bellmunt, Associació Per a la Recerca Oncològica (APRO), 00 3493 227 47 60, oncologia.apro@gmail.com
Scientific contact	Joaquim Bellmunt, Associació Per a la Recerca Oncològica (APRO), 00 3493 227 47 60, oncologia.apro@gmail.com

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 November 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 April 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of TAK-228 (orally administered 3 days each week) in combination with weekly IV paclitaxel as assessed by objective response rate in patients with metastatic, previously treated urothelial carcinoma (UC).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 May 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: 22
Worldwide total number of subjects	22
EEA total number of subjects	22

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)	12
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Twenty eight patients were recruited, 6 of whom were considered screening failures (noncompliance with selection criteria). Therefore, 22 patients composed the modified intended to treat (mITT) population in this study conducted in 5 Spanish hospitals.

Pre-assignment

Screening details:

Patients must have a diagnosis of metastatic or advanced histologically confirmed urothelial cancer (UC), having received prior systemic chemotherapy treatment for UC, with no limit for number of prior systemic chemotherapeutic or investigational treatment regimens.

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	TAK-228 and paclitaxel

Arm description:

All patients included in the clinical trial received the combination of TAK-228 (orally) and Paclitaxel (IV infusion) regimen in 28-day cycles. Treatment was given until disease progression, unacceptable toxicity or patient withdrawal.

Arm type	Experimental
Investigational medicinal product name	TAK-228
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

TAK-228 was administered orally at a dose of 4 mg once daily, 3 days per week (on Days 2-4, 9-11, 16-18, and 23-25 of a 28-day cycle) of a 28-day treatment cycle.

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel was administered at a dose of 80mg/m2 IV infusion over 60 minutes once weekly for 3 consecutive weeks (on Days 1, 8, and 15 of a 28-day treatment cycle).

Number of subjects in period 1	TAK-228 and paclitaxel
Started	22
Completed	21
Not completed	1
Consent withdrawn by subject	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	22	22	
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)	12	12	
From 65-84 years	10	10	
85 years and over	0	0	
Age continuous Units: years			
median	62.5		
inter-quartile range (Q1-Q3)	54.0 to 74.0	-	
Gender categorical Units: Subjects			
Female	4	4	
Male	18	18	
ECOG PS Units: Subjects			
ECOG 0	9	9	
ECOG 1	13	13	
Patients with previous immunotherapy treatment Units: Subjects			
Yes	16	16	
No	6	6	
Number of metastatic locations at screening Units: Locations			
median	2.0		
inter-quartile range (Q1-Q3)	2.0 to 3.0	-	
Hemoglobin levels Units: g/L			
median	117.5		
inter-quartile range (Q1-Q3)	112.0 to 127.0	-	
Time from last prior line before inclusion Units: months			
median	5.4		

inter-quartile range (Q1-Q3)	3.1 to 10.9	-	
Number of pevious systemic treatments Units: Units			
median	3.0		
inter-quartile range (Q1-Q3)	2.0 to 4.0	-	
Number of lesions at screening Units: Lesions			
median	3.5		
inter-quartile range (Q1-Q3)	3.0 to 5.0	-	

End points

End points reporting groups

Reporting group title	TAK-228 and paclitaxel

Reporting group description:

All patients included in the clinical trial received the combination of TAK-228 (orally) and Paclitaxel (IV infusion) regimen in 28-day cycles. Treatment was given until disease progression, unacceptable toxicity or patient withdrawal.

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

Subject analysis set description:

Modified intention-to-treat (mITT) population: included all randomized patients who received at least one dose of study treatment (N=22).

Primary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)[1]

End point description:

Percentage of patients with either a complete response (CR) or a partial response (PR) according to RECIST criteria (version 1.1).
The response rate (RR) is the proportion of all patients with confirmed PR or CR according to RECIST v1.1 from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best overall response assignment will depend on the achievement of both measurement and confirmation criteria. A CR or PR is confirmed if a subsequent assessment (no less than 4 weeks after the initial response is noted) indicates no additional disease or growth of disease relative to the prior assessment. An assessment of SD does not require confirmation. If there are no post-baseline scans available for a patient, then the best response will be not available (NA).

End point type	Primary

End point timeframe:

From the start of the treatment until disease progression/recurrence.

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: No statistical analysis was planned for this end point.

End point values	mITT			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Percentage of patients				
number (confidence interval 95%)	18.2 (5.2 to 40.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall Survival (OS), defined as the time from randomization date until the date of death, regardless of the cause of death.

End point type	Secondary

End point timeframe:

From randomization date to death from any cause.

End point values	mITT			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: months				
median (confidence interval 95%)	6.1 (1.8 to 13.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)

End point description:

Progression-free survival (PFS), defined as the time from randomization date until the first (radiologically) documented progression of disease or death from any cause, whichever occurred first.

End point type	Secondary

End point timeframe:

From randomization to disease progression or death from any cause.

End point values	mITT			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: months				
median (confidence interval 95%)	3.4 (1.8 to 6.1)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs received from the first day of the first cycle through 30 days after the last dose.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	v22.0

Reporting groups

Reporting group title	Adverse events

Reporting group description: -

Serious adverse events	Adverse events		
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 22 (68.18%)		
number of deaths (all causes)	15		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Spinal cord compression			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Disease progression			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Death			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
General physical health deterioration			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			

subjects affected / exposed	2 / 22 (9.09%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hydronephrosis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Oral candidiasis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	1 / 22 (4.55%)		
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	Adverse events		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 22 (90.91%)		
Investigations			
Blood creatine increased			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	2		
Nervous system disorders			
Neurotoxicity			
subjects affected / exposed	4 / 22 (18.18%)		
occurrences (all)	15		
Dysgeusia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	2		
Paraesthesia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	4		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	7 / 22 (31.82%)		
occurrences (all)	8		
Pyrexia			
subjects affected / exposed	4 / 22 (18.18%)		
occurrences (all)	4		
Asthenia			

subjects affected / exposed	9 / 22 (40.91%)		
occurrences (all)	23		
Discomfort			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 22 (36.36%)		
occurrences (all)	14		
Neutropenia			
subjects affected / exposed	5 / 22 (22.73%)		
occurrences (all)	8		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	6 / 22 (27.27%)		
occurrences (all)	8		
Dyspepsia			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Constipation			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	6		
Vomiting			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	3		
Alopecia			
subjects affected / exposed	4 / 22 (18.18%)		
occurrences (all)	4		
Skin toxicity			

subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 2		
Musculoskeletal and connective tissue disorders Musculoskeletal pain subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all)	 4 / 22 (18.18%) 4 3 / 22 (13.64%) 4 3 / 22 (13.64%) 3		
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	 2 / 22 (9.09%) 3		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 6 / 22 (27.27%) 10		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 April 2018	Amendment 1: Changes in frequency of study schedule assessments after baseline visits. Modification of the Patient Information Sheet (PIS) to adapt it to the new schedule of assessments. Added definition of TIA (transient ischemic attack), on page 10. Description of an interim analysis (page 70), which will be carried out after the inclusion of the first 17 patients. Clarification on the duration of treatment and the possibility of maintaining TAK-228 when paclitaxel is suspended due to toxicity. Modification of the frequency of carrying out the TCs to adjust it to a temporary term instead of a determined number of cycles.

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 could not demonstrate the primary endpoint (ORR) due to insufficient number of patients finally enrolled.

Notes: