CLINICAL STUDY REPORT

A Phase IIa Exploratory Study of CriPec®Docetaxel Monotherapy in Subjects with Platinum Resistant Ovarian Cancer.

Trial code:	CINOVA	Trial development phase:	IIa
EudraCT number:	2018-002117-36	Investigational medicinal product:	CriPec®docetaxel
Trial Initiation		Trial Completion	
Date of first patient in:	19Oct2018	Last patients last visit:	06Jul2020
Date of first site initiation visit:	19/20Oct2018	Last follow-up date before statistical analysis:	06Jul2020
		Final database lock:	22Sep2020
Sponsor:	Cristal Therapeutics	Indication:	Platinum resistant ovarian cancer
Version:	1.0, final	Date:	30Nov2020

Document history - This version of the Clinical Study Report includes:

- NA (first version)

Principal Investigator:	Prof. J. Ledermann, UCL Cancer Institute, London, United Kingdom
Sponsor signatories:	Dr. A. Mescheder, Chief Medical Officer Dr. Rob Hanssen, Study Director Cristal Therapeutics, Maastricht, The Netherlands

This study was conducted according to the ethical principles of Good Clinical Practices (GCP) as described in the ICH Guideline E6, 1996, including the archiving of essential documents.

1 SIGNATURES

Trial Title: A Phase IIa Exploratory Study of CriPec®docetaxel Monotherapy in Subjects with Platinum Resistant Ovarian Cancer.

Date of Final Clinical Study Report: 30Nov2020

I have read this report and confirm that, to the best of my knowledge, it accurately describes the conduct and results of the trial.

Principal Coordinating Investigator:

DocuSigned by:
Jonathan Ledermann
Signer Name: Jonathan Ledermann
Signing Reason: I approve this document
Signing Time: 30-Nov-2020 | 05:33 PST
C5BE7428BBDB4F4D83E693EECF280F39

30-Nov-2020 | 05:34 PST

Signature	Prof. J. Ledermann UCL Cancer Institute, 90 Tottenham Court Road London WIT 4TJ United Kingdom	Date

Cristal Therapeutics Signatories:

DocuSigned by:
Axel Mescheder
Signer Name: Axel Mescheder
Signing Reason: I approve this document
Signing Time: 30-Nov-2020 | 08:18 PST
C6652E4231C94FF0832C4852AC16AA3C

30-Nov-2020 | 08:18 PST

Signature	Dr. A. Mescheder, Chief Medical Officer Cristal Therapeutics, Oxfordlaan 55 6229 EV Maastricht The Netherlands	Date

DocuSigned by:
Rob Hanssen
Signer Name: Rob Hanssen
Signing Reason: I approve this document
Signing Time: 30-Nov-2020 | 05:35 PST
999F5ED1B7BA4A4D9A8FDEB32EC34A84

30-Nov-2020 | 05:36 PST

	Dr. R. Hanssen, Study Director	
Signature	Cristal Therapeutics, Oxfordlaan 55 6229 EV Maastricht The Netherlands	Date

CATO SMS Signatory:

DocuSigned by:
Oana Draghiciu
Signer Name: Oana Draghiciu
Signing Reason: I approve this document
Signing Time: 01-Dec-2020 | 00:21 PST
7CB80AB058F44BC1B350621B28F7BCA7

01-Dec-2020 | 00:21 PST

	Oana Draghiciu, PhD, Medical Writer	
Signature	CATO SMS, Stationsplein Noord-Oost 438 1117 CL Schiphol The Netherlands	Date

Confidentiality Statement

2 SYNOPSIS

TITLE OF TRIAL:

A Phase IIa exploratory study of CriPec®docetaxel monotherapy in subjects with platinum resistant ovarian cancer.

PRINCIPAL INVESTIGATORS AND TRIAL CENTERS:

- Dr. P.B. Ottevanger, Radboud UMC, Nijmegen, NL
- Dr. M. Jalving, University Medical Center Groningen (UMCG), Groningen, NL
- Dr. I. Boere, Erasmus Medical Center (EMC), Rotterdam, NL
- Dr. A.J. van de Wouw, VieCuri, Venlo, NL
- Dr. S.M. van den Heiligenberg, Dijklander Ziekenhuis, Hoorn, NL
- Prof. Dr. I. Vergote, UZ Leuven (UZL), Leuven, Belgium
- Dr. C. Gennigens, Centre Hospitalier Universitaire (CHU) de Liège, Liège, Belgium
- Prof. J. Ledermann and Dr. A. Lockley, UCL Cancer Institute, London, UK

PUBLICATION(S) BASED ON THE TRIAL (REFERENCE):

- Not applicable.

TRIAL PERIOD:

First patient in/screened: 19Oct2018
Last patient last visit: 06Jul2020

PHASE OF DEVELOPMENT: IIa

All objectives are per the Clinical Trial Protocol version 5.0 dated 24Jun2019 (Appendix 16.1.1).

OBJECTIVES:

The primary objective was:

- To determine the Objective Response Rate (ORR) as assessed by Response Evaluation Criteria in Solid Tumour (RECIST) V1.1 of CriPec®docetaxel monotherapy in subjects with ovarian cancer who are resistant to prior platinum-based therapy.

The secondary objectives were:

- To evaluate the safety and tolerability of CriPec®docetaxel according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) criteria (version 5.0)
- To evaluate the clinical activity of CriPec®docetaxel as measured by:

- Progression free survival (PFS) at 6 months based on RECIST V1.1 and combined assessment using Gynecological Cancer Intergroup (GCIG) definitions for cancer antigen 125 (CA-125)
- GCIG CA-125 response criteria
- Duration of response (DOR) based on RECIST V1.1 and combined assessment using GCIG definitions for CA-125
- Time to progression (TTP)
- Disease control rate (DCR)

Endpoints are per the Statistical Analysis Plan (SAP) version 1.0 dated 21Sep2020 (Appendix 16.1.2).

ENDPOINTS:

The primary endpoint was:

- ORR as assessed by RECIST V1.1 and calculated as the proportion of subjects who achieved a Complete Response (CR) or Partial Response (PR) at any time point prior to end of trial (when the subject had either discontinued trial treatment or received six cycles of treatment, whichever occured first).

The secondary endpoints were:

- Safety, evaluated by means of physical examinations, body weight, vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, laboratory assessments (hematology, biochemistry and urinalysis), electrocardiogram (ECG), and recording of concomitant medications/procedures and adverse events (AEs).
- Clinical activity of CriPec®docetaxel, evaluated by means of assessing:
  - PFS at 6 months
  - Best Overall Response (BOR) using a combination of RECIST V1.1 and CA-125 based on the GCIG CA-125 response criteria
  - GCIG-125 response criteria
  - DOR
  - TTP
  - DCR

METHODOLOGY:

This was a single-arm, Phase IIa exploratory trial to assess the efficacy, safety and tolerability of CriPec®docetaxel monotherapy administered intravenously (IV) every three weeks (Q3W) to subjects with ovarian cancer that were resistant to prior platinum-based therapy.

Subjects were treated with the recommended Phase 2 dose (RP2D) of 60 mg/m^2 of CriPec®docetaxel and with corticosteroid premedication (three times 8.0 mg oral dexamethasone before each CriPec®docetaxel dose) that was determined in the Phase I trial (CT-CL01), until disease progression, unacceptable toxicity, or discontinuation for any other reason. Originally planned as a Simon 2-Stage design trial, the first stage included 13 subjects. One response was recorded in Stage 1, justifying the enrolment of the planned additional 14 subjects.

The Simon 2-Stage design was no longer applicable for Stage 2 of the trial as the inclusion

criteria were adapted to match those of landmark docetaxel trials. In Stage 2, a maximum of seven patients could be replaced if they failed to receive at least three administrations of CriPec®docetaxel or if they failed to receive any efficacy assessment after baseline measurement. The above-mentioned and all other adaptations and modifications performed to update the clinical trial protocol are detailed in Section 9.8. The end of trial was defined as the time point when all subjects either discontinued trial treatment or received more than six cycles of treatment, whichever occured sooner. Any subject eligible for further treatment cycles at that time could continue to receive further treatment cycles with CriPec®docetaxel until discontinuation or withdrawal.

Data below are per Table 14.1.1.3.

NUMBER OF SUBJECTS (PLANNED AND ANALYZED):

Stage 1

Number of subjects planned:	13
Subjects enrolled:	13
Safety population (SAF):	13
Full Analysis Set (FAS):	13
Per Protocol Set (PPS):	13
CA-125 Set (CA-125):	9

Stage 2

Number of subjects planned:	14
Subjects enrolled:	12
Safety population (SAF):	12
Full Analysis Set (FAS):	7
Per Protocol Set (PPS):	4
CA-125 Set (CA-125):	4

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION AND EXCLUSION:

Inclusion criteria (for both stages):

To be eligible to participate in this trial, subjects were required to meet all of the following eligibility criteria:

1. Age ≥ 18 years.
2. Histologically or cytologically confirmed diagnosis of epithelial ovarian, fallopian or peritoneal cancer.
3. Platinum-resistant recurrent epithelial ovarian cancer (defined as progression within 6 months after last platinum dose).
4. For Stage 1 (per protocol V3.0 dated 25Sep2018; Appendix 16.1.1): There is no limit to the number of previous treatment lines, but a maximum of 3 lines of therapy for platinum-resistant disease, of which one could have been taxane-based. For Stage 2 (per protocol V5.0 dated 24Jun2019; Appendix 16.1.1): Subjects who have received a maximum of 2 prior treatment lines, of which one could have been taxane-based.
5. Measurable disease according to RECIST V1.1. Only CA-125 progression without any clinical or radiological progression was not allowed.
6. Performance status (WHO scale/ECOG) ≤ 1.

7. Estimated life expectancy of at least 12 weeks (for Stage 1; per protocol V3.0 dated 25Sep2018; Appendix 16.1.1) or 5 months (for Stage 2; per protocol V5.0 dated 24Jun2019; Appendix 16.1.1).
8. Toxicities incurred as a result of previous anti-cancer therapy (radiation therapy, chemotherapy, or surgery) must have been resolved to ≤ Grade 2 (as defined by NCI-CTCAE version 5.0).
9. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L; platelets ≥ 100 x 10^9/L; hemoglobin ≥ 5.58 mmol/L (≥ 9.00 g/dL).
10. Creatinine ≤ 1.75 x Upper Limit of Normal (ULN) and estimated creatinine clearance ≥ 30 mL/min according to Cockcroft-Gault formula; serum albumin levels > 25g/L
11. Serum bilirubin ≤ 1.5 x ULN except for subjects with Will Gilbert's syndrome, alkaline phosphatase, aspartate transaminase (ASAT) and alanine transaminase (ALAT) ≤ 2.5 x ULN, unless related to liver metastases, in which case ≤ 5 x ULN is allowed.
12. Written informed consent according to local guidelines.

Exclusion criteria (for both stages):

Subjects who met ANY of the following criteria at screening were excluded from trial entry:

1. Subjects with platinum-refractory disease. Refractory disease was defined by subjects who progressed during the preceding treatment or within 4 weeks after last dose of platinum containing therapy.
2. Less than four weeks since the last treatment with other anti-cancer therapies (i.e. endocrine therapy, immunotherapy, radiotherapy, chemotherapy, etc.); less than eight weeks for cranial radiotherapy, and less than six weeks for nitrosoureas and mitomycin C prior to first study treatment.
3. Current or recent (within 28 days of first study treatment) treatment with another investigational drug or participation in another investigational study.
4. Active or symptomatic brain metastases. Subjects must have been on a stable or decreasing dose of corticosteroids and/or must have had no requirement for anticonvulsants for five days prior to Cycle 1 Day1 (C1D1).
5. Current malignancies other than epithelial ovarian, fallopian or peritoneal cancer, with exception of adequately treated cone-biopsied in situ carcinoma of the cervix uteri and basal or squamous cell carcinoma of the skin.
6. Major surgical procedure (including open biopsy, excluding central line IV and portacath) within 28 days prior to the first study treatment, or anticipation of the need for major surgery during the course of the study treatment.
7. Uncontrolled hypertension (systolic > 150 mm Hg and/or diastolic > 100mm Hg).
8. Grade ≥ 2 motor or sensory neuropathy symptoms (as defined by CTCAE version 5.0).
9. Known hypersensitivity to any of the study drugs or excipients or taxanes.
10. Any skin toxicity in the medical history of the subject of Grade ≥ 2 associated with impaired skin integrity (skin toxicity defined as any form of rash, hand-foot syndrome (HFS), skin ulceration, toxic epidermal necrolysis, eczema) or any skin toxicity for which systemic treatment was needed.
11. Clinically significant (i.e. active) cardiovascular disease defined as stroke, transient ischemic attack (TIA) or myocardial infarction within ≤ 6 months prior to first trial treatment.

12. Subjects who were pregnant or breastfeeding. Serum pregnancy test had to be performed within 7 days prior to study treatment start in subjects of childbearing potential.
13. Absence of highly effective method of contraception as of C1D1 in female subjects of childbearing potential (defined as < 2 years after last menstruation and not surgically sterile).
14. Known hypersensitivity to dexamethasone or any other reason that made the subject not eligible to receive dexamethasone.
15. Evidence of any other medical conditions (such as psychiatric illness, infectious diseases, drug or alcohol abuse, physical examination or laboratory findings) that could have interfered with the planned treatment, affected subject compliance or placed the subject at high risk from treatment-related complications.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

Subjects eligible for the trial received CriPec®docetaxel Q3W at the RP2D of 60 mg/m^2. Each treatment cycle consisted of 21 days. On Day 1 of each cycle, a single dose of CriPec®docetaxel was administered IV at a constant rate for ~1 hour.

Pre-treatment with dexamethasone 8.0 mg orally was given three times before each CriPec®docetaxel administration (night before, morning and 1 hour before treatment).

The batch numbers of CriPec®docetaxel used during this trial were:

- CT15D02 (sites #02 UMCG, #11 UZL, and #13 CHU);
- CT17B01 (sites #02 UMCG, #11 UZL, #13 CHU, #01 UMCN, #03EMC, and #05 VieCuri).

Site #31 UCL received this batch, but did not use it because it did not recruit any subjects. Site #07 Dijklander Ziekenhuis was initiated but did not receive the IMP and did not recruit any subjects.

REFERENCE THERAPY PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

None applicable, the trial was a single arm trial.

DURATION OF TREATMENT:

The trial included a maximum of four weeks of screening and three weeks per treatment cycle. Subjects could continue to receive additional cycles of treatment until the subject experienced disease progression, unacceptable toxicity, request by subject or physician to discontinue treatment, death, or termination of the trial by the Sponsor. The duration of the trial for each individual subject was therefore variable. The subject had to attend an end of treatment (EOT) visit on Day 22 of last cycle and a follow up (FU) visit 28 days after the EOT visit for vital status. The end of trial was reached when all subjects either discontinued trial treatment or received more than six cycles of treatment, whichever occured sooner.

All statistical methods are per the Clinical Trial Protocol version 5.0 dated 24Jun2019 (Appendix 16.1.1) and the SAP V1.0 dated 21Sep2020 (Appendix 16.1.2).

STATISTICAL METHODS:

This exploratory trial planned to enrol 27 subjects.

Originally planned as a Simon 2-Stage design trial, the first stage included 13 subjects. One response was recorded in Stage 1, which per protocol justified the enrolment of the planned additional 14 subjects in Stage 2.

The Simon 2-Stage design was no longer applicable for the second stage of the trial, as the inclusion criteria for the remaining subjects changed (see Section 9.3 for eligibility criteria and Section 9.8 for futher explanations). The inclusion criteria were adapted to match those of landmark docetaxel trials. Stage 2 of the trial was evaluated independent of Stage 1. In Stage 2, up to 7 subjects were planned to be replaced if they failed to receive at least 3 administrations of CriPec®docetaxel, if the baseline tumor assessment did not occur as scheduled during screening, or if they failed to undergo any efficacy assessment after baseline measurement.

Safety Analysis:

Safety data was summarized for the safety population.

Efficacy Analysis:

Tumor response for target lesions was assessed at baseline and specified time points throughout the trial. The tumor response was evaluated according to RECIST V1.1. The calculation of ORR as primary endpoint was based on disease status as determined by tumor assessments. The analysis of the tumor marker CA-125 was performed on the efficacy population as per GCIG criteria. The variables were evaluated using appropriate descriptive statistics for each assessment point and for the changes from baseline.

All data collected in this trial were documented using summary tables, figures, and patient data listings. Continuous variables were summarized using descriptive statistics (N, mean, standard deviation, quartiles, median, minimum, and maximum). Categorical variables were summarized using counts, frequencies and percentages

TRIAL SUBJECTS:

Informed consent was obtained from 25 subjects between 08Oct2018 and 16Jan2020, before the Data Review Committee provided the recommendation to stop the trial prematurely (see Section 9.8 for further details). At screening, two subjects (Subject 03-02 and Subject 05-01, both from Stage 2) did not meet one of the inclusion criteria and were excluded from the PPS population. Subject 01-02 (Stage 2) was also excluded from the PPS population, because of non-compliance to trial treatment (the subject had an incorrect treatment schedule, with CriPec®docetaxel administration 2 days out of window).

The SAF population consisted of 25 subjects (Stage 1: 13 subjects; Stage 2: 12 subjects) who received at least one dose of CriPec®docetaxel. The FAS population consisted of 20 subjects (Stage 1: 13 subjects; Stage 2: seven subjects) who received at least one (Stage 1) or three (Stage 2) doses of trial drug and had a baseline and at least one post-baseline tumor assessment. The PPS population (17 subjects; Stage 1: 13 subjects; Stage 2: four subjects) was defined as subjects in the FAS population, excluding subjects who were not compliant to trial treatment or had at least one major protocol deviation that affected the interpretation of efficacy. The CA-125 population (13 subjects; Stage 1: nine subjects; Stage 2: four

subjects) consisted of all subjects from the FAS population who were evaluable by CA-125 (had a pre-treatment sample that was within 2 weeks before starting the treatment, had not received antibodies, and there had not been medical and/or surgical interference with their peritoneum/pleura [e.g. paracentesis] during the previous 28 days before the pre-treatment sample).

EFFICACY RESULTS:

Per RECIST V1.1, no subject had PR or CR in the FAS population. In the FAS population, seven subjects (35.0%) had stable disease (SD); in the PPS population, five subjects (29.4%) had SD. Therefore, the DCR in the FAS population was 35% per RECIST V1.1 criteria (three subjects had SD in Stage 1 [23.1%]; four subjects had SD in Stage 2 [57.1%]). In the PPS population, the DCR was 29.4% (three subjects had SD in Stage 1 [23.1%]; two subjects had SD in Stage 2 [50.0%]). Analysis of best overall response (by RECIST V1.1) by number of previous anti-cancer therapy lines showed that all subjects from the FAS population who had previously received four or five lines of therapy had PD (four lines: three subjects in Stage 1 and one subject in Stage 2; five lines: three subjects in Stage 1); in addition, two subjects who had previously received two lines of therapy in Stage 2 and four subjects who had previously received three lines of therapy in Stage 1 also had PD. Similar results were observed in the PPS population. Subjects who achieved SD during the trial (FAS population: three subjects in Stage 1 and four subjects in Stage 2; PPS population: three subjects in Stage 1 and two subjects in Stage 2) had previously received two or three lines of therapy. Median PFS for the FAS population was 1.41 months in Stage 1 of the trial and 3.02 months in Stage 2 of the trial; median PFS for the PPS population was 1.41 months in Stage 1 of the trial and 2.58 months in Stage 2 of the trial.

Per combined GCIG criteria, no CRs were recorded in the CA-125 population; one subject in Stage 1 of the trial (Subject 02-01) achieved a PR (duration of response: 1.12 months) and one subject in Stage 2 of the trial (Subject 02-05) had SD (duration of SD: 4.24 months). The remaining subjects either had PD (six subjects in Stage 1 and two subjects in Stage 2) or were not evaluable (two subjects in Stage 1 and one subject in Stage 2). Analysis of best overall response (per GCIG criteria) by number of previous anti-cancer therapy lines showed that Subject 02-01 had previously received three lines of therapy and Subject 02-05 had previously received two lines of therapy. All subjects who had previously received four or five lines of therapy had PD. From the CA-125 population, one subject achieved SD during the trial (Stage 2); this subject had previously received two lines of therapy. Median PFS for the FAS and PPS populations were the same as when assessed by RECIST V1.1; median PFS for the CA-125 population was 1.41 months in Stage 1 and 2.12 months in Stage 2 of the trial.

SAFETY RESULTS:

All subjects treated with CriPec®docetaxel experienced AEs during the trial, the majority of which were treatment-emergent AEs (TEAEs; 297/320, 92.8%). A total of 46 Grade ≥3 TEAEs occurred in 16 subjects of the SAF population during the trial (64.0%; Stage 1: 21 in seven subjects; Stage 2: 25 in nine subjects), of which 14 Grade ≥3 TEAEs occurring in nine subjects of the SAF population (36.0%; Stage 1: six in four subjects; Stage 2: eight in five subjects) were related to the trial drug. Noteworthy, Grade 3 trial drug-related febrile neutropenia, a TEAE considered a DLT for conventional docetaxel, was encountered in only

one subject (4.0%; Subject 11-07), in Stage 1 of the trial. In total, 34 SAEs were experienced by 16 subjects (64.0%; Stage 1: 15 SAEs in eight subjects; Stage 2: 18 SAEs in eight subjects), of which one was not treatment-emergent (Subject 11-01 in Stage 1 had worsening dyspnea that occurred prior to trial treatment). In total, 28 of the 33 serious TEAEs that occurred during the trial were of Grade 3 and were encountered in 13 subjects (52.0%; Stage 1: 12 serious TEAEs in six subjects; Stage 2: 16 serious TEAEs in seven subjects), with common (≥20%) Grade 3 serious TEAEs including gastrointestinal disorders (14 serious Grade 3 TEAEs in eight subjects [32.0%]; Stage 1: six in three subjects; Stage 2: eight in five subjects) and general disorders and administration site conditions (six serious TEAEs in six subjects [24.0%]; Stage 1: four in four subjects; Stage 2: two in two subjects). Of the 28 serious Grade 3 TEAEs encountered during the trial, seven serious Grade 3 TEAEs encountered in five subjects (20.0%) were possibly related to the trial drug (Stage 1: two serious TEAEs in one subject, namely nausea at two different time points, one of which due to constipation, in Subject 02-01; Stage 2: five serious TEAEs in four subjects, namely worsening of chronic kidney disease in Subject 01-02, general physical health deterioration in Subject 02-02, T-cell prolymphocytic leukemia in Subject 02-03, medical observation and dehydration in Subject 02-04).

In total, 15 AEs leading to dose modification/drug discontinuation were encountered in 10 subjects (40.0%; Stage 1: four AEs in three subjects; Stage 2: 11 AEs in seven subjects). Of the nine deaths recorded in the SAF population, one was due to the Grade 5 serious TEAE of general physical health deterioration (recorded as due to disease progression), not related to the trial drug.

Clinical laboratory evaluations, as well as assessments of vital signs, physical examination parameters, electrocardiogram (ECG), and Eastern Cooperative Oncology Group (ECOG) performance status were also performed. Clinically significant laboratory abnormalities were recorded in 24 subjects (96.0%) of the SAF population, namely in 12 of 13 subjects in Stage 1 and all subjects in Stage 2. Clinically significant ECG abnormalities were recorded in one subject in Stage 2 (Subject 13-01; 4.0%). For six (24.0%), two (8.0%) and one (4.0%) subjects, who all started with an ECOG baseline category of 0, the ECOG changed to 1, 2 or, respectively, 3 during the trial. For five subjects (20.0%) and two subjects each (8.0%), who all started with an ECOG baseline category of 1, the ECOG performance status changed to 2 or, respectively, 3 during the trial. Lastly, no AEs were related to the coronavirus-19 (COVID-19) pandemic.
In conclusion, occurences of TEAEs, Grade ≥3 TEAEs, Grade ≥3 trial-drug related TEAEs, serious TEAEs and Grade ≥3 serious TEAEs were balanced between the two stages. Serious trial drug-related TEAEs and Grade ≥3 serious trial-drug related TEAEs occurred in higher numbers of subjects in Stage 2 than in Stage 1 (four subjects in Stage 2 vs one subject in Stage 1 and, respectively, three subjects in Stage 2 vs one subject in Stage 1). ECOG performance status changes also occurred in a higher number of subjects in Stage 2 vs Stage 1 (nine subjects in Stage 2 vs four subjects in Stage 1). A possible explanation for these differences could be the longer time duration for Stage 2 of the trial versus Stage 1.

OVERALL CONCLUSIONS:

Based on the aforementioned results, CriPec®docetaxel displays a similar efficacy as that of conventional docetaxel in early Phase I clinical trials (Extra et al, 1993; Cortes and Pazdur, 1995). The low efficacy observed with CriPec®docetaxel in this trial could potentially be explained by factors such as:

- The small sample size that limited evaluation of responses;
- The major and minor protocol deviations due to the COVID-19 pandemic (such as exclusion of/delays in efficacy assessments at EOT for several subjects; for specific details, see Section 10.3.1);
- Previous lines of treatment, including taxanes, received by all subjects enrolled in the trial:
    - PD was recorded in all subjects who had previously received four or five lines of therapy (four lines: three subjects in Stage 1 and one subject in Stage 2; five lines: three subjects in Stage 1), as well as in two subjects who had previously received two lines of therapy in Stage 2 and four subjects who had previously received three lines of therapy in Stage 1.
- Advanced disease, stage III or above, recorded in the majority of subjects at baseline;
- Noteworthy, based on the results of the CRITAX trial (results shown below, Section 7.2.2) the intratumoral released docetaxel concentration after CriPec®docetaxel administration in patients with advanced, unresectable and/or refractory solid tumors was not significantly different from that of free docetaxel upon conventional docetaxel administration.

Common (≥20% in Stage 1, Stage 2 or in total) trial-drug related toxicities encountered during treatment with CriPec®docetaxel in this trial, gastrointestinal disorders and skin and subcutaneous tissue disorders, are similar in terms of grade and frequency to those previously encountered in clinical trials investigating conventional docetaxel (Katsumata 2003). In this trial, treatment with CriPec®docetaxel led to only one trial-drug related TEAE of febrile neutropenia (of Grade 3) encountered in one subject (4.0%). This is in contrast to published Phase II clinical trials in patients with ovarian cancer, in which conventional docetaxel was reported to lead to Grade 3-4 febrile neutropenia in 90-96% of patients (Aapro et al, 1994; Francis et al, 1994; Piccart et al, 1995; Kavanagh et al, 1996; see Katsumata 2003 for a comprehensive summary), therefore highlighting that CriPec®docetaxel leads to a lower incidence of febrile neutropenia than its conventional counterpart

Taken together, these results suggest that the choice of indication and of target population may have contributed to the low efficacy observed in this trial with CriPec®docetaxel. In terms of safety, severe (febrile) neutropenia was much lower (see Section 12.2.1) and no new toxicities were found compared to what has been reported for the active ingredient docetaxel.

DATE OF THE REPORT:

30Nov2020