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# Evaluation of the safety of C-1311 (SYMADEX) administered in a phase 1 dose escalation trial as a weekly infusion for 3 consecutive weeks in patients with advanced solid tumours

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ABSTRACT

*Purpose:* C-1311 is a member of the novel imidazoacridinone family of anticancer agents. This phase 1 trial was designed to investigate the safety, tolerability and preliminary anti-tumour activity of C-1311.

*Patients and methods:* This was a phase 1, inter-subject dose escalating and pharmacokinetic study of intravenous (IV) C-1311, administered weekly during 3 consecutive weeks followed by 1 week rest (constituting 1 cycle) in subjects with advanced solid tumours.

*Results:* Twenty-two (22) patients were treated with C-1311, the highest dose given was 640 mg/m$^2$. All subjects experienced one or more treatment-related adverse events (AEs). The most frequently observed treatment-related AEs were neutropaenia and nausea (50% each), followed by vomiting (27%), anaemia (23%), asthenia (23%) and diarrhoea (18%). Most treatment-related AEs were of Common Terminology Criteria for Adverse Events (CTCAE) grades 1–2, except for the blood and lymphatic system disorders, which were primarily of grades 3–4. The recommended dose (RD) of C-1311 administered as once weekly IV infusions for 3 weeks every 4 weeks is 480 mg/m$^2$, with the dose limiting toxicity (DLT) being grade 4 neutropaenia lasting more than 7 days. Treatment at this dose offers a predictable safety profile and excellent tolerability.

*Conclusion:* The safety profile and preliminary anti-tumour efficacy of C-1311, observed in this broad-phase dose-finding study, warrants further evaluation of the compound.



## 1. Introduction

Because many solid tumours are still incurable despite the availability of a variety of conventional treatment modalities such as surgery, radiotherapy, and systemic treatment, it is necessary to continue to develop new therapies.

C-1311 was selected as the most promising member of the imidazoacridinone anticancer drug family.[1,2] The imidazoacridinone family was developed based on modified anthracycline and anthracendione structures and was expected to have similar mechanisms of action, i.e. inhibition of topoisomerase II and DNA intercalate.[3,4] Preliminary studies

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confirmed the activity of C-1311 against these targets. In addition, these studies showed that it induced lysosomal rupture, an unusual mechanism, and apoptosis in tumour cells without irreversible inhibition of DNA synthesis.[5]

The preclinical biological activity of C-1311 has been shown in several models. This drug exhibits significant cytotoxic activity towards various tumour cell lines *in vitro* (L1210, P388, MAC15A, MAC29 and HT29) and *in vivo* in various animal studies.[2,6–8] Moreover, in a series of studies examining the effects of C-1311 versus several multidrug resistant cell lines, it was demonstrated that C-1311 is less affected by resistance mechanisms than that seen with established agents such as doxorubicin.[9–11]

Finally, the lack of oxygen-free radicals observed after reduction of the compound by enzymes of the microsomal fraction of rat liver suggests that C-1311 would not display cardiotoxicity that is linked to compounds such as doxorubicin and other anthracyclines.[9,12] Therefore chemical modifications within the structure of C-1311 are aimed at reducing toxicity and enhancing efficacy.

According to these interesting characteristics of this drug, a phase 1 trial was designed with a classical anticancer agent dosing schedule of once a week for three weeks with one week off to determine the profile of tolerance of this drug. This phase I study is the first report of the use of C-1311 in humans with a weekly schedule in subjects with advanced solid tumours.

## 2. Patients and methods

### 2.1. Eligibility criteria

Subjects were eligible if they had histologically proven cancer disease for which standard curative or palliative measures did not exist. Prior treatments were allowed under the following circumstances: $\geqslant$4 weeks must have elapsed since major surgery or since completion of radiation or chemotherapy and must have recovered from prior surgery or adverse events (AEs) due to agents administered >4 weeks earlier.

Patients had to be $\geqslant$18 years of age with an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2 or a Karnofsky score $\geqslant$60% with an expected survival of $\geqslant$12 weeks.

Patients had to have at least one measurable or evaluable lesion outside of a previous radiation field ($\geqslant$20 mm on CT scan, X-ray or MRI and $\geqslant$10 mm on spiral CT scan).

Required laboratory values at entry included adequate haematological status: total white blood count (WBC) $\geqslant 3.0 \times 10^9$/L (3000/mL), neutrophils $\geqslant 1.5 \times 10^9$/L (1500/mL), platelets $\geqslant 100 \times 10^9$/L (100,000/mL) and haemoglobin $\geqslant$10.0 g/dL; adequate renal function as evidenced by serum creatinine within normal institutional limits, or creatinine clearance $\geqslant$60 mL/min/1.73 m$^2$ for subjects with creatinine levels above normal institutional limits; adequate hepatic function as evidenced by serum bilirubin $\leqslant 1.5 \times$ ULN, alkaline phosphatase $\leqslant 2.5 \times$ ULN ($\leqslant 5 \times$ ULN, in case of liver metastases), serum AST or ALT $\leqslant 2.5 \times$ ULN ($\leqslant 5 \times$ ULN in case of liver metastases). A negative pregnancy test (urine or blood) and an effective contraception method in women of childbearing potential were mandatory. The study was approved by an independent ethics committee and all patients gave written informed consent and conducted in two centres located in France: Centre Georges-François Leclerc, Dijon and Centre René Gauducheau, Nantes.

### 2.2. Exclusion criteria

Patients who were pregnant or lactating were excluded. Other exclusion criteria included myocardial infarction within 3 months of signature of the informed consent, unstable angina pectoris, cardiac insufficiency (NYHA Classes III–IV), uncontrolled arrhythmia or uncontrolled hypertension at the time of signature of the consent form; left ventricular ejection fraction (LVEF) <50%; uncontrolled hypercalcemia; clinically significant active infections; other prior malignancies except for cured non-melanoma skin cancer or curatively treated *in situ* carcinoma of the cervix; symptomatic peripheral neuropathy $\geqslant$2 (according to Common Terminology Criteria for Adverse Events v3.0 (CTCAE)); clinical evidence of brain or leptomeningeal metastasis.

### 2.3. Treatment and dose escalation rules

C-1311 was administered weekly as a 1-h infusion via injection into a running intravenous (IV) line during 3 consecutive weeks followed by 1 week rest. This constituted one cycle. The starting dose was 15 mg/m$^2$, corresponding of 10% of the lethal dose observed in pre clinical models. The dose escalation scheme was divided into two phases, an initial accelerated phase and a standard phase. Cohorts of one subject per dose level at 100% increment dose steps were used during the initial accelerated stage of the trial. When a subject experienced a grade 2 non-haematological or a grade 3 haematological toxicity during the first cycle, the standard escalation scheme began for all further cohorts (Fibonacci method). In the standard phase, cohorts consisted of three subjects per dose level, where the dose escalation steps represented one 33% increment and 25% increments thereafter. If two subjects of three experienced a dose limiting toxicity (DLT) during their first cycle, the maximum tolerated dose (MTD) was defined. If one of three subjects experienced DLT during cycle 1, the cohort was expanded to six subjects. If no further DLT was experienced by the additional three subjects, dose escalation was continued. Conversely, if one of the additional three subjects experienced a DLT (therefore, two out of the total of six subjects experienced a DLT) the MTD was defined. The recommended dose (RD) was defined as the dose level under the MTD. A total of nine subjects were to be included in the cohort to firmly establish the RD at the level under the MTD.

During the first three doses (cycle 1) subjects were required to remain in the hospital overnight. Thereafter, subjects were to remain under medical supervision for 1 h following the completion of the infusion. Patients were allowed to continue C-1311 treatment until disease progression or unacceptable toxicity, at the discretion of the investigator.

C-1311 was manufactured by Antisoma Research Limited, Inc. (Cambridge, MA, USA).

### 2.4. Oral administration

An oral bioavailability cohort was also included in the study. In this cohort of 6 subjects enrolled after the completion of the RD cohort, the oral bioavailability, safety and pharmacokinetics of a single oral dose of C-1311 was investigated during cycle 1 in a crossover study design. In arm A, subjects received a single oral dose of C-1311 on Day 1 and IV doses of on Day 8 and Day 15. In arm B, subjects received a single oral dose of C-1311 on Day 8 and IV doses on Day 1 and Day 15. Subjects were enrolled in alternate sequence where the first subject was entered in Arm A, the second subject in Arm B and so forth up to six subjects. C-1311 was to be administered as an IV infusion in subsequent cycles. This oral preparation consisted of the reconstituted IV dosage form of C-1311, given in a glass of orange juice. Subjects were asked to have fasted 8 h prior to study drug intake. They were allowed a light meal 2 h after the study drug intake.

### 2.5. Required data

Potential subjects were seen for a screening evaluation during the pre-treatment period (Day 6 to Day 0). Tumour assessments performed within 4 weeks of the first C-1311 administration as part of the subject's normal medical care were accepted as tumour assessment required at screening. The following assessments were to be completed within 7 days prior to the treatment: signed written informed consent form; collection of demographic data; complete medical history including concomitant medications; complete physical exam; height, weight and ECOG PS; haematology; blood chemistry; troponin I (cTnI); urinalysis; serum or urine pregnancy test (women of childbearing potential only); vital signs; New York Heart Association Classification (NYHA class); ECG (12-lead); LVEF assessed by both cardiac echography and MUGA scan. Before each administration of the drug, AEs and concomitant medications review, weight, haematology, blood chemistry, vital signs and ECG were performed. Tumour measurements were carried out every two cycles and the efficacy of the treatment was defined using the Response Evaluation Criteria in Solid Tumours.[13]

### 2.6. DLT

DLT was defined as the dose which produced a side-effect considered to be unacceptable for further patients at that level. DLT was defined using the CTCAE version 3.0. DLT was considered to have been reached in the following circumstances: a grade 3 or 4 non-haematological toxicity except alopecia or fatigue or unpremedicated nausea/vomiting. Concerning haematological toxicity, DLT was defined as: nadir neutrophils $<0.5 \times 10^9$/L for at least 7 days or $<0.1 \times 10^9$/L for at least 3 days; febrile neutropaenia (absolute neutrophil count $<0.5 \times 10^9$/L and fever [three measured temperatures >38 °C in 24 h or one >38.5°C]); platelets $<25 \times 10^9$/L or thrombocytopaenia with bleeding or requiring platelet transfusion. Omission of injections on Day 8, Day 15 or Day 1 of the next cycle because of neutrophil or platelet counts below those required was considered a DLT.

The MTD was defined as the highest dose level at which either two of three subjects or two of six subjects experienced DLT after the first administration of C-1311. The RD was the dose level below the MTD, at which level a total of nine subjects was to be included to firmly establish the RD. The data of all subjects who received at least 1 treatment cycle, or went off study during the first treatment cycle due to toxicities were used for the determination of DLT.

### 2.7. Pharmacokinetics

Blood samples were obtained on Days 1, 8 and 15 of cycle 1 at baseline, 50 min after the start of the infusion, 10, 20 and 40 min and 1, 2, 4, 8 and 24 h after the end of the infusion.

Concentrations of C-1311 in the plasma samples were determined by liquid chromatograph–tandem mass spectroscopy (LC/MS/MS). Plasma concentrations of C-1311 were analysed by model-independent methods using WinNonlin™ version 5.2 (Pharsight Corp., Mountain View, CA) when feasible.

### 2.8. Oral bioavailability

To determine the oral bioavailability of the drug, blood samples were collected during the first cycle on all subjects enrolled in this cohort. Samples were collected at the following time points: oral treatment (Day 1 or Day 8): pre-dose, 10, 15, 30, 45 min, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 h after drug intake; first IV treatment (Day 1 or Day 8): pre-dose, 50, 60, 65, 70, 80, 100 min, 2, 3, 4, 6, 8, 12, 16 and 24 h after start of the infusion; second IV treatment (Day 15): pre-dose, 50 min, 2 and 24 h after start of the infusion.

### 2.9. Statistical analysis

Because of the nature of this study, no formal statistical analysis was planned. Evaluation of the data consisted primarily of summary displays (i.e. descriptive statistics and graphs). The qualitative data were summarised by frequency and percentages, while the quantitative data were summarised by descriptive statistics.

No inferential statistics were conducted on the safety variables. The adverse events were coded using standard dictionaries and their incidences were described per preferred term and treatment, overall, and regarding their severity and their relationship with the study drug. The same analysis was carried out for all grade 3/4 toxicities.

## 3. Results

Between May 2004 and September 2005, twenty two patients were enrolled in the study from two centres located in France: Centre Georges-François Leclerc, Dijon and Centre René Gauducheau, Nantes. The characteristics of the 22 treated patients at baseline are listed in Tables 1 and 2. The main tumour type was breast cancer with 6 (27%) patients included, followed by colon or rectal cancer (14%) and head and neck cancer (14%). All patients were included after receiving standard treatment according to their tumour type.

**Table 1 – Patient characteristics (*N* = 22).**

| Characteristics | N |
|---|---|
| *Gender* | |
| Male | 11 |
| Female | 11 |
| *Age, years* | |
| Median | 56.5 |
| Range | 41–75 |
| *ECOG performance status* | |
| 0 | 9 |
| 1 | 11 |
| 2 | 2 |
| *Type of cancer* | |
| Breast cancer | 6 |
| Colon or colorectal cancer | 3 |
| Gastric cancer | 1 |
| Pancreatic cancer | 1 |
| Head and neck cancer | 3 |
| Non-small-cell-lung cancer | 1 |
| Endometrial cancer | 1 |
| Ovarian cancer | 2 |
| Renal cancer | 1 |
| Thyroid cancer | 1 |
| Others malignancies | 2 |

**Table 2 – Prior treatment; safety population (*N* = 22).**

| Treatment | N | % |
|---|---|---|
| Systemic therapy | 22 | 100 |
| Surgery | 21 | 95 |
| Radiotherapy | 14 | 64 |
| Systemic therapy plus surgery plus radiotherapy | 14 | 64 |
| Systemic therapy plus surgery without radiotherapy | 7 | 32 |

As mentioned previously, the starting dose was 15 mg/m$^2$. The dose level scheme was summarised in Tables 3 and 4. In the initial accelerated phase, patients were treated with 15 mg/m$^2$/week up to 480 mg/m$^2$/week for three consecutive weeks followed by one week of rest. The first patient treated at a dose of 480 mg/m$^2$/week had neutropaenia grade 3 at Day 22 and Day 1 of his second cycle was postponed. Two other patients were entered at this dose. As these two additional patients did not present any DLT, only a slight decrease of their neutrophil counts during their cycle 1, then a higher dose level was required to reach the MTD. Then, two patients were treated at 640 mg/m$^2$/week. Both experienced a DLT consisting of a grade 4 neutropaenia with more than 7 days without infection. This dose was considered the MTD. Six more patients were enrolled and treated at 480 mg/m$^2$ without experiencing any DLT. This dose was determined to be the RD.

**Table 3 – Dose levels by cohort assignment.**

| Level | Dose per week (mg/m$^2$) | Total dose per cycle (mg/m$^2$) |
|---|---|---|
| *Accelerated dose escalation schedule* | | |
| 1 | 15 | 45 |
| 2 | 30 | 90 |
| 3 | 60 | 180 |
| 4 | 120 | 360 |
| 5 | 240 | 720 |
| 6 | 480 | 1440 |
| *Standard dose escalation schedule* | | |
| 7 | 640 | 1920 |

To study the oral bioavailability 6 additional patients were enrolled at the RD and the safety and pharmacokinetics of a single oral dose of C-1311 was investigated during cycle 1 in a crossover study design.

### 3.1. *Drug exposure*

A total of 69 cycles of chemotherapy were received. The majority of the subjects 17/22 (77%) received two cycles of study treatment. One subject in the 60 mg/m$^2$ cohort received four cycles. Two patients, one in the 120 mg/m$^2$ and one in the 480 mg/m$^2$ dose cohort, received six cycles and one received 11 cycles at the dose of 640 (1st cycle) and 480 mg/m$^2$. Mean (median) total exposure to C-1311 was 480 mg/m$^2$.

### 3.2. *Safety*

All subjects experienced one or more treatment-related AEs. The most frequently observed treatment-related AEs were neutropaenia and nausea, each reported for 11 subjects (50%), followed by vomiting in 6 subjects (27%), and anaemia and asthenia each in five subjects (23%) and diarrhoea reported in four subjects (18%). Most treatment-related AEs were of CTCAE grades 1–2, except for the blood and lymphatic system disorders, which were primarily of grades 3–4. Incidence of possibly, probably or definitely C-1311-related adverse events, by worst grade per subject is presented in Table 5.

There were 22 SAEs, experienced by 15 subjects; two of these SAEs occurring in two subjects, in both cases grades 1–2 fever, were considered study treatment-related. All subjects had one or more abnormal haematology values in the course of the study, but these were primarily of grades 1–2. CTCAE grades 3–4 abnormal total WBC, neutrophil counts and lymphocyte counts were observed in 36–55% of the subjects. The most frequently observed abnormal blood chemistry parameter was hypo-albuminemia which was recorded in 86% of the subjects, followed by hyponatremia (55%) and abnormal liver function tests (36–50%). Most of these abnormal values were of CTCAE grades 1–2. There were a few grade 3 and no grade 4 abnormal blood chemistry values.

### 3.3. *Efficacy*

Twenty one patients were evaluable for response. One patient (DL: 480 mg/m$^2$) was not evaluable because he died before the evaluation was performed. No completed or partial responses were observed. However, stable disease was observed in 6 patients (27%) for a median duration of 4 months (range: 2–10 months). They had the following tumour types: head and neck carcinoma (2 patients), ovarian cancer (1 patient), renal

**Table 4 – Phase 1 results.**

| Cohort | Total dose per cycle | No. of patients entered | No. of cycles |
|---|---|---|---|
| 1 | 15 mg/m$^2$ | 1 | 2 |
| 2 | 30 mg/m$^2$ | 1 | 2 |
| 3 | 60 mg/m$^2$ | 1 | 4 |
| 4 | 120 mg/m$^2$ | 1 | 6 |
| 5 | 240 mg/m$^2$ | 1 | 3 |
| 6 | 480 mg/m$^2$ IV | 9 | 32 |
| | IV/PO | 6 | 18 |
| 7 | 640 mg/m$^2$ | 2[a] | 2 |

a Grade 4 neutropaenia more than 7 days observed in both patients dosed at 640 mg/m$^2$. This dose was designated as maximum tolerated dose (MTD).

**Table 5 – >5% Incidence of possibly, probably or definitely C-1311-related adverse events, by worst grade per subject; safety population (*N* = 22).**

| System organ class | | CTCAE grade | | | | No. of subjects with events | |
|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | *n* | % |
| Blood and lymphatics system disorders | Anaemia | 1 | 3 | 1 | 0 | 5 | 23 |
| | Febrile neutropaenia | 0 | 0 | 2 | 0 | 2 | 9 |
| | Neutropaenia | 0 | 0 | 6 | 5 | 11 | 50 |
| | Thrombocytopaenia | 1 | 0 | 1 | 0 | 2 | 9 |
| Gastrointestinal disorders | Aphthous stomatitis | 0 | 2 | 0 | 0 | 2 | 9 |
| | Diarrhoea | 3 | 1 | 0 | 0 | 4 | 18 |
| | Nausea | 8 | 3 | 0 | 0 | 11 | 50 |
| | Vomiting | 4 | 2 | 0 | 0 | 6 | 27 |
| General disorders and administration site conditions | Asthenia | 4 | 1 | 0 | 0 | 5 | 23 |
| | Pyrexia | 3 | 0 | 0 | 0 | 3 | 14 |

cell carcinoma (1 patient), sarcoma (1 patient) and thyroid cancer (1 patient). Two of the three patients with head and neck tumour experienced the longer period of stable disease (10 months).

### 3.4. *Pharmacokinetics*

Following 15–640 mg/m$^2$ 1-h IV infusion in cancer patients, the plasma concentrations of C-1311 declined rapidly in a biphasic manner, with mean plasma clearance ($CL_p$) ranging from 41.2 to 116 L/h, and mean terminal elimination half-life ($t_{1/2}$) ranging from 3.8 to 9.3 h. Mean volume of distribution ($V_{ss}$) ranged from 129 to 638 L, higher than the volume of total body water in human indicating extensive tissue distribution and binding.

Comparison of AUC values for C-1311 following 480 mg/m$^2$ oral versus IV dosing in a cross over design indicated a mean (±SD) systemic bioavailability of 12.5% (±11.7%) for C-1311 ($n$ = 6).

## 4. Discussion

The imidazoacridinone derivative, C-1311, is a new anti-tumour agent that exhibits anti-tumour activity against experimental colorectal and breast cancer and has been selected for entry into clinical trial.[2,6,7]

This study was the first study with C-1311 in humans. The starting dose was established at 15 mg/m$^2$/week, representing one-sixth of the rat MTD total dose fractionated in three (three weekly treatments per cycle). The choice of repeated doses was made according to the observations in the preclinical results. Indeed, studies in cell systems L1210 and HeLaS3 indicated that C-1311 induced accumulation of tumour cells in the G2 phase of the cell cycle.[6,14] The kinetics of this induction of G2 arrest was dependent on both the dose and the duration of treatment. Cell-cycle arrest was reversible for up to 3 h of treatment but irreversible at longer incubation times.

The study was designed to assess the MTD, the DLT, the RD, the pharmacokinetic profile and the safety of C-1311, as well as to provide preliminary evidence of anti-tumour activity of C-1311 in subjects with advanced solid tumours.

The criteria for MTD were reached at the dose of 640 mg/m$^2$. Indeed, this dose was poorly tolerated during the first cycle in two patients with grade 4 neutropaenia, which was the DLT. Therefore C-1311 480 mg/m$^2$ on day 1, 8 and 15 every 3 weeks (dose level 6) was considered to be the recommended dose.

Results of the present study have shown that the C-1311 is safe and manageable. The main AEs reported were in the blood and lymphatic systems with neutropaenia but the incidence of complications was low: none patient experienced febrile neutropaenia. In these patients experiencing grades 3–4 haematological toxicities the median number of previous

lines of chemotherapy administered was 4 (range : 1–7). The incidences of grades 3–4 non-haematological adverse events, mainly gastrointestinal disorders or General Disorder, were also low with no grade 3 or 4 episode reported at the RD. No cardiac toxicity was observed but a cardiac monitoring is necessary in the future studies to confirm that.

In term of anti-tumour activity, three subjects died on study; two of progressive disease (PD) and one subject after experiencing aspiration pneumonia.

The patients included in the present study were considered patients with a very poor prognosis. They had advanced metastatic disease and were progressive on previous cytotoxic therapy. This may have contributed to the modest anti-tumour efficacy of C-1311 observed in the present study. None of the subjects achieved a complete or partial response. Best response to treatment was SD, which was seen in six subjects (27%), especially for two patients with head and neck tumour experienced the longer period of stable disease (10 months).

Systemic bioavailability of C-1311 following dosing with oral C-1311 was 12.5%.

## 5. Conclusion

In conclusion, the RD of C-1311 administered as once weekly IV infusions for 3 weeks every 4 weeks is 480 mg/m$^2$, the DLT being grade 4 neutropaenia. Treatment at this dose offers a predictable safety profile and good tolerability. The modest anti-tumour efficacy of C-1311, observed in this broad-phase 1 dose finding study, warrants further evaluation of the compound.

## Conflict of interest statement

None declared.

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