FINAL STUDY REPORT

Full title of the trial:	Multiorgan Metabolic imaging response assessment of Abemaciclib
Short title of the trial:	MiMe-A trial
EudraCT Number:	2017-000123-28
Sponsor protocol number:	IJB-MULTI-MIME-A-2017
ClinicalTrials.gov Number:	NCT03339843
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Report date	26/02/2024

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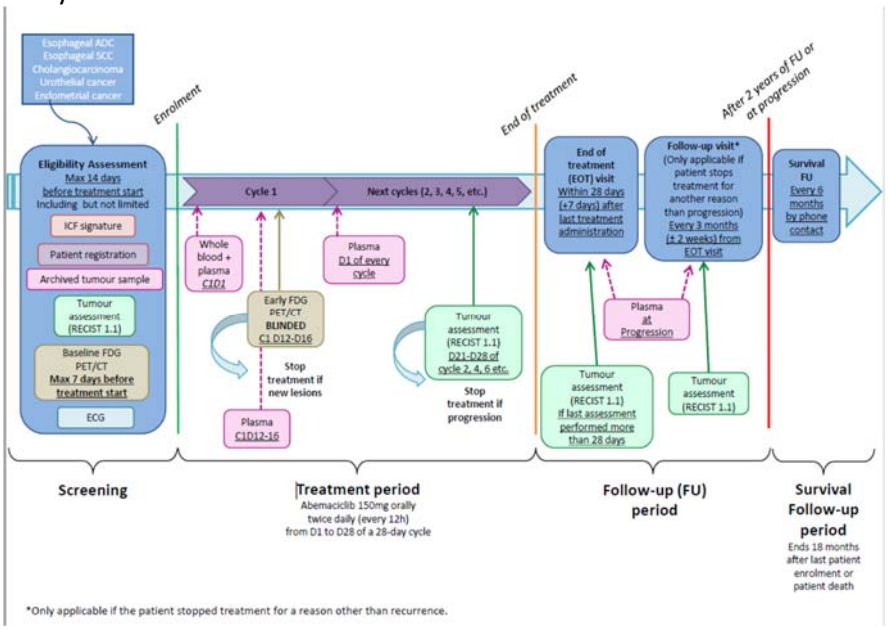
1 TRIAL INFORMATION

PHASE	Phase II
TRIAL DESIGN	This was an open-label, phase II, basket study that included subjects with histologically confirmed cancer corresponding to predefined tumour types that were metastatic or unresectable and for which standard platinum regimens were no longer effective. This study was a screening program for abemaciclib efficacy in multiple tumour types progressive after platinum-based chemotherapy (with any delay) by using metabolic imaging (PERCIST) and RECIST. This study contained two stages; during the first stage, a maximum of 17 subjects were enrolled in each tumour type cohort. After 13 evaluable subjects were enrolled, an interim analysis was performed on that tumour cohort. If 3 or more subjects were seen to have experienced a treatment success, then the cohort passed into the second stage in which a maximum of 20 more subjects were enrolled. If 2 or less subjects were seen to have experienced a treatment success, then that cohort was closed and was proceeded into the second stage. A treatment success was defined as a subject who had metabolic response according to PERCIST with a response cut off set at 15% at the early FDG-PET/CT and a morphological disease control after 2 cycles measured by RECIST v1.1 (disease control is defined as complete response (CR), partial response (PR) or stable disease (SD)). And evaluable subject was defined as a subject that had a clear treatment success or nontreatment success. Based on the rate of FDG-avidity and the absence of deactivation of the Rb gene function in more than 95% of cases, we proposed to define 5 tumour types of interest in a preliminary stage: • Esophageal adenocarcinoma, • Esophageal squamous cell carcinoma • Cholangiocarcinoma • Urothelial cancer • Endometrial cancer Subjects received 150 mg of abemaciclib orally, two times a day, during cycles of 28 days each. If the treatment with abemaciclib 150 mg twice daily was well tolerated, the dose could be increased to 200 mg twice daily at investigator's discretion. The subject underwent: • A baseline FDG-PET/CT (D-7 to D0) and a baseline CT scan (D-14 to D0) • A blinded early FDG-PET/CT at D14 +/- 2 days (between D12 and D16) of study treatment.

	If the early FDG-PET/CT showed any new lesion, it was unblinded for the oncologists and the study treatment was stopped. If there were no new lesions, the subject continued the treatment and proceed with a radiological assessment (RECIST v1.1 criteria) after 2 cycles of treatment (between D21 and D28 of cycle 2). If progressive disease was showed at this assessment the study treatment was stopped. If there is no progressive disease, the study treatment was continued.  Primary archived tumour tissues (1 formalin-fixed paraffin-embedded (FFPE tumour tissue block) or 20 unstained slides freshly cut for the study purpose), if available prior to enrolment must have been provided. Whole-blood and plasma samples were collected at baseline (before start of study treatment administration) and plasma samples were collected at C1D14(+/-2 days), the beginning (D1) of every treatment cycle for cell-free DNA (cfDNA) analysis, and at progression.
SCIENTIFIC BACKGROUND/ RATIONALE	Abemaciclib (A) activity against breast cancer as monotherapy or combined with endocrine therapy warrants further investigations in other cancer types. However, its significant toxicity profile illustrates the challenge of defining more precisely the patients unlikely to benefit from it, sparing them from useless toxicities. FDG-PET/CT can identify treatment-refractory disease with high negative predictive value, soon after the treatment onset and before morphological changes are observed. MiMe-A was built on the assumption that a therapy that does not induce tumoral metabolic changes 14 days after its onset is unlikely to achieve a significant clinical benefit.
OBJECTIVES	**Primary objective**: To evaluate the anti-tumour activity of abemaciclib in the five tumour types studied in this trial using the combination of FDG-PET/CT during the first

	cycle of therapy (early FDGPET/CT) and RECIST v1.1 after 2 cycles of therapy as a screening tool. **Secondary objective**: In each tumour type population: • To evaluate Progression-free survival (PFS define as the time from treatment start until disease progression or death) and Overall Survival (OS defined as the time from treatment start until death) at 24 weeks from treatment start • To evaluate median progression-free survival (PFS) and median overall survival (OS) • To evaluate safety/toxicity profile • To evaluate the correlation of early metabolic response using FDG-PET/CT with morphological response to treatment assessed by RECIST
ENDPOINTS	**Primary endpoint:** Therapy success rate defined as: • PERCIST 15%-assessed Metabolic Response at early FDG-PET/CT (D12-D16) and • RECIST v1.1-assessed Disease Control (DC) after 2 treatment cycles (CR or PR or SD) **Secondary endpoints:** In each tumour type population: • RECIST v1.1-based radiological response assessment performed at 24 weeks from the treatment start to determine the PFS and OS. • Progression Free Survival • Overall Survival • Safety/Toxicity profile according to CTCAE version 5.0
INCLUSION CRITERIA	1. Age ≥ 18 years old 2. Female or male 3. ECOG performance status ≤ 1 4. Life expectancy of greater than 12 weeks 5. Must have histologically confirmed cancer corresponding to the predefined tumour subtypes (esophageal adenocarcinoma, esophageal squamous cell carcinoma, cholangiocarcinoma, urothelial cancer (progressive after immunotherapy;), endometrial cancer) that are metastatic or non-resectable and progressive after standard a platinum regimens (with any delay) and progressive after immunotherapy for the urothelial cancer (if available) and hormonotherapy for endometrial carcinoma hormonal receptors postives (if indicated). 6. Presence of at least one metabolically measurable tumour lesion on FDG-PET/CT, according to PERCIST. If previously irradiated, must have been more than 2 months before the baseline FDG PET/CT. 7. Measurable disease according to RECIST v 1.1 8. Negative serum pregnancy test (for subjects of childbearing potential)

	9. Women of childbearing potential must agree to the use of 1 highly effective method of contraception (see protocol section 6.3.1.) prior to study entry, during the course of the study and at least 3 months after the last administration of study treatment. 10. Men with childbearing potential partner must agree to use a condom during the course of this study and for at least 3 months after the last administration of the study treatment. 11. Adequate coagulation: International Normalized Ratio (INR) ≤ 1.5 x UNL unless subject is receiving anticoagulant therapy as long as INR and activated partial thromboplastin time [aPTT] are within therapeutic range of intended use of anticoagulants. 12. Adequate bone marrow function as defined below: • Hemoglobin ≥ 10 g/dL • Absolute neutrophil count ≥ 1500/µL or $1.5x10^9$/L • Platelets ≥ 100000/µL or $100x10^9$/L • Leukocytes ≥ 3,000/µL 13. Adequate liver function as defined below: • Serum total bilirubin within 1.5 × normal institutional limits (except for Gilbert syndrome where direct bilirubin should be <1.5 x institutional UNL) • AST/ALT/ALP) levels < 3 × institutional upper normal limit (or ALT and AST <5 x upper limit of normal if liver metastases are present). 14. Adequate renal function as defined below: Cockcroft-Gault creatinine clearance >50ml/min 15. Completion of all necessary screening procedures 16. Ability to swallow capsules/tablets 17. Grade ≤ 1 toxicity due to any previous cancer therapy according to the National Cancer Institute Common Terminology Criteria of Adverse Events (NCI-CTCAE, v.5.0). Grade 2 is allowed in case of alopecia and peripheral sensory neuropathy 18. If primary archived tumour tissue block available, it must be provided. (1 FFPE tumour tissue or 20 unstained slides freshly cut for the study purposes) 19. Signed Informed Consent form (ICF) obtained prior to any study related procedure. **Inclusion criterion applicable to FRANCE only** 20. Affiliated to the French Social Security System
EXCLUSION CRITERIA	Subjects meeting one of the following criteria were not eligible for this study: 1. Have had chemotherapy, radiotherapy, immunotherapy, or targeted therapy within 3 weeks prior study enrolment 2. Receiving concomitantly any other experimental agents 3. Have received prior therapy with other CDK4/6 inhibitors

	4. Known brain metastasis; unless the metastasis are asymptomatic and have been stable since at least 2 months prior to treatment start 5. Known meningeal carcinomatosis 6. Have had major surgery within 28 days prior to the start of the treatment to allow for post-operative healing of the surgical wound 7. History of allergic reactions attributed to compounds of similar chemical or biologic composition 8. Bleeding diathesis, thromboembolic event, history of cardiovascular ischemic disease or cerebrovascular incident within the last six months 9. Uncontrolled concurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, severe dyspnea at rest or requiring oxygen therapy. 10. Substance abuse, psychiatric illness/social situations, any psychological, familial, sociological, geographical condition, significant medical or surgical condition currently uncontrolled by treatment that would limit compliance with study requirements or interfere with the patient's ability to understand informed consent and participation in the study 11. Pregnant and/or lactating women 12. Uncontrolled Diabetes 13. Known history of HIV infection, or active hepatitis B or C requiring treatment with anti-viral therapy 14. Have received recent (within 28 days prior the enrolment) yellow fever vaccination 15. Individuals with a history of a different malignancy are ineligible except for the following circumstances. Individuals with a history of other malignancies are eligible if they have been disease-free and are deemed by the investigator to be at low risk for recurrence of that malignancy **Exclusion criterion applicable to FRANCE only** 16. Vulnerable persons according to the article L.1121-6 of the CSP, adults who are the subject of a measure of legal protection or unable to express their consent according to article L.1121-8 of the CSP
INVESTIGATIONAL MEDICINAL PRODUCTS	Abemaciclib was continuously administrated orally at a dose of 150 mg twice daily until disease progression, until new lesions are observed at the early FDG-PET/CT, until the lack of tolerability or the subject 's consent withdrawal. One cycle is 28 days.
INDICATION OF USE	• Esophageal adenocarcinoma (ADC) • Esophageal squamous cell carcinoma (SCC) • Cholangiocarcinoma • Urothelial cancer (progressive after immunotherapy) • Endometrial cancer
TARGETED POPULATION	Participants must have histologically confirmed cancer corresponding to the predefined tumour cohorts (i.e. esophageal ADC, esophageal SCC,

	Cholangiocarcinoma, urothelial cancer (progressive after immunotherapy), or endometrial cancer) that was metastatic or unresectable and for which standard platinum regimens were no longer effective. Subjects with urothelial cancer must have been pre-treated with nivolumab or another immune checkpoint inhibitor.
PARTICIPATING COUNTRIES	Belgium and France
PARTICIPATING SITES NUMBER	Belgium: 6 France: 5
START DATE OF THE TRIAL	24/09/2018
LENGTH OF THE STUDY	• Actual start date of recruitment to the protocol: 19/12/2018 • Actual date stop date of recruitment to the protocol: 15/09/2021 • Long term follow-up planned? Yes for efficacy– Duration: 18 months
INDEPENDENT DATA MONITORING COMMITTEE	Yes
PROTECTION OF TRIAL SUBJECTS	Both dose suppression (within a cycle) and cycle delay are permitted in case of clinically significant toxicities. Abemaciclib may be held up to 14 days within a cycle or at the start of next cycle to permit sufficient time recovery from the toxicity. If a dose suspension occurs, the investigator may resume abemaciclib dosing at the same dose level for the remainder of the cycle or at reduced dose (assuming resolution to at least grade 1 for the non-hematological and at least grade 2 for hematological toxicity). If the subject experiences the same toxicity with the same or greater severity requiring a dose suspension within a cycle or at start of the next cycle, the subject must be dose reduced and non rechallenged a second time at the prior dose level. Subject not recovering from toxicity within 14 days should be considered for discontinuation of abemaciclib. In exceptional circumstances, a delay > 14 days is permitted upon agreement of the Investigator and the Sponsor. Subjects who were taking strong CYP3A inhibitors were recommended to reduce the abemaciclib dose. Very close monitoring of side effects was organized (for example medical visit after 10 days of taking abemaciclib) in order to adapt supportive treatments and doses of abemaciclib in the event of side effects.
ANALYSIS STAGE & DATE	Final Date of final analysis: 21/11/2023

PRIMARY COMPLETION DATA	• Is this the analysis of the primary completion data? Yes • Primary completion date: 12/11/2021
GLOBAL END OF TRIAL DATE	• Global end of trial reached? Yes • Global end of trial date: 20/12/2023
PREMATURE END OF TRIAL	No

2 POPULATION OF TRIAL SUBJECTS

The number of subjects enrolled in the MiMe-A trial per country is:

Country	Number of subjects
Belgium	62
France	23

The number of subjects enrolled per age is displayed in the below table.

Age of subjects	Number of subjects
In utero	-
Preterm newborn - gestational age <37 wk	-
Newborns (0-27 days)	-
Infants and toddlers (28 days - 23 months)	-
Children (2-11 years)	-
Adolescents (12-17 years)	-
Adults (between 18 and 64 years)	26 (30.6%)
From 65 to 84 years	57 (67.1%)
85 years and over	2 (2.4%)

The baseline characteristics of the population are further described in section 4.

3 SUBJECT DISPOSITION

Period	1
Period title	Overall study (overall period)
Allocation method	Non-randomised - controlled
Blinding	Not applicable

3.1 Arms information and IMP information

- Are the arms mutually exclusive? Yes

ARM INFORMATION	
Arm title	Cohort 1: Esophageal adenocarcinoma
Arm description	Subjects with histologically confirmed esophageal adenocarcinoma that is metastatic or unresectable and for which standard platinum regimens are no longer effective.
Arm type	Experimental
IMP INFORMATON	
IMP name	Abemaciclib
Route of administration	Oral use
Pharmaceutical form	Capsule
Dosage and administration details	Abemaciclib will be continuously administrated orally at a dose of 150mg twice daily until disease progression, until new lesions are observed at the early FDG-PET/CT, until the lack of tolerability or the subject 's consent withdrawal. One cycle is 28 days.

ARM INFORMATION	
Arm title	Cohort 2: Esophageal squamous cell carcinoma
Arm description	Subjects with histologically confirmed esophageal squamous cell carcinoma that is metastatic or unresectable and for which standard platinum regimens are no longer effective.
Arm type	Experimental
IMP INFORMATON	
IMP name	Abemaciclib
Route of administration	Oral use
Pharmaceutical form	Capsule
Dosage and administration details	Abemaciclib will be continuously administrated orally at a dose of 150mg twice daily until disease progression, until new lesions are observed at the early FDG-PET/CT, until the lack of tolerability or the subject 's consent withdrawal. One cycle is 28 days.

ARM INFORMATION	
Arm title	Cohort 3: Cholangiocarcinoma
Arm description	Subjects with histologically confirmed cholangiocarcinoma that is metastatic or unresectable and for which standard platinum regimens are no longer effective.
Arm type	Experimental
IMP INFORMATON	
IMP name	Abemaciclib
Route of administration	Oral use
Pharmaceutical form	Capsule
Dosage and administration details	Abemaciclib will be continuously administrated orally at a dose of 150mg twice daily until disease progression, until new lesions are observed at the early FDG-PET/CT, until the lack of tolerability or the subject 's consent withdrawal. One cycle is 28 days.

ARM INFORMATION	
Arm title	Cohort 4: Urothelial cancer
Arm description	Subjects with histologically confirmed urothelial cancer that is metastatic or unresectable and for which standard platinum regimens are no longer effective. Subjects must have been pre-treated with nivolumab or another immune checkpoint inhibitor.
Arm type	Experimental
IMP INFORMATON	
IMP name	Abemaciclib
Route of administration	Oral use
Pharmaceutical form	Capsule
Dosage and administration details	Abemaciclib will be continuously administrated orally at a dose of 150mg twice daily until disease progression, until new lesions are observed at the early FDG-PET/CT, until the lack of tolerability or the subject 's consent withdrawal. One cycle is 28 days.

ARM INFORMATION	
Arm title	Cohort 5: Endometrial cancer
Arm description	Subjects with histologically confirmed endometrial cancer a that is metastatic or unresectable and for which standard platinum regimens are no longer effective.
Arm type	Experimental
IMP INFORMATON	
IMP name	Abemaciclib
Route of administration	Oral use
Pharmaceutical form	Capsule
Dosage and administration details	Abemaciclib will be continuously administrated orally at a dose of 150mg twice daily until disease progression, until new lesions are observed at the early FDG-PET/CT, until the lack of tolerability or the subject 's consent withdrawal. One cycle is 28 days.

3.2 Number of subjects in period

In this trial, subjects who stopped the treatment for disease progression are considered as subjects who completed the arm. The detail of abemaciclib administration is described in Section 5.1.

Cohort 1: Esophageal adenocarcinoma	
Started	18
Completed	11*
Not completed	7
Reason for non-completion	
Adverse event, not serious	1
Adverse event, serious fatal	1
Adverse event, serious non-fatal	1
Consent withdrawn by subject	3
Physician decision	0
Subject non-compliant (not eligible)	1**

Cohort 2: Esophageal squamous cell carcinoma	
Started	17
Completed	14*

Cohort 2: Esophageal squamous cell carcinoma	
Not completed	3
Reason for non-completion	
Adverse event, not serious	0
Adverse event, serious fatal	2
Adverse event, serious non-fatal	1
Consent withdrawn by subject	0
Physician decision	0
Other (specify)	0

Cohort 3: Cholangiocarcinoma	
Started	17
Completed	15*
Not completed	2
Reason for non-completion	
Adverse event, not serious	0
Adverse event, serious fatal	1
Adverse event, serious non-fatal	1
Consent withdrawn by subject	0
Physician decision	0
Other (specify)	0

Cohort 4: Urothelial cancer	
Started	17***
Completed	16*
Not completed	1
Reason for non-completion	
Adverse event, not serious	0
Adverse event, serious fatal	0
Adverse event, serious non-fatal	1
Consent withdrawn by subject	0
Physician decision	0

Cohort 4: Urothelial cancer	
Other (specify)	0

Cohort 5: Endometrial cancer	
Started	17
Completed	16*
Not completed	1
Reason for non-completion	
Adverse event, not serious	0
Adverse event, serious fatal	0
Adverse event, serious non-fatal	1
Consent withdrawn by subject	0
Physician decision	0
Other (specify)	0

* All subjects who completed had disease progressions and stopped the treatment.
** One subject in esophageal adenocarcinoma cohort did not start the treatment (non-compliant) and considered non-eligible.
***One subject in urothelial cancer cohort did not start the treatment since had a disease progression on Day 1 Cycle 1 (D1C1).

4 BASELINE CHARACTERISTICS

Reporting group title	Cohort 1: Esophageal adenocarcinoma
Reporting group description	Subjects with histologically confirmed esophageal adenocarcinoma that is metastatic or unresectable and for which standard platinum regimens are no longer effective.
Reporting group title	Cohort 2: Esophageal squamous cell carcinoma
Reporting group description	Subjects with histologically confirmed esophageal squamous cell carcinoma that is metastatic or unresectable and for which standard platinum regimens are no longer effective.
Reporting group title	Cohort 3: Cholangiocarcinoma
Reporting group description	Subjects with histologically confirmed cholangiocarcinoma that is metastatic or unresectable and for which standard platinum regimens are no longer effective.
Reporting group title	Cohort 4: Urothelial cancer
Reporting group description	Subjects with histologically confirmed urothelial cancer that is metastatic or unresectable and for which standard platinum regimens are no longer effective. Subjects must have been pre-treated with nivolumab or another immune checkpoint inhibitor.
Reporting group title	Cohort 5: Endometrial cancer
Reporting group description	Subjects with histologically confirmed endometrial cancer a that is metastatic or unresectable and for which standard platinum regimens are no longer effective.

	Cohort 1: Esophageal adenocarcinoma	Cohort 2: Esophageal squamous cell carcinoma	Cohort 3: Cholangiocarcinoma	Cohort 4: Urothelial cancer	Cohort 5: Endometrial cancer	All cohorts
Number of eligible subjects						
	17	17	17	17	17	85
Age						
Units : Years						
N	17	17	17	17	17	85
Mean	62.4	67.3	70.2	65.8	68.9	66.9
SD	11.64	5.84	8.66	8.66	7.41	8.88
Range	36.0, 83.0	56.0, 77.0	50.0, 85.0	46.0, 80.0	57.0, 84.0	36.0, 85.0
Median (IQR)	65.0 (55.0, 68.0)	67.0 (63.0, 71.0)	70.0 (67.0, 74.0)	67.0 (63.0, 71.0)	68.0 (64.0, 73.0)	68.0 (62.0, 71.0)
Age categories						
Units: Subjects						
In utero	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Preterm newborn - gestational age <37 wk	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Newborns (0-27 days)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Infants and toddlers (28 days - 23 months)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

	Cohort 1: Esophageal adenocarcinoma	Cohort 2: Esophageal squamous cell carcinoma	Cohort 3: Cholangiocarcinoma	Cohort 4: Urothelial cancer	Cohort 5: Endometrial cancer	All cohorts
Children (2-11 years)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Adolescents (12-17 years)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Adults (between 18 and 64 years)	8 (47.1%)	5 (29.4%)	3 (17.6%)	5 (29.4%)	5 (29.4%)	26 (30.6%)
From 65 to 84 years	9 (52.9%)	12 (70.6%)	12 (70.6%)	12 (70.6%)	12 (70.6%)	57 (67.1%)
85 years and over	0 (0.0%)	0 (0.0%)	2 (11.8%)	0 (0.0%)	0 (0.0%)	2 (2.4%)
Gender						
Units: Subjects						
Female	3 (17.6%)	6 (35.3%)	11 (64.7%)	2 (11.8%)	17 (100.0%)	39 (45.9%)
Male	14 (82.4%)	11 (64.7%)	6 (35.3%)	15 (88.2%)	0 (0.0%)	46 (54.1%)
ECOG						
Units: Subjects						
0	7 (41.2%)	6 (35.3%)	5 (29.4%)	6 (35.3%)	10 (58.8%)	34 (40.0%)
1	10 (58.8%)	11 (64.7%)	12 (70.6%)	11 (64.7%)	7 (41.2%)	51 (60.0%)
BMI						
Units: Kg/m^2						
N	17	16	16	17	16	82
Mean	23.7	22.6	25.1	23.8	28.0	24.6

	Cohort 1: Esophageal adenocarcinoma	Cohort 2: Esophageal squamous cell carcinoma	Cohort 3: Cholangiocarcinoma	Cohort 4: Urothelial cancer	Cohort 5: Endometrial cancer	All cohorts
SD	5.27	3.84	5.03	4.27	8.13	5.67
Range	16.1, 32.4	18.1, 30.5	17.8, 36.4	18.8, 36.8	18.6, 47.4	16.1, 47.4
Median (IQR)	23.4 (19.1, 27.8)	21.6 (19.3, 25.8)	23.7 (22.1, 28.5)	23.2 (21.1, 25.4)	26.1 (22.3, 30.9)	23.6 (20.4, 27.4)
BMI Categories						
Units: Subjects						
Underweight	4 (23.5%)	2 (11.8%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	7 (8.2%)
Normal	7 (41.2%)	9 (52.9%)	9 (52.9%)	12 (70.6%)	7 (41.2%)	44 (51.8%)
Overweight	3 (17.6%)	4 (23.5%)	3 (17.6%)	4 (23.5%)	4 (23.5%)	18 (21.2%)
Obese	3 (17.6%)	1 (5.9%)	3 (17.6%)	1 (5.9%)	5 (29.4%)	13 (15.3%)
Not available (NA)	0 (0.0%)	1 (5.9%)	1 (5.9%)	0 (0.0%)	1 (5.9%)	3 (3.5%)
Previous radiotherapy						
Units: Subjects						
Yes	8 (47.1%)	15 (88.2%)	4 (23.5%)	5 (29.4%)	11 (64.7%)	43 (50.6%)
No	9 (52.9%)	2 (11.8%)	13 (76.5%)	12 (70.6%)	6 (35.3%)	42 (49.4%)
Previous surgery						
Units: Subjects						
Yes	6 (35.3%)	4 (23.5%)	12 (70.6%)	13 (76.5%)	15 (88.2%)	50 (58.8%)
No	11 (64.7%)	13 (76.5%)	5 (29.4%)	4 (23.5%)	2 (11.8%)	35 (41.2%)

	Cohort 1: Esophageal adenocarcinoma	Cohort 2: Esophageal squamous cell carcinoma	Cohort 3: Cholangiocarcinoma	Cohort 4: Urothelial cancer	Cohort 5: Endometrial cancer	All cohorts
Previous chemotherapy						
Units: Subjects						
Yes	17 (100.0%)	17 (100.0%)	17 (100.0%)	17 (100.0%)	17 (100.0%)	85(100.0%)
No	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Previous hormone therapy						
Units: Subjects						
Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (52.9%)	9 (10.6%)
No	17 (100.0%)	17 (100.0%)	17 (100.0%)	17 (100.0%)	8 (47.1%)	76 (89.4%)
Previous immuno therapy						
Units: Subjects						
Yes	6 (35.3%)	2 (11.8%)	1 (5.9%)	16 (94.1%)	3 (17.6%)	28 (32.9%)
No	11 (64.7%)	15 (88.2%)	16 (94.1%)	1 (5.9%)	14 (82.4%)	57 (67.1%)
Previous targeted therapy						
Units: Subjects						
Yes	6 (35.3%)	1 (5.9%)	0 (0.0%)	5 (29.4%)	0 (0.0%)	12 (14.1%)
No	11 (64.7%)	16 (94.1%)	17 (100.0%)	12 (70.6%)	17 (100.0%)	73 (85.9%)

5 STATISTICAL ANALYSIS

The first subject (0001) was recruited on 31 Dec 2018 and the last subject (0099) was recruited on 21 September 2021. One subject in Esophageal adenocarcinoma cohort was considered not eligible as the subject never started the treatment. Other deviations from the inclusion or exclusion criteria were considered tolerable by the study investigators. The baseline characteristics of each cohort can be found in section 4.

5.1 Abemaciclib administration summary

	Cohort 1: Esophageal adenocarcinoma	**Cohort 2: Esophageal squamous cell carcinoma**	**Cohort 3: Cholangiocarcinoma**	**Cohort 4: Urothelial cancer**	**Cohort 5: Endometrial cancer**
Started treatment	17 (100.0%)	17 (100.0%)	17 (100.0%)	16 (94.1%)*	17 (100.0%)
Started and stopped treatment during the 1st cycle	5 (29.4%)	3 (17.7%)	3 (17.7%)	0 (0.0%)	2 (11.8%)
-Adverse event (AE):	2 (11.8%)	1 (5.9%)	1 (5.9%)	0 (0.0%)	0 (0.0%)
AE, not serious	1 (5.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
AE, serious	1 (5.9%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)
AE, fatal	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
-Progressive disease	1 (5.9%)	2 (11.8%)	2 (11.8%)	0 (0.0%)	2 (11.8%)
-Subject's withdrawal	2 (11.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Stopped treatment during the 2nd cycle	2 (11.8%)	1 (5.9%)	2 (11.8%)	3 (17.6%)	1 (5.9%)

	Cohort 1: Esophageal adenocarcinoma	Cohort 2: Esophageal squamous cell carcinoma	Cohort 3: Cholangiocarcinoma	Cohort 4: Urothelial cancer	Cohort 5: Endometrial cancer
- Adverse event (AE):	0 (0.0%)	1 (5.9%)	1 (5.9%)	0 (0.0%)	0 (0.0%)
AE, not serious	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
AE, serious	0 (0.0%)	1 (5.9%)	0 (0.0%)	1 (5.9%)	0 (0.0%)
AE, fatal	0 (0.0%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)
- Progressive disease	1 (5.9%)	0 (0.0%)	1 (5.9%)	2 (11.8%)	1 (5.9%)
- Subject's withdrawal/Other	1 (5.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Stopped treatment after the 2nd cycle	10 (58.8%)	13 (82.4%)	12 (70.6%)	13 (82.4%)	1 (5.9%)
- Adverse event (AE):	1 (5.9%)	1 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)
AE, not serious	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
AE, serious	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)
AE, fatal	1 (5.9%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
- Progressive disease	9 (52.9%)	12 (70.6%)	12 (70.6%)	13 (82.4%)	13 (82.4%)
- Subject's withdrawal	0 (0.0%)	0 (0.0%)	0 (0.0%)	(0.0%)	(0.0%)
Total treatment duration (days)					
N	16**	17	17	17	17
Mean	66.3	57.5	81.5	114.1	86.6
SD	59.21	37.20	75.82	148.84	103.28

	Cohort 1: Esophageal adenocarcinoma	Cohort 2: Esophageal squamous cell carcinoma	Cohort 3: Cholangiocarcinoma	Cohort 4: Urothelial cancer	Cohort 5: Endometrial cancer
Range	2.0, 232.0	10.0, 140.0	14.0, 259.0	0.0*, 513.0	14.0, 443.0
Median (IQR)	56.0 (27.5, 73.5)	53.0 (28.0, 62.0)	53.0 (27.0, 132.0)	55.0 (38.0, 95.0)	55.0 (43.0,76.0)
Total Nb of Cycles					
N	17	17	17	17	17
Mean	2.6	2.4	3.4	4.8	3.5
SD	2.12	1.46	2.67	5.45	3.69
Range	1.0, 9.0	1.0, 6.0	1.0, 10.0	0.0*, 19.0	1.0, 16.0
Median (IQR)	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	2.0 (2.0, 5.0)	3.0 (2.0, 4.0)	2.0 (2.0, 3.0)
At least one dose reduction during cycle 1 and 2* **					
- Adverse Events	2 (11.8%)	10 (58.8%)	14 (82.4%)	6 (35.3%)	13 (76.5%)
- Non Compliance or Dosing Error	4 (23.5%)	2 (11.8%)	4 (23.5%)	3 (17.6%)	4 (23.5%)
- Either due to AE or Non Compliance or Dosing Error	5 (29.4%)	12 (70.6%)	14 (82.4%)	8 (47.1%)	14 (82.4%)
At least one trt interruption during cycle 1 and 2					
- Adverse Events	6 (35.3%)	11 (64.7%)	14 (82.4%)	14 (82.4%)	10 (58.8%)
- Non Compliance	2 (11.8%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

	Cohort 1: Esophageal adenocarcinoma	Cohort 2: Esophageal squamous cell carcinoma	Cohort 3: Cholangiocarcinoma	Cohort 4: Urothelial cancer	Cohort 5: Endometrial cancer
- Either due to AE or Non Compliance or Dosing Error	6 (35.3%)	12 (70.6%)	14 (82.4%)	14 (82.4%)	10 (58.8%)
RDI for cycle 1 and 2****					
N	16***	17	17	17	17
Mean	70.7	64.5	62.2	64.5	68.7
SD	34.08	24.69	26.65	30.25	23.64
Range	3.6, 100.0	17.9, 100.0	20.3, 94.9	0.0*, 98.2	24.1, 100.0
Median (IQR)	85.0 (45.6, 99.6)	76.5 (49.1, 83.3)	73.0 (38.1, 82.1)	75.0 (59.2, 85.7)	76.6 (52.2, 84.4)

*One subject in cohort urothelial cancer cohort stopped treatment due to disease progression at Day 1 Cycle 1 (D1C1). This subject is considered eligible.
**One subject withdrew his consent during cycle 1 and did not return his dosing diary, therefore there is no information on the exact end of treatment date
*** One subject withdrew his consent during cycle 1 and did not return his dosing diary, therefore there is no information on the exact end of treatment date
****RDI is calculated by (total dose for cycle 1 and cycle 2)/(max dose for cycle 1 and cycle 2* 56). Maximum dose is 400 mg for subjects starting their treatment by 1/10/2022 and 300 mg afterwards except for four subjects who had 400 mg despite starting after 1/10/2019.

5.2 Metabolic assessment summary

	Cohort 1: Esophageal adenocarcinoma	Cohort 2: Esophageal squamous cell carcinoma	Cohort 3: Cholangiocarcinoma	Cohort 4: Urothelial cancer	Cohort 5: Endometrial cancer
Delay from baseline PET to D1C1 (Day 1 of Cycle 1) (days)					
N	17	17	17	16*	17
Mean	4.2	4.9	3.4	4.1	4.6
SD	2.33	2.12	1.80	2.36	2.00
Range	1.0, 7.0	1.0, 7.0	1.0, 7.0	1.0, 7.0	2.0, 8.0**

	Cohort 1: Esophageal adenocarcinoma	Cohort 2: Esophageal squamous cell carcinoma	Cohort 3: Cholangiocarcinoma	Cohort 4: Urothelial cancer	Cohort 5: Endometrial cancer
Median (IQR)	5.0 (2.0, 7.0)	6.0 (4.0, 6.0)	3.0 (2.0, 5.0)	5.5 (1.0, 6.0)	4.0 (3.0, 6.0)
Delay from D1C1 to 2nd PET (days)					
N	15	16	15	15	16
Mean	13.3	13.0	13.2	13.3	13.6
SD	1.35	1.71	1.01	1.11	0.96
Range	11.0, 15.0***	10.0, 17.0	12.0, 15.0***	11.0, 15.0***	12.0, 15.0***
Median (IQR)	14.0 (12.0, 14.0)	13.0 (12.0, 14.0)	13.0 (12.0, 14.0)	13.0 (13.0, 14.0)	14.0 (13.0, 14.0)
2nd PET done (Y=Yes, N=No), n (%)					
N	2 (11.8%)	1 (5.9%)	2 (11.8%)	2 (11.8%)	1 (5.9%)
Y	15 (88.2%)	16 (94.1%)	15 (88.2%)	15 (88.2%)	16 (94.1%)
	One subject withdrew after 2 days of treatment; Another subject stopped trt after 12 days due to AE Renal Insufficiency	One subject died from sepsis before PET	One subject interrupted trt from C1D8 until C1D22 because of an AE; Another subject stopped trt early due to AE	One subject stopped trt due to disease progression bfr PET Another subject had trt interruption btw d13c1 and d22c1	One subject baseline FDG-PET/CT scan not evaluable, C1D12-16 FDG-PET/CT scan not done
Missing dose in 5 days that precedes 2nd PET (Y=Yes, N=No), n (%)	1	0	2****	1	2

	Cohort 1: Esophageal adenocarcinoma	Cohort 2: Esophageal squamous cell carcinoma	Cohort 3: Cholangiocarcinoma	Cohort 4: Urothelial cancer	Cohort 5: Endometrial cancer
	One subject treatment not given on 7-8 January due to prosthesis placement. 2nd PET was done but considered not evaluable		The two subjects missed one and two doses before PET but considered as PERCIST evaluable	One subject stopped trt at D8C1 (Day 8 of cycle 1) due to adverse event= acute kidney injury	For one subject, the PET/CT scan done in the correct time window on 07/05/19 but no abemaciclib was administered between 02/05/19 am and 04/05/2019 pm For another subject, the PET/CT done in the correct time window on 24/07/19, but no abemaciclib was administrated on 21, 22 and 23/07
2nd PET done but no lesion found	0	0	0	1	0
				One subject had PET done but no lesion found	
Nb pts with 2nd PET done, and no missing dose 5 days bfr PET	14	16	15	13	14

D1C1 = first day of first cycle
* One subject stopped treatment due to disease progression at D1C1
** One subject had 8-day delay between baseline PET and treatment start.
***The number of days between treatment start and 2nd PET was 10 days for one subject in cohort SCC; 11 days for two subjects in cohort ADC, one subject in cohort URO, and two subjects in cohort SCC; 17 days for one subject in cohort SCC.
****Two subjects missed one and two doses before PET but considered as PERCIST evaluable

5.3 Efficacy analysis

An interim analysis was performed on each tumour cohort in the first stage, which includes the first 13 evaluable subjects in each cohort. Based on the protocol, if there are 2 or less subjects with treatment success in these 13 evaluable subjects in a specific cohort then the accrual in that cohort will be stopped. If there are 3 or more subjects with treatment success, then the trial will continue to the second stage.

The minimal 3 subjects with overall success results out of the first 13 evaluable subjects was not reached for all 5 cohorts, therefore the accruals in all the cohorts were stopped after the interim assessment. The detail information on the interim analysis are presented below.

5.3.1 Metabolic response (PERCIST) assessment

RESPONSE CATEGORY	**Cohort 1: Esophageal adenocarcinoma**	**Cohort 2: Esophageal squamous cell carcinoma**	**Cohort 3: Cholangiocarcinoma**	**Cohort 4: Urothelial cancer**	**Cohort 5: Endometrial cancer**
Complete Metabolic Response	0	0	0	0	0
Partial Metabolic Response	2	5	1	0	2
Stable Metabolic Disease	8	6	5	8	7
Progressive Metabolic Disease	4	5	9	6	4
PERCIST results available	14	16	15	14	13
Not evaluable*	3	1	2	3	4
Percent Complete or Partial Metabolic Response in the population (95%CI Exact)	11.8% (1.5%,36.4%)	29.4% (10.3%,56.0%)	5.9% (0.1%,28.7%)	0% (0%,19.5%)	11.8% (1.5%,36.4%)

* A subject is considered "not evaluable" for PERCIST when 2nd PET is not done, no lesion found for 2nd PET, or this subject had treatment interruption before the 2nd PET.

5.3.2 Response evaluation by RECIST

A treatment is considered a failure based on RECIST when the overall response of RECIST evaluation shows progressive disease (PD), or this subject had stopped the treatment due to clinical PD, adverse event, or withdrawal from the study before RECIST evaluation.

	Cohort 1: Esophageal adenocarcinoma	**Cohort 2: Esophageal squamous cell carcinoma**	**Cohort 3: Cholangiocarcinoma**	**Cohort 4: Urothelial cancer**	**Cohort 5: Endometrial cancer**
Never start a treatment	0	0	0	0	0
	Evaluation done during 1st abemaciclib cycle				
-Stop treatment due to clinically documented progression, no RECIST	1	2	2	1°	2
-Stop treatment due to adverse event, no RECIST	2*	1 §	1**	0	0
-Subject's withdrawal, no RECIST	2	0	0	0	0
-Early progression, RECIST done	0	0	0	1°	0

-Adverse event, RECIST done	0	0	0	1°°	0
	Evaluation done during 2nd abemaciclib cycle				
- No RECIST assessment, only clinically documented progression	1	0	1	0	1
- Stop treatment due to adverse event, no RECIST	0	0	1***	0	0
- Subject's withdrawal, no RECIST	1	0	0	0	0
- Nb of days btw first RECIST and end of cycle 2					
Median	3.5	4.0	4.0	3.0	3.0
Range	-1 - 8	-12 - 6	-10 - 6	-12 - 27	-14 - 7
RECIST Evaluable	10	14	12	16	14
Response on target lesions					
-PR	1	1	0	0	0
-SD	7	5	6	12	7
-PD	2	8	6	4	7
-Missing/Not evaluable	7	3	5	1	3
Response on non target lesions					
-No CR / No PD	5	6	4	9	7
-PD	4	6	4	4	3
-NE / Not assessed	1	2	4	2	0
-Missing	7	3	5	2	7
New lesions					
-Present	1	4	5	5	4
-Absent	9	10	7	10	8
-Missing	7	3	5	2	5
Overall response					
-PR	1	1	0	0	0
-SD	3	2	5	8	5
-PD	6	11	7	8	9
-Not available (Stop treatment)	7	3	5	1	3
Overall response / failure					
-Response	4	3	5	8	5
-Failure	13	14	12	9	12
Percent response (95% CI) of total subjects in the cohort	23.5% (6.8%, 49.9%)	17.6% (5.0%,39.6%)	29.4% (10.3%, 56.0%)	47.1% (23.0%, 72.2%)	29.4% (10.3%, 56.0%)

*One subject had interstitial pneumonitis, another had renal insufficiency
**One subject had a billiary sepsis
***One subject had a pulmonary embolism
§ One subject had an acute respiratory insufficiency
° One subject was included in the study but had a Progressive Disease (PD) on D1C1
°° One subject had an acute kidney injury

5.3.3 Primary endpoint: Overall response (combining PERCIST and RECIST evaluations)

Based on the protocol, a subject is considered evaluable if he/she has a clear treatment success or non-treatment success. Treatment success is defined as when a subject has metabolic response according to PERCIST with a response cut off set at 15% at the early FDG-PET/CT and a morphological disease control after 2 cycles measured by RECIST v1.1 (disease control is defined as complete response (CR), partial response (PR) or stable disease (SD)). As noted above, a treatment is considered

a failure based on RECIST when the overall response of RECIST evaluation shows progressive disease (PD), or this subject had stopped the treatment due to clinical PD, adverse event, or withdrawal from the study before RECIST evaluation. If either PERCIST or RECIST shows a treatment failure for a subject, the treatment will be considered a non-success overall even if other evaluation shows otherwise, not evaluable, or missing. The summary of overall response results by cohort are shown below:

Overall response	Cohort 1: Esophageal adenocarcinoma	Cohort 2: Esophageal squamous cell carcinoma	Cohort 3: Cholangiocarcinoma	Cohort 4: Urothelial cancer	Cohort 5: Endometrial cancer
Nb of Treatment Success	0	0	0	1	0
Nb of Treatment Failure	17	17	17	16	17
Percent of Treatment Success (95% CI) of total subjects in the cohort	0.0% (0.0%, 19.5%)	0.0% (0.0%, 19.5%)	0.0% (0.0%, 19.5%)	5.9% (0.1%, 28.7%)	0.0% (0.0%, 19.5%)

As the minimal 3 subjects with overall success results out of the first 13 evaluable subjects was not reached for all 5 cohorts, therefore the accruals in all the cohorts were stopped after the interim assessment.

The details of the PERCIST and RECIST results by each cohort are reported below:

Cross tabulation of early metabolic response (PERCIST) evaluation by RECIST evaluation:

Cohort 1: Esophageal adenocarcinoma (ADC):

	PERCIST Results				
RECIST Results	PMR	SMD	PMD	Not evaluable°	Total
RECIST success response	0	4	0	0	4
RECIST failure	2	2	2	0	6
RECIST not assessed (Death, PD, or AE) (considered as a RECIST failure)	0	1	1	2	4
RECIST not assessed (Withdrawal)	0	1	1	1	3

(considered as a RECIST failure)					
Total	2	8	4	3	17

PMR= partial metabolic response, SMD=stable metabolic disease, PMD=progressive metabolic disease. °A subject is considered "not evaluable" for PERCIST when 2nd PET is not done, no lesion found for 2nd PET, or this subject had treatment interruption before the 2nd PET.

In blue: 2 subjects' clinical progression before RECIST, 2 AEs before RECIST

In green: subjects' withdrawals before RECIST

In yellow: 2 AEs before PET, 1 withdrawal before PET

There is no subject who has metabolic response according to PERCIST and a disease control based on RECIST (denoted in pink) out of 17 subjects in the ADC cohort.

Cohort 2: Esophageal squamous cell carcinoma (SCC):

	PMR	SMD	PMD	Not evaluable°	Total
RECIST success response	0	2	1	0	3
RECIST failure	5	3	3	0	11
RECIST not assessed (Death, PD, or AE) (considered as a RECIST failure)	0	1	1	1	3
Total	5	6	5	1	17

PMR= partial metabolic response, SMD=stable metabolic disease, PMD=progressive metabolic disease. °A subject is considered "not evaluable" for PERCIST when 2nd PET is not done, no lesion found for 2nd PET, or this subject had treatment interruption before the 2nd PET.

In blue: AE death before PET for one subject, considered as treatment failure

There is no subject who has metabolic response according to PERCIST and a disease control based on RECIST (denoted in pink) out of 17 subjects in the SCC cohort.

Cohort 3: Cholangiocarcinoma (CHO):

	PERCIST Results				
RECIST Results	PMR	SMD	PMD	Not evaluable°	Total
RECIST response	0	2	3	0	5

RECIST failure	1	2	4	0	7
RECIST not assessed (Death, PD, or AE) (considered as a RECIST failure)	0	1	2	2	5
Total	1	5	9	2	17

PMR= partial metabolic response, SMD=stable metabolic disease, PMD=progressive metabolic disease. °A subject is considered "not evaluable" for PERCIST when 2nd PET is not done, no lesion found for 2nd PET, or this subject had treatment interruption before the 2nd PET.

In blue: One subject had clinical progression disease (degradation of general status)

In green: One subject interrupted trt from (Day 8 of Cycle 1) D8C1 until D22C1 (Day 22 of Cycle 1) because of an AE; Another subject stopped trt early due to AE

There is no subject who has metabolic response according to PERCIST and a disease control based on RECIST (denoted in pink) out of 17 subjects in the CHO cohort.

Cohort 4: Urothelial cancer (URO):

	PERCIST results				
RECIST Results	PMR	SMD	PMD	Not evaluable°	Total
RECIST response	1	3	2	2 (*)	8
RECIST failure	1	4	2	1 (**)	8
RECIST not assessed (Death, PD, or AE) (considered as a RECIST failure)	0	0	0	1 (***)	1
Total	2	7	4	4	17

PMR= partial metabolic response, SMD=stable metabolic disease, PMD=progressive metabolic disease. °A subject is considered "not evaluable" for PERCIST when 2nd PET is not done, no lesion found for 2nd PET, or this subject had treatment interruption before the 2nd PET.

In green:

- (*) One subject had stopped treatment on Day 8 of Cycle 1 (D8C1) due to dehydration and acute kidney failure before PET and had SD based on RECIST assessment. This subject is considered an overall non-success. Another subject had treatment interruption between D13C1 and D24C1 before PET, continued the treatment and had SD based on RECIST.

- (**) One subject had no lesion found for PET evaluation, completed the two cycles, and had a PD (presence of a new lesion) based on RECIST. Despite of no result for PET, this subject is considered a RECIST failure and an overall non-success.
- (***) One subject had stopped treatment on Day 3 of Cycle 1 (D3C1) due to clinical PD before PET and RECIST evaluation. This subject is considered an overall non-success.

There is one subject who has metabolic response according to PERCIST and a disease control based on RECIST (denoted in pink) out of 17 subjects in the URO cohort.

Cohort 5: Endometrial Cancer (EDM):

	PERCIST results				
RECIST Results	PMR	SMD	PMD	Not evaluable°	Total
RECIST response	0	3	1	1 (*)	5
RECIST failure	0	5	3	1 (**)	9
RECIST not assessed (Death, PD, or AE) (considered as a RECIST failure)	0	0	2	1 (***)	3
Total	0	8	6	3	17

PMR= partial metabolic response, SMD=stable metabolic disease, PMD=progressive metabolic disease. °A subject is considered "not evaluable" for PERCIST when 2nd PET is not done, no lesion found for 2nd PET, or this subject had treatment interruption before the 2nd PET.

In green : (*) PET scan was not done; (**) missing dose before PET scan; (***) new lesion was found by PET;.

There is no subject who has metabolic response according to PERCIST and a disease control based on RECIST (denoted in pink) out of 17 subjects in the EDM cohort.

5.3.4 Progression-free and overall survival

The progression-free and overall survival assessment should be considered as exploratory, due to lack of number subjects, especially since the accruals were stopped due to futility at the interim analysis.

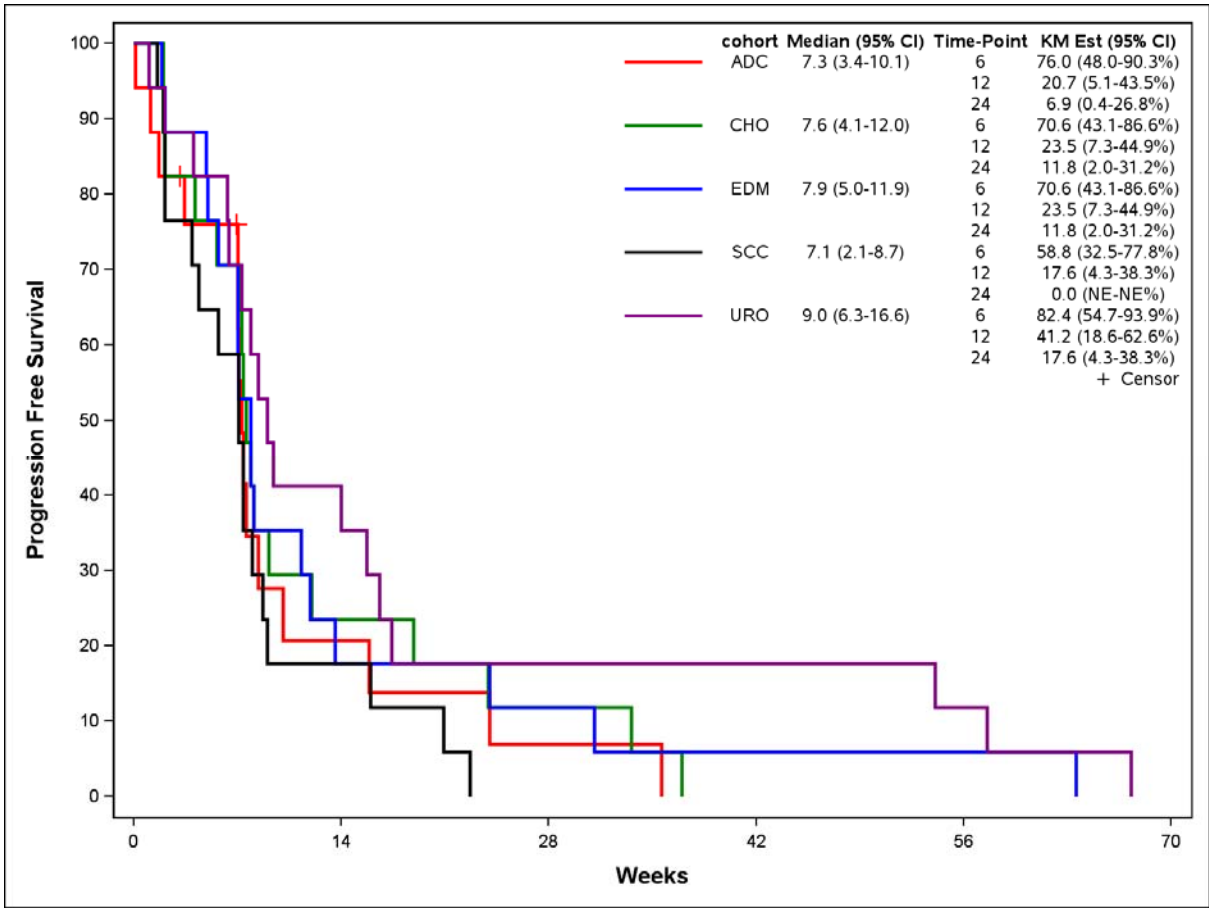
The analysis of progression-free and overall survival applies only to eligible subjects.

Progression-free survival is defined as the time length (number of weeks) from randomization to time of disease progression based on RECIST or treatment discontinuation due to disease progression or death. Subjects' treatment discontinuation due to adverse events or withdrawals are considered as

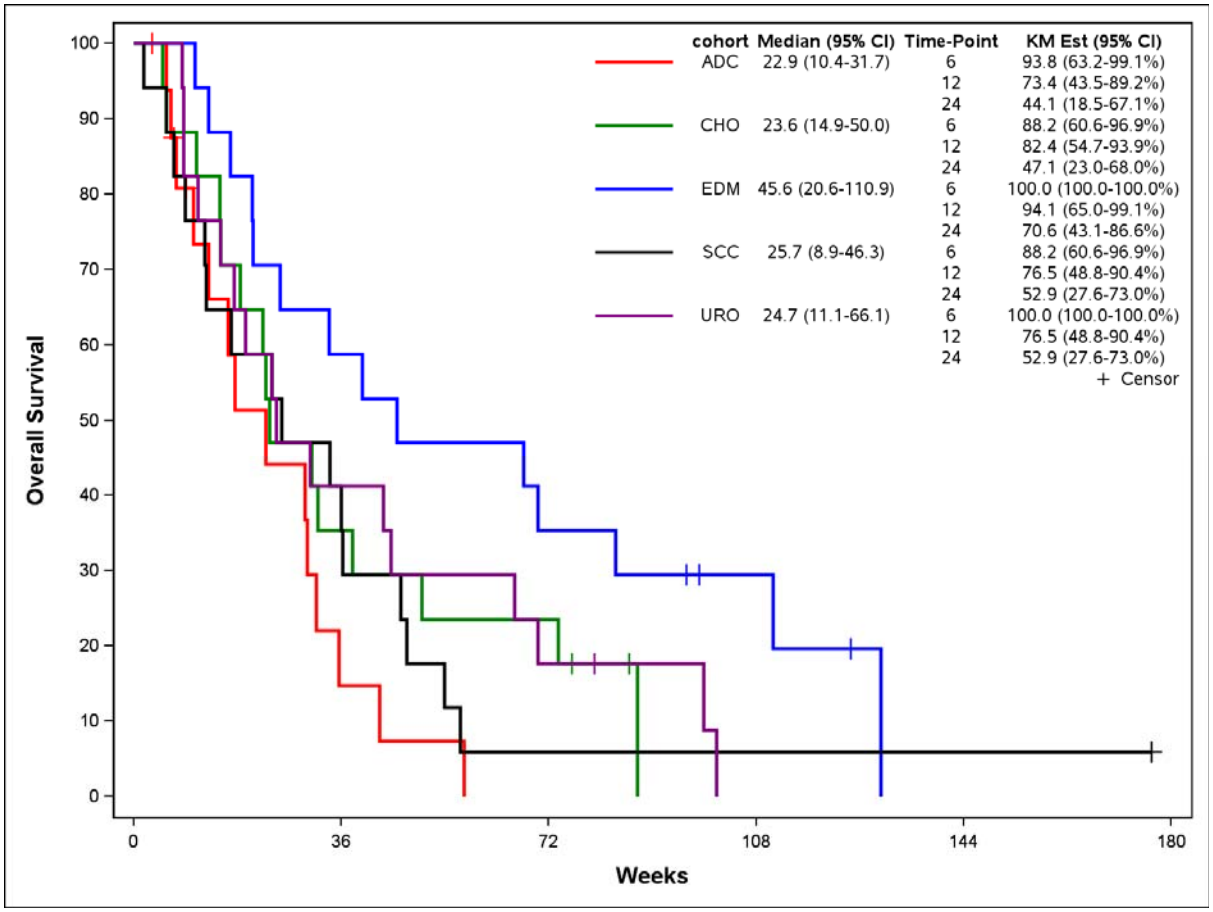
censoring events. If no treatment discontinuations are observed, then the subject is censored at the time of last treatment.

Overall survival is defined as the time length (number of weeks) from randomization to time of death. If no death is observed then the subject is censored at the time of last contact.

The progression-free and overall survival for each cohort are described in the figures below. The Kaplan Meier estimate of survival of 6, 12, and 24 weeks are described in the figures.



Progression-Free Survival by cohort



Overall Survival by cohort

6 ADVERSE EVENTS

6.1 Adverse events information

Non-serious adverse events (AEs) were collected and reported from the first administration of abemaciclib until 28 days after the last administration of abemaciclib.

Serious adverse events (SAEs) related to a protocol-mandated intervention were collected and reported from the Informed Consent Form signature until the initiation of abemaciclib.

All SAEs were collected and reported from the first administration of abemaciclib until 28 days after the last administration of abemaciclib.

From day 29 after the last administration of abemaciclib, SAEs which have a reasonable possibility to be related to abemaciclib (even if the study has been closed)

In the cohort 1: esophageal adenocarcinoma cohort

17 subjects were exposed to the investigational medicinal products.

3 subjects were affected by serious adverse events.

14 subjects were affected by non-serious adverse events.

In the cohort 2: esophageal squamous cell carcinoma cohort

17 subjects were exposed to the investigational medicinal products.

4 subjects were affected by serious adverse events.

16 subjects were affected by non-serious adverse events.

In the cohort 3: cholangiocarcinoma

17 subjects were exposed to the investigational medicinal products.

6 subjects were affected by serious adverse events.

17 subjects were affected by non-serious adverse events.

In the cohort 4: urothelial cancer

17 subjects were exposed to the investigational medicinal products.

6 subjects were affected by serious adverse events.

16 subjects were affected by non-serious adverse events.

In the cohort 5: endometrial cancer

17 subjects were exposed to the investigational medicinal products.

3 subjects were affected by serious adverse events.

16 subjects were affected by non-serious adverse events.

Notes:

1. The adverse event and serious adverse event assessment method was systematic.
2. The MedDRA version used was the version 26.1
3. Exceptions to AEs/SAEs reporting:

Some hospitalisation scenarios do not require reporting as an SAE such as:

- Elective hospitalisation for pre-existing conditions that have not been exacerbated by study medication.
- Hospitalisation planned before the subject consented for study participation and where admission did not take longer than anticipated.
- Hospitalisations for reasons described in the protocol (e.g. hospitalisation for study medication administration, hospitalisation for study related procedures). However, event requiring hospitalisation or prolongation of hospitalisation as a result of a complication of study medication administration or study related procedures is reported as SAE.
- Hospitalisation or prolonged hospitalisation in absence of an AE (social, technical, practical reason and/or convenience admission to a hospital, palliative care, rehabilitation).

Progression of underlying malignancy should not be reported as an AE or SAE if it is clearly consistent with the progression of the underlying cancer but will be reported on the CRF. Unrelated SPM [i.e. a cancer that is unrelated to the study treatment(s) and is not a metastasis from the initial malignancy] should not be reported as an AE or SAE but is to be reported on the CRF on the appropriate form (SPM form).

Hospitalisation due solely to the progression of underlying malignancy should NOT be reported as an SAE.

Clinical symptoms of underlying malignancy under study should not be reported as AEs or SAEs unless the symptoms cannot be determined as exclusively due to the underlying malignancy, or does not fit the expected pattern of the underlying malignancy.

Clinical symptoms of confirmed progression of underlying malignancy should not be reported as AEs or SAEs unless the symptoms cannot be determined as exclusively due to the confirmed progression of the underlying malignancy, or does not fit the expected pattern of confirmed progression for the disease under study.

Deaths related to progression of the underlying disease during the course of the study were not be reported as a SAE, but should be reported on the Death CRF page section (unless the subject has withdrawn consent).

6.2 Serious adverse events

The table hereunder presents all serious adverse events sorted by MedDRA System Organ Class (SOC) and MedDRA Preferred Terms (PT).

Cohort 1: esophageal adenocarcinoma cohort

MedDRA Primary SOC *MedDRA PT*	**Number of subjects affected**	**All SAE occurrences**	**SAEs occurrences related to abemaciclib**	**Number of fatalities**	**Number of fatalities causally related to abemaciclib**
Respiratory, thoracic and mediastinal disorder					
Interstitial lung disease	1	1	1		
Pneumonitis	1	1	1	1	1

Cohort 2: esophageal squamous cell carcinoma cohort.

MedDRA Primary SOC *MedDRA PT*	**Number of subjects affected**	**All SAE occurrences**	**SAEs occurrences related to abemaciclib**	**Number of fatalities**	**Number of fatalities causally related to abemaciclib**
Gastrointestinal disorders					
Bezoar	1	1	1		
Diarrhoea	1	1	1		
Dysphagia	1	1	1		
Infections and infestations					
Pneumonia	1	1		1	
Pulmonary sepsis	1	1		1	
Metabolism and nutrition disorders					
Decreased appetite	1	1	1		

Cohort 3: cholangiocarcinoma

MedDRA Primary SOC *MedDRA PT*	**Number of subjects affected**	**All SAE occurrences**	**SAEs occurrences related to abemaciclib**	**Number of fatalities**	**Number of fatalities causally related to abemaciclib**
Gastrointestinal disorders					
Abdominal pain	1	1	1		
Diarrhoea	1	1	1		
Vomiting	1	1	1		
General disorders and administration site conditions					
Fatigue	2	2	2		
Sudden death	1	1		1	
Infections and infestations					
Biliary sepsis	1	1			
Gastroenteritis	1	1			
Sepsis	1	1			
Metabolism and nutrition disorders					
Diabetic metabolic decompensation	1	1			

Cohort 4: urothelial cancer

MedDRA Primary SOC *MedDRA PT*	**Number of subjects affected**	**All SAE occurrences**	**SAEs occurrences related to abemaciclib**	**Number of fatalities**	**Number of fatalities causally related to abemaciclib**
Gastrointestinal disorders					
Intestinal obstruction	1	1			
Nausea	1	1	1		
Subileus	1	1			
Vomiting	2	2	2		
Infections and infestations					
Pyelonephritis	1	3			
Sepsis	1	1			
Urinary tract infection	1	1			
Injury, poisoning and procedural complications					
Ureteric anastomosis complication	1	1			
Renal and urinary disorders					
Acute kidney injury	2	2			

Cohort 5: endometrial cancer

MedDRA Primary SOC *MedDRA PT*	**Number of subjects affected**	**All SAE occurrences**	**SAEs occurrences related to abemaciclib**	**Number of fatalities**	**Number of fatalities causally related to abemaciclib**
Ear and labyrinth disorders					
Vertigo	1	1			
Gastrointestinal disorders					

MedDRA Primary SOC *MedDRA PT*	Number of subjects affected	All SAE occurrences	SAEs occurrences related to abemaciclib	Number of fatalities	Number of fatalities causally related to abemaciclib
Diarrhoea	1	1	1		
Nausea	1	1	1		
Vomiting	1	1			
General disorders and administration site conditions					
Influenza like illness	1	1			
Infections and infestations					
Pyelonephritis acute	1	1			

6.3 Non-serious adverse events

The frequency threshold for reporting non-serious adverse events is 0 %.

The below table presents all non-serious adverse events sorted by MedDRA System Organ Class (SOC), MedDRA Preferred Terms (PT).

Cohort 1: esophageal adenocarcinoma cohort

MedDRA Primary SOC *MedDRA PT*	Number of subjects affected	All AE occurrences	AEs occurrences related to abemaciclib
Blood and lymphatic system disorders			
ANAEMIA	5	5	4
LEUKOPENIA	1	1	1
NEUTROPENIA	1	1	1
Eye disorders			
LACRIMATION INCREASED	1	1	1
Gastrointestinal disorders			
CONSTIPATION	1	1	1
DIARRHOEA	10	12	11
DRY MOUTH	1	1	1
DYSPEPSIA	1	1	1
DYSPHAGIA	1	1	0
GASTROOESOPHAGEAL REFLUX DISEASE	1	1	0
NAUSEA	5	5	5
ORAL PAIN	1	1	1
STOMATITIS	1	1	1
VOMITING	4	4	3
General disorders and administration site conditions			
ASTHENIA	1	1	1
CHEST PAIN	1	1	0
FATIGUE	11	12	10
OEDEMA	1	1	0
Infections and infestations			

MedDRA Primary SOC *MedDRA PT*	**Number of subjects affected**	**All AE occurrences**	**AEs occurrences related to abemaciclib**
BRONCHITIS	1	1	0
Investigations			
BLOOD CREATINE INCREASED	1	1	1
BLOOD CREATININE INCREASED	1	1	1
WEIGHT DECREASED	2	2	1
Metabolism and nutrition disorders			
ANOREXIA	1	1	1
DECREASED APPETITE	1	1	1
HYPOALBUMINAEMIA	1	1	0
HYPOGLYCAEMIA	1	1	0
Musculoskeletal and connective tissue disorders			
BACK PAIN	1	1	0
Nervous system disorders			
DISTURBANCE IN ATTENTION	1	1	1
HEADACHE	1	1	1
TREMOR	1	1	0
Psychiatric disorders			
INSOMNIA	1	1	1
Renal and urinary disorders			
RENAL FAILURE	2	2	1
Respiratory, thoracic and mediastinal disorders			
COUGH	1	1	0
EPISTAXIS	1	1	1
PULMONARY EMBOLISM	1	1	0
PULMONARY HAEMORRHAGE	1	1	0

Cohort 2: esophageal squamous cell carcinoma cohort.

MedDRA Primary SOC *MedDRA PT*	**Number of subjects affected**	**All AE occurrences**	**AEs occurrences related to abemaciclib**
Blood and lymphatic system disorders			
ANAEMIA	7	7	6
LYMPHOPENIA	2	2	2
NEUTROPENIA	2	2	2
THROMBOCYTOPENIA	1	1	1
Cardiac disorders			
ATRIAL FIBRILLATION	2	2	0
Congenital, familial and genetic disorders			
TRACHEO-OESOPHAGEAL FISTULA	1	1	0
Ear and labyrinth disorders			
VERTIGO	1	1	0
Endocrine disorders			
HYPERTHYROIDISM	1	1	0

MedDRA Primary SOC *MedDRA PT*	**Number of subjects affected**	**All AE occurrences**	**AEs occurrences related to abemaciclib**
Eye disorders			
XEROPHTHALMIA	1	1	1
Gastrointestinal disorders			
ABDOMINAL PAIN	1	1	0
ABDOMINAL PAIN UPPER	3	3	0
CONSTIPATION	4	4	1
DIARRHOEA	7	10	10
DRY MOUTH	1	1	0
DYSPEPSIA	1	1	0
DYSPHAGIA	1	1	1
FLATULENCE	1	1	1
GASTROOESOPHAGEAL REFLUX DISEASE	1	1	1
INGUINAL HERNIA	1	1	0
NAUSEA	1	1	0
STOMATITIS	1	1	1
VOMITING	1	1	0
General disorders and administration site conditions			
ASTHENIA	8	8	5
FATIGUE	5	5	5
INFLAMMATION	1	1	0
MUCOSAL INFLAMMATION	2	2	2
OEDEMA PERIPHERAL	1	2	0
PYREXIA	1	1	0
Infections and infestations			
FUNGAL OESOPHAGITIS	1	1	0
PNEUMONIA	1	1	0
Injury, poisoning and procedural complications			
FALL	1	1	0
Investigations			
BLOOD CREATININE INCREASED	2	2	1
WEIGHT DECREASED	1	1	1
Metabolism and nutrition disorders			
ANOREXIA	1	1	0
DECREASED APPETITE	7	7	6
DEHYDRATION	1	1	1
HYPERGLYCAEMIA	1	1	0
HYPOKALAEMIA	1	1	1
MALNUTRITION	1	1	0
Musculoskeletal and connective tissue disorders			
MUSCULOSKELETAL CHEST PAIN	1	1	**0**
Nervous system disorders			
DYSGEUSIA	1	1	1

MedDRA Primary SOC *MedDRA PT*	Number of subjects affected	All AE occurrences	AEs occurrences related to abemaciclib
MONOPARESIS	1	1	0
PARAESTHESIA	1	1	1
Psychiatric disorders			
ANXIETY	1	1	0
INSOMNIA	1	1	1
Renal and urinary disorders			
RENAL FAILURE	2	2	2
Respiratory, thoracic and mediastinal disorders			
BRONCHOPNEUMOPATHY	1	1	1
COUGH	2	2	1
DYSPNOEA	2	2	0
LUNG DISORDER	1	1	0
PRODUCTIVE COUGH	1	1	0
Skin and subcutaneous tissue disorders			
DRY SKIN	1	1	1
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	1	1	1
RASH	1	1	1

Cohort 3: cholangiocarcinoma

MedDRA Primary SOC *MedDRA PT*	Number of subjects affected	All AE occurrences	AEs occurrences related to abemaciclib
Blood and lymphatic system disorders			
ANAEMIA	5	5	2
NEUTROPENIA	4	6	3
THROMBOCYTOPENIA	6	9	6
Cardiac disorders			
ARTERIOSPASM CORONARY	1	1	0
TACHYCARDIA	1	1	0
Ear and labyrinth disorders			
VERTIGO	2	2	1
Gastrointestinal disorders			
ABDOMINAL PAIN	3	3	2
CONSTIPATION	4	5	0
DIARRHOEA	9	15	14
NAUSEA	6	6	5
VOMITING	2	2	2
General disorders and administration site conditions			
ASTHENIA	2	3	2
FATIGUE	8	8	8
MALAISE	1	1	1

MedDRA Primary SOC *MedDRA PT*	**Number of subjects affected**	**All AE occurrences**	**AEs occurrences related to abemaciclib**
OEDEMA PERIPHERAL	2	2	0
PAIN	1	1	0
PYREXIA	1	1	0
Infections and infestations			
BILIARY TRACT INFECTION	1	1	0
BRONCHITIS	1	1	0
CESTODE INFECTION	1	1	0
CHOLANGITIS INFECTIVE	1	1	0
CONJUNCTIVITIS	2	2	0
VULVOVAGINAL MYCOTIC INFECTION	1	1	1
Investigations			
BILIRUBIN CONJUGATED INCREASED	1	1	0
BLOOD BILIRUBIN INCREASED	1	1	0
BLOOD CREATININE INCREASED	1	2	2
WEIGHT DECREASED	1	1	1
WHITE BLOOD CELL COUNT DECREASED	1	1	1
Metabolism and nutrition disorders			
DECREASED APPETITE	12	13	9
HYPERKALAEMIA	1	1	0
HYPOKALAEMIA	3	3	2
HYPOPHOSPHATAEMIA	1	1	0
Musculoskeletal and connective tissue disorders			
BACK PAIN	1	1	0
Nervous system disorders			
ALTERED STATE OF CONSCIOUSNESS	1	1	0
DYSGEUSIA	1	1	1
HEADACHE	1	1	0
Psychiatric disorders			
DEPRESSION	1	1	0
Renal and urinary disorders			
RENAL FAILURE	1	1	1
Respiratory, thoracic and mediastinal disorders			
DYSPNOEA	2	2	1
Skin and subcutaneous tissue disorders			
DRY SKIN	2	2	1
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	1	1	1
PRURITUS	1	1	0
SKIN LESION	1	1	1
Vascular disorders			
HYPOTENSION	2	2	0

Cohort 4: urothelial cancer

MedDRA Primary SOC *MedDRA PT*	**Number of subjects affected**	**All AE occurrences**	**AEs occurrences related to abemaciclib**
Blood and lymphatic system disorders			
ANAEMIA	9	11	7
LEUKOPENIA	1	1	1
NEUTROPENIA	3	4	4
THROMBOCYTOPENIA	3	4	3
Cardiac disorders			
PALPITATIONS	1	1	0
Ear and labyrinth disorders			
VERTIGO	2	2	1
Endocrine disorders			
HYPOTHYROIDISM	1	1	0
Gastrointestinal disorders			
ABDOMINAL PAIN	1	2	1
ABDOMINAL PAIN UPPER	2	2	1
ABDOMINAL RIGIDITY	1	1	0
CONSTIPATION	6	6	0
DIARRHOEA	10	14	12
DYSPEPSIA	1	1	0
GASTROOESOPHAGEAL REFLUX DISEASE	1	1	0
INTESTINAL OBSTRUCTION	1	1	0
NAUSEA	7	10	7
VOMITING	8	10	7
General disorders and administration site conditions			
ASTHENIA	10	12	5
CHEST PAIN	2	2	0
FATIGUE	4	4	2
GENERAL PHYSICAL HEALTH DETERIORATION	1	1	0
INFLUENZA LIKE ILLNESS	1	1	0
NOT YET CLASSIFIED	1	1	0
OEDEMA PERIPHERAL	1	1	0
PYREXIA	2	2	0
Hepatobiliary disorders			
HEPATIC PAIN	1	1	0
Immune system disorders			
HYPERSENSITIVITY	1	1	0
Infections and infestations			
COVID-19	1	1	0
FUNGAL INFECTION	1	1	0
PNEUMONIA	1	1	0
PYELONEPHRITIS	1	1	0

MedDRA Primary SOC *MedDRA PT*	**Number of subjects affected**	**All AE occurrences**	**AEs occurrences related to abemaciclib**
TOOTH ABSCESS	1	1	0
URINARY TRACT INFECTION	3	3	0
Investigations			
ASPARTATE AMINOTRANSFERASE INCREASED	1	1	0
BLOOD ALKALINE PHOSPHATASE INCREASED	1	1	1
BLOOD CREATININE INCREASED	6	7	5
GAMMA-GLUTAMYLTRANSFERASE INCREASED	1	1	1
WHITE BLOOD CELL COUNT DECREASED	1	2	2
Metabolism and nutrition disorders			
DECREASED APPETITE	7	8	4
DEHYDRATION	1	1	0
HYPERKALAEMIA	1	1	0
MALNUTRITION	1	1	0
Musculoskeletal and connective tissue disorders			
ARTHRALGIA	1	1	0
ARTHRITIS	1	1	0
BACK PAIN	1	1	0
MYALGIA	1	1	0
Nervous system disorders			
DIZZINESS	1	1	0
DYSGEUSIA	2	3	1
HEADACHE	3	3	1
Psychiatric disorders			
INSOMNIA	2	2	0
Renal and urinary disorders			
ACUTE KIDNEY INJURY	1	1	0
BLADDER PAIN	1	3	0
CHRONIC KIDNEY DISEASE	1	1	1
CYSTITIS HAEMORRHAGIC	1	1	0
DYSURIA	1	1	0
HAEMATURIA	1	1	0
POLLAKIURIA	1	1	0
RENAL FAILURE	2	2	1
Reproductive system and breast disorders			
PROSTATISM	1	1	0
Respiratory, thoracic and mediastinal disorders			
COUGH	2	2	0
DYSPNOEA	4	5	0
EPISTAXIS	2	2	2
HAEMOPTYSIS	1	1	0
Skin and subcutaneous tissue disorders			
INGROWING NAIL	1	1	0

MedDRA Primary SOC *MedDRA PT*	**Number of subjects affected**	**All AE occurrences**	**AEs occurrences related to abemaciclib**
RASH	1	1	1
Vascular disorders			
PELVIC VENOUS THROMBOSIS	1	1	0

Cohort 5: endometrial cancer

MedDRA Primary SOC *MedDRA PT*	**Number of subjects affected**	**All AE occurrences**	**AEs occurrences related to abemaciclib**
Blood and lymphatic system disorders			
ANAEMIA	9	9	9
NEUTROPENIA	4	4	4
THROMBOCYTOPENIA	4	6	6
Ear and labyrinth disorders			
TINNITUS	1	1	0
Eye disorders			
LACRIMATION INCREASED	1	1	0
Gastrointestinal disorders			
ABDOMINAL DISTENSION	1	1	1
ABDOMINAL PAIN	7	7	7
ANAL HAEMORRHAGE	1	1	1
CONSTIPATION	1	1	0
DIARRHOEA	14	21	21
DRY MOUTH	1	1	1
DYSPEPSIA	2	2	1
GASTROOESOPHAGEAL REFLUX DISEASE	1	1	1
GINGIVAL SWELLING	1	1	0
NAUSEA	6	6	6
STOMATITIS	1	1	1
VOMITING	2	2	2
General disorders and administration site conditions			
ASTHENIA	1	1	1
FATIGUE	8	8	7
MALAISE	4	4	3
MUCOSAL INFLAMMATION	1	1	1
Infections and infestations			
CYSTITIS	1	2	0
INFLUENZA	1	1	0
ORAL HERPES	1	1	0
PNEUMONIA	1	1	0
URINARY TRACT INFECTION	1	1	0

MedDRA Primary SOC *MedDRA PT*	**Number of subjects affected**	**All AE occurrences**	**AEs occurrences related to abemaciclib**
Injury, poisoning and procedural complications			
UPPER LIMB FRACTURE	1	1	0
Investigations			
ALANINE AMINOTRANSFERASE INCREASED	1	1	1
ASPARTATE AMINOTRANSFERASE INCREASED	1	1	1
BLOOD CREATININE INCREASED	4	4	3
WEIGHT DECREASED	3	3	3
WHITE BLOOD CELL COUNT DECREASED	3	3	3
Metabolism and nutrition disorders			
DECREASED APPETITE	10	10	10
Musculoskeletal and connective tissue disorders			
ARTHRALGIA	1	1	0
MUSCULOSKELETAL PAIN	2	2	0
MYALGIA	1	1	0
Nervous system disorders			
DIZZINESS	1	1	0
DYSGEUSIA	3	4	4
HEADACHE	1	1	0
PARAESTHESIA	1	1	0
Psychiatric disorders			
CONFUSIONAL STATE	1	1	0
DEPRESSION	1	1	0
INSOMNIA	1	1	1
NERVOUSNESS	1	1	0
Renal and urinary disorders			
ACUTE KIDNEY INJURY	2	2	2
DYSURIA	1	1	0
POLLAKIURIA	1	1	0
Respiratory, thoracic and mediastinal disorders			
COUGH	3	3	0
DYSPNOEA	2	3	1
NASAL DRYNESS	1	1	1
Skin and subcutaneous tissue disorders			
ALOPECIA	1	1	1
DERMATITIS BULLOUS	1	1	0
DRY SKIN	2	2	2
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	1	1	1
PRURITUS	1	1	0
RASH	1	2	2
Vascular disorders			
PALLOR	1	1	1

MedDRA Primary SOC *MedDRA PT*	Number of subjects affected	All AE occurrences	AEs occurrences related to abemaciclib
THROMBOPHLEBITIS SUPERFICIAL	1	1	0

6.4 Adverse events with grade 3 or higher

The below table presents all adverse events with grade 3 or higher sorted by MedDRA System Organ Class (SOC), MedDRA Preferred Terms (PT).

Cohort 1: esophageal adenocarcinoma cohort

MedDRA Primary SOC *MedDRA PT*	Number of subjects affected	All AE occurrences	AEs occurrences related to abemaciclib	Number of subjects with grade 3	Number of subjects with grade 4	Number of subjects with grade 5 (death)
Blood and lymphatic system disorders						
ANAEMIA	1	1	1	1	0	0
NEUTROPENIA	1	1	1	1	0	0
Gastrointestinal disorders						
NAUSEA	1	1	1	1	0	0
General disorders and administration site conditions						
FATIGUE	3	3	2	3	0	0
Renal and urinary disorders						
RENAL FAILURE	1	1	0	1	0	0
Respiratory, thoracic and mediastinal disorders						
INTERSTITIAL LUNG DISEASE	1	1	1	1	0	0
PNEUMONITIS	1	1	1	0	0	1

Cohort 2: esophageal squamous cell carcinoma cohort

MedDRA Primary SOC *MedDRA PT*	Number of subjects affected	All AE occurrences	AEs occurrences related to abemaciclib	Number of subjects with grade 3	Number of subjects with grade 4	Number of subjects with grade 5 (death)
Blood and lymphatic system disorders						
ANAEMIA	1	1	1	1	0	0
LYMPHOPENIA	1	1	1	1	0	0
NEUTROPENIA	2	2	2	2	0	0
THROMBOCYTOPENIA	1	1	1	1	0	0
Congenital, familial and genetic disorders						

MedDRA Primary SOC *MedDRA PT*	**Number of subjects affected**	**All AE occurrences**	**AEs occurrences related to abemaciclib**	**Number of subjects with grade 3**	**Number of subjects with grade 4**	**Number of subjects with grade 5 (death)**
TRACHEO-OESOPHAGEAL FISTULA	1	1	0	1	0	0
Gastrointestinal disorders						
BEZOAR	1	1	1	1	0	0
DIARRHOEA	1	1	1	1	0	0
DYSPHAGIA	1	2	2	0	1	0
General disorders and administration site conditions						
ASTHENIA	2	2	1	2	0	0
FATIGUE	2	2	2	2	0	0
Infections and infestations						
PNEUMONIA	1	1	0	0	0	1
PULMONARY SEPSIS	1	1	0	0	0	1
Metabolism and nutrition disorders						
DECREASED APPETITE	1	1	1	1	0	0
HYPOKALAEMIA	1	1	1	1	0	0
Respiratory, thoracic and mediastinal disorders						
DYSPNOEA	1	1	0	1	0	0

Cohort 3: cholangiocarcinoma

MedDRA Primary SOC *MedDRA PT*	**Number of subjects affected**	**All AE occurrences**	**AEs occurrences related to abemaciclib**	**Number of subjects with grade 3**	**Number of subjects with grade 4**	**Number of subjects with grade 5 (death)**
Blood and lymphatic system disorders						
ANAEMIA	2	2	0	2	0	0
NEUTROPENIA	3	4	2	3	0	0
THROMBOCYTOPENIA	2	2	2	2	0	0
Gastrointestinal disorders						
ABDOMINAL PAIN	1	1	1	1	0	0
DIARRHOEA	2	2	2	2	0	0
NAUSEA	1	1	1	1	0	0
VOMITING	1	1	1	1	0	0
General disorders and administration site conditions						
FATIGUE	5	5	5	5	0	0
MALAISE	1	1	1	1	0	0
SUDDEN DEATH	1	1	0	0	0	1
Infections and infestations						

MedDRA Primary SOC *MedDRA PT*	**Number of subjects affected**	**All AE occurrences**	**AEs occurrences related to abemaciclib**	**Number of subjects with grade 3**	**Number of subjects with grade 4**	**Number of subjects with grade 5 (death)**
BILIARY SEPSIS	1	1	0	0	1	0
BILIARY TRACT INFECTION	1	1	0	1	0	0
CHOLANGITIS INFECTIVE	1	1	0	1	0	0
SEPSIS	1	1	0	1	0	0
Investigations						
BILIRUBIN CONJUGATED INCREASED	1	1	0	1	0	0
Metabolism and nutrition disorders						
DIABETIC METABOLIC DECOMPENSATION	1	1	0	1	0	0
HYPOKALAEMIA	3	3	2	3	0	0
HYPOPHOSPHATAEMIA	1	1	0	1	0	0
Musculoskeletal and connective tissue disorders						
BACK PAIN	1	1	0	1	0	0
Respiratory, thoracic and mediastinal disorders						
DYSPNOEA	1	1	1	1	0	0

Cohort 4: urothelial cancer

MedDRA Primary SOC *MedDRA PT*	**Number of subjects affected**	**All AE occurrences**	**AEs occurrences related to abemaciclib**	**Number of subjects with grade 3**	**Number of subjects with grade 4**	**Number of subjects with grade 5 (death)**
Blood and lymphatic system disorders						
ANAEMIA	4	4	2	4	0	0
NEUTROPENIA	2	2	2	1	1	0
THROMBOCYTOPENIA	1	1	1	1	0	0
Gastrointestinal disorders						
INTESTINAL OBSTRUCTION	1	1	0	1	0	0
NAUSEA	1	1	1	1	0	0
VOMITING	2	2	2	2	0	0
General disorders and administration site conditions						
FATIGUE	1	1	1	1	0	0
GENERAL PHYSICAL HEALTH DETERIORATION	1	1	0	0	0	1
Infections and infestations						
PYELONEPHRITIS	1	2	0	0	1	0
SEPSIS	1	1	0	0	1	0
URINARY TRACT INFECTION	1	1	0	1	0	0
Injury, poisoning and procedural complications						

MedDRA Primary SOC *MedDRA PT*	**Number of subjects affected**	**All AE occurrences**	**AEs occurrences related to abemaciclib**	**Number of subjects with grade 3**	**Number of subjects with grade 4**	**Number of subjects with grade 5 (death)**
URETERIC ANASTOMOSIS COMPLICATION	1	1	0	1	0	0
Investigations						
BLOOD CREATININE INCREASED	2	2	1	2	0	0
GAMMA-GLUTAMYLTRANSFERASE INCREASED	1	1	1	1	0	0
Metabolism and nutrition disorders						
DECREASED APPETITE	1	1	1	1	0	0
DEHYDRATION	1	1	0	1	0	0
HYPERKALAEMIA	1	1	0	1	0	0
Renal and urinary disorders						
ACUTE KIDNEY INJURY	2	2	0	2	0	0
RENAL FAILURE	1	1	0	1	0	0

Cohort 5: endometrial cancer

MedDRA Primary SOC *MedDRA PT*	**Number of subjects affected**	**All AE occurrences**	**AEs occurrences related to abemaciclib**	**Number of subjects with grade 3**	**Number of subjects with grade 4**	**Number of subjects with grade 5 (death)**
Blood and lymphatic system disorders						
ANAEMIA	3	3	3	3	0	0
NEUTROPENIA	1	1	1	1	0	0
THROMBOCYTOPENIA	2	3	3	1	1	0
Ear and labyrinth disorders						
VERTIGO	1	1	0	1	0	0
Gastrointestinal disorders						
DIARRHOEA	2	2	2	2	0	0
NAUSEA	1	1	1	1	0	0
VOMITING	1	1	1	1	0	0
General disorders and administration site conditions						
FATIGUE	1	1	1	1	0	0
MALAISE	2	2	2	2	0	0
Infections and infestations						
PYELONEPHRITIS ACUTE	1	1	0	1	0	0
Investigations						
BLOOD CREATININE INCREASED	1	1	1	1	0	0
WHITE BLOOD CELL COUNT DECREASED	1	1	1	1	0	0

MedDRA Primary SOC *MedDRA PT*	Number of subjects affected	All AE occurrences	AEs occurrences related to abemaciclib	Number of subjects with grade 3	Number of subjects with grade 4	Number of subjects with grade 5 (death)
Skin and subcutaneous tissue disorders						
RASH	1	1	1	1	0	0

7 ADDITIONAL INFORMATION

7.1 Global substantial protocol amendments

The global substantial protocol amendments are summarised in the below table.

BELGIUM

Amendment reference	Date	Description
AMD-0045	10/12/2018	• New/amended patient information sheet / informed consent (including addendum)
AMD-0052	19/02/2019	• New/amended documents or information related to IMP or IMPD • New/amended patient information sheet / informed consent (including addendum) • New/amended protocol
AMD-0056	22/05/2019	• Addition of at least a new site or a site whose LEC did not reply initially or moved site
AMD-0063	09/07/2019	• Addition of at least a new site or a site whose LEC did not reply initially or moved site
AMD-0064	12/09/2019	• New/amended IDMC charter • New/amended patient information sheet / informed consent (including addendum) • New/amended protocol • New/amended patient diary
AMD-0070	17/10/2019	• New/amended patient information sheet / informed consent (including addendum)
AMD-0074	15/10/2019	• Change of PI - already approved site
AMD-0081	30/06/2020	• Closure of an approved site • Addition of at least a new site or a site whose LEC did not reply initially or moved site
AMD-0117	21/10/2020	Addition of at least a new site or a site whose LEC did not reply initially or moved site

FRANCE

Amendment reference	Date	Description
AMD-0068	18/09/2019	• New/amended patient information sheet / informed consent (including addendum) • New/amended patient diary • New/amended protocol
AMD-0082	13/03/2020	• Addition of at least a new site or a site whose LEC did not reply initially or moved site • Change of PI - already approved site
AMD-0083	13/05/2020	• Changes in the logistics of the trial, which are NOT site-related (e.g. :lab, CRO etc)

7.2 Global interruptions and re-starts

There were no global interruptions to the trial.

7.3 Limitations, addressing sources of potential bias and imprecisions and caveats

An interim analysis was performed on each tumour cohort in the first stage, which includes the first 13 evaluable subjects. Since there were 2 or less subjects with treatment success in these 13 evaluable subjects (futility criteria) in all cohorts, accruals in all cohorts were stopped.
Due to lack number of subjects, the Progression-Free and Overall Survival assessment should be interpreted with caution and considered as exploratory.