

2. SYNOPSIS

Name of Sponsor: I.R.I.S., 50 rue Carnot - 92284 Suresnes Cedex - France		<i>(For National Authority Use only)</i>
Test drug Name of Finished Product: Not applicable Name of Active Ingredient: S81694 Associated agent: paclitaxel		
Individual Study Table Referring to Part of the Dossier	Volume:	Page:
Title of study: Phase I/II trial of S81694 administered intravenously in combination with paclitaxel to evaluate the safety, pharmacokinetic and efficacy in metastatic breast cancer. Protocol No.: CL1-81694-003 EudraCT No.: 2017-002459-27 The description of the study protocol given hereafter includes the modifications of the 4 substantial amendments to the protocol.		
International coordinator [REDACTED]		
Study countries: Multicentre study. Phase I: dose escalation (Belgium, France, Japan, The Netherlands). 6 centres in 4 countries included a total of 22 patients: 8 patients in France, 4 Patients in Japan, 7 patients in Belgium, and 3 patients in The Netherland. Phase II was not initiated.		
Publication (reference): Not applicable		
Studied period: Initiation date: 04 January 2018 Completion date: 08 June 2020 (Date of last follow-up)		Phase of development of the study: Phase I/II
Objectives: The purpose of this study was to determine the safety profile, the maximum tolerated dose (MTD) and the associated dose-limiting toxicities (DLTs) of S81694 in combination with paclitaxel in metastatic breast cancer (mBC) patients, as well as to investigate the antitumour activity of the combination in metastatic triple negative breast cancer (mTNBC) patients.		
Phase I: Dose escalation part <u>Primary objectives:</u> <ul style="list-style-type: none"> - To determine the safety profile and tolerability of S81694 given in combination with paclitaxel by assessment of the DLT [during cycle (C) 1] and the MTD based on safety data described using National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 in patients with mBC, - To establish the recommended phase II dose (RP2D) of S81694 in combination with paclitaxel. <u>Secondary objectives:</u> <ul style="list-style-type: none"> - To characterise the plasma pharmacokinetic (PK) profiles of S81694 and of paclitaxel and its metabolites (if applicable) in combination. - To investigate any preliminary antitumour activity of this combination. 		
Phase II: not initiated The purpose of this phase II was to evaluate the Progression Free Survival (PFS) in patient receiving S81694 in combination with paclitaxel or paclitaxel alone. The phase II part of the study was not initiated. The sponsor decided to discontinue the recruitment into the study CL1-81694-003, with S81694 in combination with paclitaxel in mBC and to stop the whole development programme. This decision notified on 2 December 2019 was related to the likely narrow therapeutic margin of S81694 in combination with paclitaxel and the emergence of effective immune therapies in mTNBC (very recent changes in competitive environment).		

Methodology:

This was an international, multicentre, open label phase I/II trial.

This study was conducted in two successive parts:

- A dose escalation phase I part, which was a single arm, non-randomised and non-comparative study in patients with mBC
- A randomised phase II part, which was not initiated.

A 5-parameter Bayesian Logistic Regression Model (BLRM) for drug combination trials, was used for the dose allocation process in phase I.

This study was performed in strict accordance with Good Clinical Practice.

Number of patients:

Planned: up to 117 patients (up to 27 for phase I and 90 for phase II with 45 patients per arm).

Included: 22 patients for phase I.

Diagnosis and main criteria for inclusion

Of note, criteria specific to phase II were not detailed below.

Inclusion criteria:

- Male or female patient aged ≥ 18 years old, or legal age of the majority in the country.
- Histologically or cytologically confirmed mBC, refractory to any standard therapy or for which the standard therapy was considered unsuitable.
- Patient had at least one evaluable or measurable metastatic lesion [lesions as defined by revised Response Evaluation Criteria in Solid Tumours (RECIST) v1.1, 2009].
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
- Estimated life expectancy of at least 3 months.
- Adequate haematological function based on the last assessment performed within 7 days prior to the first investigational medicinal product (IMP) administration.
- Adequate renal function based on the last assessment performed within 7 days prior to the first IMP administration.
- Adequate hepatic function based on the last assessment performed within 7 days prior to the first IMP administration.
- Female patient of childbearing potential had a negative pregnancy test (serum) within 7 days prior to the first day of IMPs administration. Female patients of childbearing and male patients with partners of childbearing potential had to use an effective method of birth control.
- Written informed consent.

Main non-inclusion criteria:

- Unlikely to cooperate or comply with scheduled visits and study procedures.
- Pregnancy, breastfeeding or possibility of becoming pregnant during the study.
- Participation in another interventional study at the same time or within 4 weeks prior to the first IMP administration.
- Patient already enrolled in the study.
- Other active malignancy within the last 3 years.
- Presence of grade ≥ 2 toxic effects (excluding alopecia) due to prior cancer therapy
- Known hypersensitivity to the IMPs (S81694 and paclitaxel) or their excipients of the preparations or any agent given in association with this study (*i.e.* premedication for paclitaxel infusion).
- Evidence of peripheral neuropathy of grade 2 or higher.
- Patient who previously received paclitaxel and discontinued due to toxicity related to paclitaxel.
- Any prior anticancer therapy within 4 weeks or 5 half-lives, (whichever is the shorter) before the first IMP administration.
- Patient with current, serious, uncontrolled infections.
- Patient with brain metastasis or leptomeningeal metastasis (except patients with brain metastasis that had been stable post-radiation therapy and who were off steroids for > 2 months).
- History of cardiac disease.
- Episode(s) of clinically relevant bleeding event (CTCAE grade ≥ 3) within 3 weeks before the first IMP administration.
- Major surgery within 4 weeks prior to the first IMP administration, or patients who had not recovered from side effects of the surgery.
- Extended field radiation within 4 weeks or limited field radiation within 2 weeks before the IMP administration.
- Uncontrolled arterial hypertension.
- Presence of risk factors for torsades de pointes (*e.g.* heart failure, hypokalaemia, family history of long QT syndrome).
- Patients who, within 7 days prior to the first S81694 intake, were receiving or received strong inducers of cytochrome P450 (CYP) 3A4, strong and moderate inducers of CYP2C8, strong and moderate inhibitors of CYP2C8 or strong inducers of flavin-containing monooxygenase (FMO) 1 and FMO3.
- Patients who were receiving CYP3A4 sensitive substrates, and CYP3A4 and Breast Cancer Resistance Protein substrates with narrow therapeutic index.
- Human immunodeficiency virus (HIV) or immunodeficiency syndrome (AIDS)-related illness (positive serology to HIV antibody), or positive serology to HBs antigen or HCV antibody.
- Any clinically significant medical condition or laboratory abnormality likely to jeopardize the patient's safety or to interfere with the conduct of the study, in the investigator's opinion.

Investigational Medicinal Products (IMPs):

A treatment cycle lasted 28 days, according to the following schedule:

- Weekly S81694 given intravenously as a one-hour infusion on day (D)1, D8 and D15 of a 28-day cycle, and after approval of Amendment No. 4, on D1 and D15 of a 28-day cycle. A range of six provisional doses for S81694 was defined (13.5, 20, 30, 60, 80 and 150 mg/m²).
- Weekly paclitaxel given intravenously at 80 mg/m² as a one-hour infusion on D1, D8 and D15 of a 28-day cycle. The dose of paclitaxel could be adapted according to the PK analysis or related toxicities. Premedication prior to paclitaxel administration was required in order to reduce the risk of severe hypersensitivity reaction; this premedication consisted of corticosteroids, antihistamines and histamine H₂-receptor antagonists, their administration was in accordance with the Summary of Product Characteristics (SmPC) of paclitaxel and the standard practice in centres.

Batches:

S81694: L0067801 and L0070111

Paclitaxel: paclitaxel Amneal (Germany): L0068123, L0071760; Bendatax (Germany): L0072846, L0074103; Taxol (Japan): AAS6288, AAX5889.

Comparator (Reference product and/or placebo):

Not applicable.

Duration of treatment: 28-day treatment cycles were repeated until disease progression, unacceptable toxicity, or investigator's/patient's decision. This period ended with a withdrawal visit (WV; up to 30 days after the last dose of test drug administration).

Patients continued treatment as long as they appeared to be receiving clinical benefit, and unless occurrence of unacceptable toxicity, or investigator's/patient's decision of withdrawal. The maximum number of cycles was left to the investigator's discretion.

Follow-up period (phase I):

After discontinuation of the study drug and its associated agent, a contact or telephone call was performed every 3 months (\pm 15 days) from the WV up to 6 months. The following information were collected: outcome of AE, patient's survival, the date of first disease progression if applicable, for patients withdrawn from the study for a reason other than disease progression, first new anticancer treatment and its starting date. The patient had access to other appropriate care by his/her doctor, which was at his/her discretion. Following sponsor decision to discontinue the study, this post-withdrawal follow-up period was cancelled for 3 patients [REDACTED]

Criteria for evaluation:**Efficacy measurements:**

- There was no efficacy measurement with regard to primary endpoints of the phase I part of the study.
- Secondary endpoints: tumour assessments based on RECIST criteria.

Safety measurements:

- DLT assessment.
- MTD.
- Any change or addition of a new concomitant treatment.
- Adverse events (AEs) and toxicity (grading according to NCI-CTCAE).
- Laboratory tests: haematology, blood biochemistry, coagulation and haemolysis parameters, urinalysis.
- Physical examination, ECOG Performance Status, vital signs measurements.
- Electrocardiogram (ECG) monitoring.
- Pregnancy test performed for women of childbearing potential.

Pharmacokinetic measurements (phase I):

For S81694 and paclitaxel, blood samples were taken at the following time points:

- C1: 15 samples for the administration on D1 and 15 samples for the administration on D15:
 - 14 samples taken according to the time of S81694 infusion: before the start of infusion (pre-dose), 5 minutes before the end of infusion; afterwards at 15 minutes, 30 minutes, 2.5h, 3h, 4h, 6h, 8h, 12h, 24h, 48h, 72h and 168h (7 days) after the end of infusion of S81694 (168h after C1D1 infusion was intended to be C1D8 pre-dose collection).
 - 1 sample taken according to the time of paclitaxel infusion: 5 minutes before the end of infusion.
- C2 and C3: before the start of the infusion of S81694 (pre-dose on D1 only).

Other measurements:

Biomarkers measurements: were only planned for phase II.

Pharmacogenetics measurements (optional): not performed. The collected samples were destroyed.

Statistical methods:**Phase I dose escalation part**

In the dose escalation phase, an adaptive 5-parameter BLRM guided by the Escalation With Overdose Control (EWOC) was used to make dose recommendations and estimate the MTD for the combination of S81694 and paclitaxel, based on the occurrence of DLTs during C1. A panel of six provisional dose levels of S81694 [13.5, 20, 30, 60, 80 and 150 mg/m² on D1, D8 and D15 (then on D1 and D15 after Amendment No. 4) of a 28-days-cycle] was considered, with the possibility of adding intermediate dose levels, and 2 provisional dose levels of paclitaxel (70 and 80 mg/m² on D1, D8 and D15) were considered.

The proposed dose allocation methodology was designed to permit to consider all the combination levels, allowing the escalation or de-escalation of one agent of the combination, based on the observed DLT probability.

Analysis Sets

The following analysis sets were defined according to ICH E9 guidelines.

- Screened Set: corresponded to all screened patients.
- Included Set (IS): corresponded to all included patients.
- Safety Set (SS): corresponded to included patients who took at least one dose of IMP (S81694 or paclitaxel). Patients were analysed according to the treatment received on C1D1. Each patient was classified into and analysed consistently within one (and only one) combination dose level.
- Dose-Limiting Toxicity Evaluable Set (DLTES): all patients of the SS evaluable for DLT.

Study outcome

Descriptive statistics were provided on the IS by combination dose level and overall for the phase I part.

Efficacy analysis

Efficacy analyses were carried out in the SS.

Descriptive statistics were provided for the Best Overall Response (BOR) and Objective Response Rate (ORR). The duration of response and progression free survival (PFS) were estimated via Kaplan-Meier method. In addition, 95% CIs for median duration were computed.

Safety analysis:

Descriptive statistics were provided in patients of the SS.

Pharmacokinetic analysis:**Analytical method**

The concentrations of S81694 in human heparinised plasma samples were determined according to a validated method using liquid-liquid extraction followed by chromatographic separation and MS/MS detection. The lower limit of quantification (LLOQ) was 1.00 ng/mL in plasma.

The concentrations of paclitaxel and its metabolites in human heparinised plasma samples were determined according to a validated method using liquid-liquid extraction followed by a LC-MS/MS method. The LLOQ in plasma was 6.30 ng/ml for paclitaxel and 2.50 ng/ml for the two main metabolites.

Pharmacokinetic assessment

The pharmacokinetics of S81694 in plasma was assessed after the first (D1) and the last dose (D15) of the first cycle of treatment by standard non-compartmental analysis using Phoenix® WinNonlin® version software 8.1 (Certara, USA).

The PK analysis in plasma was conducted using actual sampling times.

Descriptive statistics (mean, SD, CV%, minimum value, median, maximum value) were calculated for plasma concentration data and PK parameters.

Statistical analysis was performed after a log-transformation of the PK parameters of S81694 treatment. For each dose level separately, a mixed effect model was fitted with day as fixed effect and subject as a random effect. For C1, D15 was compared to D1 for each dose level to evaluate the accumulation based on C_{inf} , AUC_{last} and AUC_{0-169} .

Plasma concentration of paclitaxel measured in the patients included in the study were compared to expected plasma concentrations in cancer patients using an external visual predictive check (VPC) approach based on a published population PK model.

SUMMARY - CONCLUSIONS**DISPOSITION OF PATIENTS AND ANALYSIS SETS**

	S81694 13.5 mg/m ² /W + Paclitaxel 80 mg/m ² /W (N = 4)	S81694 20 mg/m ² /W + Paclitaxel 80 mg/m ² /W (N = 9)	S81694 30 mg/m ² /EOW + Paclitaxel 80 mg/m ² /W (N = 4)	S81694 45 mg/m ² /EOW + Paclitaxel 80 mg/m ² /W (N = 5)	All (N = 22)
Included	4	9	4	5	22
Withdrawn due to					
- Adverse event	1	2	1	-	4
- Progressive disease	3	5	3	3	14
- Physician decision	-	2	-	2	4
Safety set	4	9	4	5	22
DLTES	3	7	3	3	16

BASELINE CHARACTERISTICS

All patients were female, with a median age of 53 years (mean \pm SD: 52.4 \pm 8.2 years). Out of 16 patients having provided the information, seven patients were Caucasian/White (43.8%), 4 were Asian (25.0%) and 5 of other ethnicities (31.3%). The mean \pm SD mBC duration was 8.3 \pm 6.3 years. All patients had stage IV tumours, with metastases at inclusion and were in relapse. Eleven (11) patients (50%) had a triple negative phenotype (ER- / PR- / HER2-) at inclusion.

The mean \pm SD treatment interval free interval was 38.5 \pm 30.0 days, with 12 patients having it equal to 30 days or less.

All patients had a previous drug treatment for mBC. Most of them had also a previous surgery (95.5%), and/or a previous radiotherapy (95.5%). The median number of treatment lines was 5 (Q1; Q3: 3; 6), with 12 patients (54.6%) having received 5 or more.

The most frequently reported symptoms related to breast cancer were fatigue (31.8%); dyspnoea (18.2%); ALT increased, AST increased, GGT increased and anaemia (13.6% for each of them).

Three patients had non measurable disease at baseline.

The ECOG performance status was between 0 and 1 for all the population.

EXTENT OF EXPOSURE

In the SS, global treatment duration ranged (Min, Max) between 1.7 and 45.1 weeks with a mean (\pm SD) of 16.2 \pm 9.6 weeks (median of 16.1 weeks). One patient had a global treatment duration of less than 4 weeks, 7 patients had a treatment duration between 4 and 12 weeks (included), 9 patients (40.9%) had a treatment duration between 12 and 24 weeks and 5 patients over 24 weeks. Patients completed on average 4.41 \pm 3.02 cycles.

The mean RDI for S81694 was 82.9 \pm 17.4%, (Q1, Q3: 76.7%;98.3%), and the mean RDI for paclitaxel was 87.5 \pm 12.9%, (Q1; Q3: 81.0%; 98.3%).

EFFICACY RESULTS

As a secondary objective of the phase I study, the BOR was assessed in all 22 patients of the SS. Partial response (PR) was confirmed in 4 patients (18.2%), stable disease (SD) in 11 patients (50%), progressive disease (PD) in 5 patients (22.7%) and non-complete response / non progressive disease in 2 patients (9.1%) who had non measurable disease at baseline. The objective response rate was 18.2% with a 95%CI of [7.3 ; 38.5]. The median duration of response was 29.4 weeks with a 95% confidence interval of [17.0 ; 41.9] for responder patients (n = 4). The median progression-free survival was 4.4 months with a 95% confidence interval of [2.0; 5.8] for all patients.

- Pharmacokinetic

After the first cycle of treatment, at all dose levels, on both C1D1 and C1D15, the inter-patient variability did not affect the estimates of the mean systemic exposure parameters.

At all dose levels, the maximum plasma concentrations were reached about at the end of infusion. Plasma concentrations of S81694 showed a polyexponential decline with overall average half-life of about 100 hours. The volume of distribution was high indicating a wide tissue distribution. Plasma clearance was low, suggesting a low rate of elimination from the systemic circulation.

Both on C1D1 and C1D15, the systemic exposure to S81694 appeared to increase proportionally with the dose and the accumulation ratios were in agreement with the administration schedule and the half-life of the compound.

Overall, plasma concentrations of paclitaxel measured in the study were consistent with paclitaxel PK profile described in the literature, except for the sampling time just before the end of infusion, where observations appeared to be systematically above the prediction interval, on average twice as high as the median predicted by the model.

SAFETY RESULTS

- Dose Limiting Toxicity

Overall 6 patients were not evaluable for DLT at end of C1. One DLT was observed at 20 mg/m²/W of S81694 in combination with paclitaxel 80 mg/m²/W with grade (G) 3-acute kidney injury, G3-anaemia, G3-hyperkalaemia and G4-hyperuricaemia. The primary endpoint of defining the MTD and the Recommended Phase 2 dose (RP2D) of S81694 given in combination with paclitaxel was not reached since the sponsor decided to discontinue the study. The highest combination tested was 45mg/m²/EOW of S81694 (D1, D15) in combination with paclitaxel 80 mg/m²/W (D1, D8, D15), with a median toxicity rate of 12% and a probability of being in the toxicity interval of 27%.

- Emergent adverse events

Table - Overall summary for adverse events in the Safety Set

		S81694 13.5 mg/m ² /W + Paclitaxel 80 mg/m ² /W (N = 4)	S81694 20 mg/m ² /W + Paclitaxel 80 mg/m ² /W (N = 9)	S81694 30 mg/m ² /EOW + Paclitaxel 80 mg/m ² /W (N = 4)	S81694 45 mg/m ² /EOW + Paclitaxel 80 mg/m ² /W (N = 5)	All (N = 22)
Patients having reported at least one:						
TEAE during the treatment period	n (%)	4 (100)	9 (100)	4 (100)	5 (100)	22 (100)
Treatment-related EAE						
S81694 only	n (%)	1 (25.0)	1 (11.1)	-	2 (40.0)	4 (18.2)
Paclitaxel only	n (%)	2 (50.0)	6 (66.7)	2 (50.0)	5 (100)	15 (68.2)
S81694 and paclitaxel	n (%)	4 (100)	8 (88.9)	3 (75.0)	5 (100)	20 (90.9)
Serious AE (including death) during the study	n (%)	2 (50.0)	2 (22.2)	2 (50.0)	1 (20.0)	7 (31.8)
Serious TEAE (including death)	n (%)	1 (25.0)	2 (22.2)	1 (25.0)	1 (20.0)	5 (22.7)
Treatment related serious EAE						
S81694 only	n (%)	-	-	-	-	-
Paclitaxel only	n (%)	-	-	-	-	-
S81694 and paclitaxel	n (%)	1 (25.0)	1 (11.1)	-	-	2 (9.1)
TEAE leading to treatment withdrawal						
S81694	n (%)	2 (50.0)	3 (33.3)	1 (25.0)	-	6 (27.3)
paclitaxel	n (%)	1 (25.0)	4 (44.4)	2 (50.0)	1 (20.0)	8 (36.4)
S81694 and paclitaxel	n (%)	1 (25.0)	3 (33.3)	1 (25.0)	-	5 (22.7)
Serious TEAE leading to treatment withdrawal						
S81694	n (%)	1 (25.0)	2 (22.2)	-	-	3 (13.6)
paclitaxel	n (%)	1 (25.0)	2 (22.2)	-	-	3 (13.6)
S81694 and paclitaxel	n (%)	1 (25.0)	2 (22.2)	-	-	3 (13.6)
Treatment-related EAE leading to treatment withdrawal						
S81694 (related only and withdrawn)	n (%)	-	-	-	-	-
paclitaxel (related only and withdrawn)	n (%)	-	1 (11.1)	1 (25.0)	1 (20.0)	3 (13.6)
S81694 and paclitaxel	n (%)	1 (25.0)	1 (11.1)	1 (25.0)	-	3 (13.6)
Treatment-related serious EAE leading to treatment withdrawal						
S81694 (related only and withdrawn)	n (%)	-	-	-	-	-
paclitaxel (related only and withdrawn)	n (%)	-	-	-	-	-
S81694 and paclitaxel	n (%)	1 (25.0)	-	-	-	1 (4.5)
Fatal TEAE	n (%)	-	1 (11.1)	-	-	1 (4.5)
Patients who died during the study	n (%)	1 (25.0)	4 (44.4)	2 (50.0)	-	7 (31.8)

All patients reported at least one Treatment Emergent Adverse Event (TEAE). The **most frequently affected SOC**s were gastrointestinal disorders (77.3% of patients), blood and lymphatic system disorders (72.7%), general disorders and administration site conditions (72.7%), investigations (68.2%), skin and subcutaneous tissue disorders (68.2%), nervous system disorders (59.1%), musculoskeletal and connective tissue disorders (50.0%), respiratory, thoracic and mediastinal disorders (50.0%).

The **most commonly reported TEAEs** were fatigue (59.1%), anaemia (54.5%), neutrophil count decreased (45.5%), alopecia (40.9%), and diarrhoea (36.4%).

The pooled PT “neutropenia and neutrophil count decreased” occurred in 54.5% of the patients.

Fifteen patients (68.2%) reported at least one **severe TEAE** (grade \geq 3). Investigations (40.9%) was the most frequently affected SOC in this category, followed by blood and lymphatic system disorders (18.2%). The most frequently reported severe TEAEs were neutrophil count decreased (18.2%), GGT increased (13.6%) and neutropenia (9.1%).

Overall, 5 patients (22.7%) had at least one **serious TEAE (including fatal events)**: neutropenia, pneumonia, metastases to central nervous system, malignant neoplasm progression, malignant pleural effusion, anaemia, hyperkalaemia, hyperuricemia, delirium, acute kidney injury, osteonecrosis of jaw, pulmonary embolism, and pelvic venous thrombosis (4.5% each).

TEAE related to S81694 only were reported in 4 patients (18.2%): nausea (9.1%), diarrhoea, vomiting, neutrophil count decreased, blood phosphorus decreased, and rash maculo papular (4.5% each).

TEAE related to paclitaxel only were reported in 15 patients (68.2%): alopecia (31.8%), onycholysis (18.2%), peripheral sensory neuropathy (18.2%), paraesthesia (13.6%), fatigue, dysgeusia, muscle spasms (9.1% each).

TEAE related to S81694 and paclitaxel were reported in 20 patients (90.9%): anaemia, and fatigue (45.4% each), neutrophils count decreased (36.4%), diarrhoea (18.2%), decreased appetite, nausea (13.6% each), stomatitis, neutropenia, influenza like illness, malaise, alopecia, dyspnoea (9.1% each). Overall, the pooled PT “neutropenia and neutrophil count decreased” related to both S81694 and paclitaxel occurred in 10 patients (45.5%).

Overall 7 serious TEAEs related to both S81694 and paclitaxel were reported in 2 patients (9.1%): neutropenia (2 events), pneumonia (1), anaemia (1), hyperkalaemia (1), hyperuricemia (1), and acute kidney injury (1). Among them, only 2 serious TEAEs related to both S81694 and paclitaxel (concerning 1 patient) led to S81694 and paclitaxel withdrawal (neutropenia and pneumonia).

No serious TEAE related to S81694 only and leading to S81694 withdrawal nor serious TEAE related to paclitaxel only and leading to paclitaxel withdrawal were reported.

Overall, 7 patients (31.8%) died during the study: 1 patient during the treatment period due to malignant neoplasm progression, the other 6 patients during the follow-up period and due to progressive disease. All deaths were considered as not treatment-related.

TEAEs leading to S81694 withdrawal were reported in 27.3% of the patients: malignant neoplasm progression (9.1%), neutropenia, pneumonia, AST increased, ALT increased, GGT increased, metastases to central nervous system, anaemia (4.5% each).

TEAEs leading to paclitaxel withdrawal were reported in 36.4% of the patients: malignant neoplasm progression, neutropenia, pneumonia, AST increased, ALT increased, GGT increased, metastases to central nervous system, onycholysis, dry eye, anaemia, paraesthesia, weight increased (4.5% each).

TEAEs leading to S81694 and paclitaxel withdrawal were reported in 22.7% of the patients: anaemia, neutropenia, pneumonia, AST increased, ALT increase, GGT increased, malignant neoplasm progression, metastases to central nervous system (4.5% each).

- Laboratory tests

For blood biochemical parameters rated according to the CTCAE V4.03 grading, the most frequent emergent severe abnormal values reported was G3 high GGT (18.2%).

For non-gradable biochemical parameters, the most frequent emergent out-of-range worst values were reported for high phosphorus (22.7%), low phosphorus (23.8%), low creatinine clearance (13.6%), and high urea (10.5%).

For gradable blood haematological parameters, the most frequent emergent severe abnormal values were detected for low WBC (31.8%), low neutrophils (27.3%), low lymphocytes (22.7%).

For non-gradable haematological parameters, emergent out-of-range values were most frequently detected for low haematocrit (59.1%), high reticulocytes (50.0%), low erythrocytes (40.9%), high basophils (27.3%), high eosinophils (22.7%), high leukocytes (13.6%) and high monocytes (13.6%).

For non-gradable haemolysis parameters, the most frequent emergent out-of-range worst values were reported for high LDH (27.3%) and low haptoglobin (4.5%). No emergent severe abnormal values were reported for coagulation parameters

- Other safety evaluation (ECOG performance status, weight, vital signs, ECG)

During the study, the worst ECOG PS score reported above 1 were 2 for 1 patient and 3 for 1 patient.

The median change in weight from baseline to the highest post-baseline value was 1.30 (Q1, Q3: 0.4; 3.0) kg. and -0.50 (Q1, Q3: -1.4; 0.0) kg to the lowest value.

No relevant changes in mean values over time were detected for blood pressure, heart rate and respiratory rate.

No clinically significant ECG abnormalities were reported.

CONCLUSION

In this multicentre, phase I, dose escalation study, a total of 22 patients with metastatic Breast Cancer (mBC) were included and treated with S81694 in combination with paclitaxel.

The patients' baseline characteristics were in line with the target population defined in the study protocol. After having treated 13 patients, the schedule of administration of S81694 was changed from one administration on day (D) 1, D8 and D15 to one administration on D1 and D15 of a 28-day cycle in order to increase the treatment interval to avoid neutropenia, whereas the schedule of paclitaxel administration remained the same (D1, D8 and D15 of a 28-day cycle).

One DLT was reported in a patient receiving 20 mg/m²/W of S81694 in combination with 80 mg/m²/W of paclitaxel, with acute kidney injury, anaemia, hyperkalaemia and hyperuricaemia. The primary endpoint of defining the MTD was not reached due to study discontinuation. The highest combination dose level tested was 45 mg/m²/EOW of S81694 (D1 and D15) with 80 mg/m²/W of paclitaxel, with a median toxicity rate of 12% and a probability of being in the toxicity interval of 27%.

Following administration on D1 and D15, the systemic exposure to S81694 appeared to increase proportionally with the dose and the accumulation ratios were in agreement with the administration schedule and the half-life of the compound.

Overall, plasma concentrations of paclitaxel measured in the study were consistent with paclitaxel PK profile described in the literature, except for the sampling time just before the end of infusion, where observations appeared to be systematically above the prediction interval, on average twice as high as the median predicted by the model.

Preliminary antitumour activity showed a partial response in 4 patients (18.2%) with a median duration of response of 29.4 weeks (95% confidence interval of [17.0; 41.9]).

The most frequent emergent adverse events related to S81694 and paclitaxel were: anaemia and fatigue (45.5% each), neutrophils count decreased (36.4%), diarrhoea (18.2%), decreased appetite, nausea (13.6% each), vomiting, neutropenia, influenza like illness, malaise, alopecia, dyspnoea (9.1% each). The safety of S81694 in combination with paclitaxel appeared consistent with the known safety profiles of the individual drugs, and no new safety signals were identified with the combination.

The recommended Phase 2 dose was not determined due to study discontinuation. Enrolment was stopped during the escalation part, thus the phase II part of the study was not initiated as the sponsor decided to stop the whole development programme.

Date of the report: 20 January 2020

Version of the report: Final version