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CLINICAL TRIAL

Iniparib administered weekly or twice-weekly in combination with gemcitabine/carboplatin in patients with metastatic triple-negative breast cancer: a phase II randomized open-label study with pharmacokinetics

Véronique Diéras[1,2] · Hervé Bonnefoi[3] · Emilio Alba[4] · Ahmad Awada[5] · Bruno Coudert[6] · Xavier Pivot[7] · Joseph Gligorov[8] · Agnes Jager[9] · Stefania Zambelli[10] · Geoffrey J. Lindeman[11] · Eric Charpentier[12] · Gary T. Emmons[13] · Ignacio Garcia-Ribas[14] · Robert Paridaens[15] · Jaap Verweij[9]

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Abstract

Purpose Metastatic triple-negative breast cancer (TNBC) is a phenotypic breast cancer subgroup with a very poor prognosis, despite standard treatments. Combined twice-weekly iniparib and gemcitabine/carboplatin (GC+tw-iniparib) showed benefit over gemcitabine/carboplatin in a randomized phase II trial, and a phase III was initiated comparing these regimens. The present phase II study was initiated to compare GC+tw-iniparib with a more practical once-weekly schedule (GC+w-iniparib) in TNBC.

Methods Metastatic TNBC patients were randomized to receive iniparib weekly (11.2 mg/kg on days 1 and 8) or twice-weekly (5.6 mg/kg on days 1, 4, 8, and 11) with gemcitabine (1000 mg/m^2) and carboplatin (area under the curve 2 on days 1 and 8), every 3 weeks. The primary endpoint was the overall response rate (ORR). Pharmacokinetics of iniparib and its two metabolites were analyzed.

Results A total of 163 patients were randomized, 82 GC+w-iniparib and 81 GC+tw-iniparib. Demographic and baseline characteristics were well balanced. ORR was 34.1% (95% CI 23.9–44.4%) vs. 29.6% (95% CI 19.7–39.6%) and median progression-free survival was 5.5 months (95% CI 4.2–5.7) vs. 4.3 months (95% CI 3.0–5.8) for GC+w-iniparib and GC+tw-iniparib, respectively. Safety was similar across treatment arms in terms of event severity and type. Iniparib plasma concentrations and exposure were two-fold higher with w-iniparib compared to tw-iniparib. Iniparib and its metabolites were cleared rapidly with a terminal half-life of < 1 h, without accumulation.

Conclusions Despite a doubled maximum concentration with weekly iniparib, no detectable differences in safety or efficacy were observed between the weekly and twice-weekly administration schedules in this population.

Trial registration ClinicalTrial.gov Identifier NCT01045304.

Keywords Iniparib · Metastatic triple-negative breast cancer · Pharmacokinetics · Administration schedule

Abbreviations

AE	Adverse events
AUC2	Carboplatin area under the curve
CBR	Clinical benefit rate
ER	Estrogen receptor
GC+w-iniparib	Gemcitabine-carboplatin plus weekly iniparib
GC+tw-iniparib	Gemcitabine-carboplatin plus twice-weekly iniparib
HER2	Human epidermal growth factor receptor 2
IABA	4-Iodo-3-amino-benzoic acid
IABM	4-Iodo-aminobenzamide
IHC	Immunohistochemistry
ITT	Intent-to-treat
ORR	Overall response rate
OS	Overall survival
PARP	Poly(ADP-ribose)polymerase
PFS	Progression-free survival

✉ Véronique Diéras
v.dieras@rennes.unicancer.fr

Extended author information available on the last page of the article

PR	Progesterone receptor
RECIST	Response Evaluation Criteria in Solid Tumors
TNBC	Triple-negative breast cancers
ULN	Upper limit of normal

Introduction

In breast cancer patients, routine assessment of the estrogen and progesterone receptors (ER, PR), along with the human epidermal growth factor receptor 2 (HER2) has been critical for predicting response to hormonal and targeted therapies. Approximately 15% of breast tumors are totally devoid of these three receptors [1–3], harboring thus a triple-negative breast cancers (TNBC) phenotype. In view of their specific behavior compared to other subtypes, they constitute a distinct clinical subset of aggressive breast cancers characterized by an increased risk of relapse compared to other subtypes, earlier development of distant metastases, higher rates of visceral and central nervous system metastases, and shorter overall survival [2–6]. Moreover the prognosis of patients with unresectable local relapse or distant metastasis is very poor [7]. For many years, chemotherapy has been the mainstay of treatment for these patients, and anthracyclines or taxanes are the preferred options in first-line, except in patients with germline BRCA mutations where carboplatin seems of interest versus docetaxel [8]. More recently, the immune checkpoint inhibitor atezolizumab combined with chemotherapy has shown interesting activity in first-line treatment in a phase III study [9]. Concerning targeted therapies, poly(ADP-ribose)polymerase (PARP) inhibitors provide the only treatment option that currently has shown scattered positive results in this subtype. Two PARP inhibitors have demonstrated a statistically significant progression-free survival (PFS) benefit in patients with germline BRCA mutations [10, 11]. Of note, patients with both TNBC and hormone-receptor-positive tumors were included in these two trials.

Iniparib (4-iodo-3-nitrobenzamide, BSI-201/SAR240550) was originally investigated as a PARP inhibitor. However, in subsequent preclinical analyses, it was unable to inhibit PARP enzymatic or cellular activity, and was shown to form adducts in a non-specific manner with cysteine-containing proteins [12, 13]. A randomized phase II study in metastatic TNBC showed that iniparib administered twice-weekly at a dose of 5.6 mg/kg on days 1, 4, 8 and 11 every 3 weeks, in combination with gemcitabine 1000 mg/m^2 and carboplatin area under the curve (AUC2) on days 1 and 8, improved the clinical benefit rate (CBR), PFS and overall survival (OS) without potentiating chemotherapy-related toxicity [14]. A phase III study replicating the phase II study design using the same dose and schedule was thus initiated [15]. However, given the clinical inconvenience of requiring four iniparib infusions per cycle, including two without chemotherapy (days 4 and 11), the present phase II trial was initiated in metastatic TNBC patients and performed in parallel with the phase III, investigating the tolerance and efficacy of a once-weekly schedule of administration (days 1 and 8, every 3 weeks) compared to twice-weekly administration. It was designed to evaluate a more clinically acceptable dosing regimen for iniparib administered in combination with gemcitabine and carboplatin in terms of the overall response rate (ORR). Pharmacokinetics of the weekly regimen were explored.

Patients and methods

Patient eligibility

Women had to be over 18 years, have histologically documented breast cancer that was ER and PR-negative (< 10% tumor staining by immunohistochemistry [IHC] for both), and HER2-non-overexpressing by IHC (0, 1 +) or IHC 2 + and fluorescence in situ hybridization (FISH) negative, measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1), an Eastern Cooperative Oncology Group performance status of 0 or 1, adequate hematologic, renal, and hepatic function, including absolute neutrophil count ≥ 1500/mm^3, platelets ≥ 100,000/mm^3, hemoglobin ≥ 9 g/dL, ALT/AST ≤ 2.5 × upper limit of normal (ULN) or ≤ 5 x ULN with liver involvement, bilirubin ≤ 1.0 x ULN, serum creatinine ≤ 1.5 mg/dL or creatinine clearance ≥ 60 mL/min. Up to two prior chemotherapy regimens for metastatic disease were permitted. Previous neoadjuvant/adjuvant systemic therapy was considered a prior chemotherapy line for metastatic disease if the first relapse occurred within 1 year after the last treatment. Patients with brain metastases were eligible if lesions were clinically stable and did not require steroids, as were patients with skin lesions ≥ 10 mm. Patients were ineligible if they had previous treatment with gemcitabine, platinum salts, or a PARP inhibitor, bone metastases only, or had not recovered to grade ≤ 1 for adverse events (AE) per NCI-CTCAE. The study was approved by the local and national ethics committees and conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. Informed consent was obtained from all individual participants included in the study (NCT01045304).

Study design

This open-label, randomized phase II study used a "pick-the-winner" design [16] to choose between two administration

regimens. It was performed in 20 centers in Europe and Australia between February 2010 and November 2012. Patients were randomized via an interactive voice response system to receive gemcitabine-carboplatin with iniparib administered either weekly (GC+w-iniparib) or twice-weekly (GC+tw-iniparib) in a 1:1 ratio, with stratification based on prior chemotherapy lines for metastatic disease (none versus one or two). The primary objective was to determine the ORR with each schedule. To compensate for lack of blinding and prevent any bias in assessment of clinical benefit, an Independent Radiology Review Committee blinded to the treatment reviewed responses. Safety was reviewed by a steering committee. When the study reached the predefined primary endpoint, the protocol was amended to allow patients to continue iniparib in an extension protocol.

Treatment

Gemcitabine was administered at 1000 mg/m^2 as a 30-min intravenous infusion and carboplatin AUC2 as a 60-min intravenous infusion, on days 1 and 8 of a 3-week cycle. Iniparib was administered as a 1-h intravenous infusion either weekly (days 1 and 8) at 11.2 mg/kg, or twice-weekly (days 1, 4, 8 and 11) at 5.6 mg/kg, giving a total dose of 22.4 mg/kg iniparib per cycle in both arms. Dose reductions for gemcitabine or carboplatin and a maximum 2-week treatment delay were implemented in the event of toxicity.

Clinical evaluations

Tumor assessment was performed at baseline then every two cycles. Response was evaluated according to RECIST by the Independent Radiology Review Committee, based on blinded central review of scans, although the decision on the patient's treatment was based on local assessment. Complete and partial responses required confirmation at least 4 weeks after initial documentation. Patients without a valid post-baseline tumor assessment were considered non-responders. Safety was assessed per AEs (NCI-CTCAE v 4.0), changes in vital signs, physical examinations, laboratory tests, electrocardiogram, and performance status. Laboratory tests were performed on days 1 and 8 of every cycle.

Pharmacokinetics

Pharmacokinetic sampling was planned in at least 15 patients per arm using 3-mL blood samples collected in heparinized tubes. For cycle 1, samples were collected for the first and last iniparib administration (day 8 for once-weekly and day 11 for twice-weekly), at pre-infusion, 30 min after the start of infusion, immediately prior to the end of the 60-min infusion, and 20, 40, and 60 min then 2, 4, and 9 h post-infusion. For cycle 2, samples were collected pre-infusion, 30 min after the start of infusion and immediately prior to the end of the 60-min infusion. For the twice-weekly regimen, additional samples were collected on day 4, pre-infusion and immediately prior to the end of the 60-min infusion.

Plasma concentrations of iniparib and its metabolites 4-iodo-aminobenzamide (IABM) and 4-iodo-3-aminobenzoic acid (IABA) were measured. Although inactive, the two metabolites were measured as they are products of the postulated reductive metabolic pathway of iniparib [17]. Concentrations were measured using a validated liquid chromatograph–tandem mass spectrometry method, using a 0.2 mL EDTA-containing plasma sample by separation on a 3-micron reversed phase LC column with detection by turbo-spray ESI positive ion mass spectrometry. Carbon-13 labeled standards of iniparib, IABM and IABA were used as internal standards. The lower limit of quantitation was 1 µg/mL for iniparib and 0.4 µg/mL for IABM and IABA.

Pharmacokinetic parameters of iniparib, IABM, and IABA were determined by non-compartmental analysis, and included maximum observed concentration (C_{max}), time to maximum observed concentration (t_{max}), area under the curve from time 0 to infinity (AUC), terminal half-life, volume of distribution at steady-state, and plasma clearance.

Statistical analyses

Using the "pick-the-winner" selection design, the sample size was determined on the basis of the 48% ORR observed in the interim analysis of the preceding phase II study evaluating combined gemcitabine and carboplatin with the twice-weekly schedule of iniparib in metastatic TNBC patients [14]. With 80 patients per treatment arm, the design provided 88% power to identify the superior regimen (if any), defined as the regimen with an absolute gain in ORR of at least 10% over the other regimen.

Efficacy variables were analyzed in the intent-to-treat (ITT) population (all randomized patients). The safety population included all randomized patients who received at least one (even incomplete) dose of study treatment. The cutoff date for efficacy analyses was 12 months after the first dose of the last patient treated.

The primary endpoint was ORR as assessed by the Independent Radiology Review Committee, defined as the proportion of patients with confirmed responses. Secondary efficacy endpoints were PFS, CBR and OS. PFS was the time from randomization until progression or death. Patients without progression or who were alive were censored at the last valid tumor assessment before the cutoff. CBR was the proportion of patients with confirmed complete response, partial response or stable disease after 24 weeks. OS was defined as the time from randomization until death. Surviving patients were censored at the last date the patient was known to be alive or the cutoff date, whichever was first. No

formal statistical comparison of efficacy variables between the two arms was conducted as per study design. The primary efficacy endpoint and the CBR were estimated for each arm, and the exact two-sided 95% confidence interval (CI) was calculated by normal approximation. PFS and OS were analyzed with the Kaplan–Meier method.

Results

From February 2010 to December 2010, 163 patients were randomized, 82 to the GC+w-iniparib arm and 81 to the GC+tw-iniparib arm. One patient randomized to the GC+tw-iniparib arm was not treated due to thrombocytopenia and was excluded from the safety analyses. Pharmacokinetic samples were collected from 35 GC+w-iniparib patients (42.7%) and 34 GC+tw-iniparib patients (42.0%). Patient disposition is shown in Fig. 1. All patients had discontinued from the study at the cutoff. Two patients (one in each arm) with clinical benefit at this time started the extension protocol.

Patient demographics and disease characteristics were generally well balanced between the two arms (Table 1). All but two patients (98.8%) had an ECOG of 0 or 1. All patients had a confirmed pathological diagnosis of TNBC. At least 80% of patients in both arms had tumors that were completely negative for ER and/or PR, and all other tumors exhibited < 10% immunostaining for ER and/or PR. Only 4% of patients in the GC+tw-iniparib and 10% of patients in the GC+w-iniparib arms were HER2 IHC 2 + and FISH negative. The predominant histological subtype was infiltrating ductal carcinoma (150 patients; 92.0%). Nine patients presented with metastatic disease (without prior metastatic treatment), while all other patients had progressed following

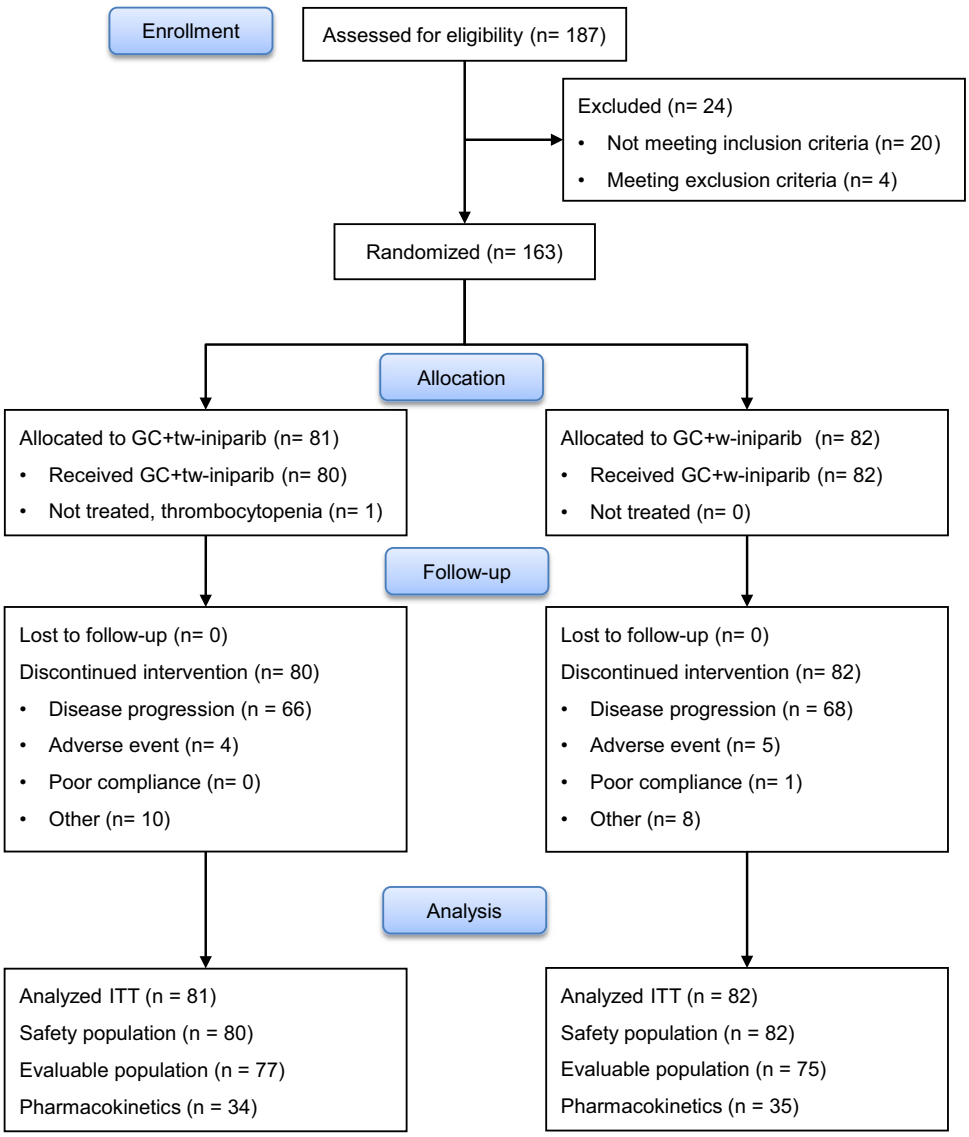

Fig. 1 Patient disposition flowchart. GC+*w-iniparib*: iniparib administered weekly in combination with gemcitabine/carboplatin. GC+*tw-iniparib* iniparib administered twice-weekly in combination with gemcitabine/carboplatin

Table 1 Patient and disease characteristics

	GC+w-iniparib ($N=82$)	GC+tw-iniparib ($N=81$)
Age in years, median (range)	49.5 (27–76)	48 (32–78)
Menopausal, *N* (%)	53 (64.6%)	49 (60.5%)
ECOG performance status, *N* (%)		
0	45 (54.9%)	51 (63.0%)
1–2	37 (45.1%)	30 (37.0%)
Hormone receptor status, *N* (%)		
Triple-negative	82 (100%)	80 (100%)
Estrogen receptor		
< 10%	82 (100%)	80 (100%)
< 1%	65 (79.3%)	69 (86.3%)
Progesterone receptor		
< 10%	80 (97.6%)	80 (100%)
< 1%	70 (85.4%)	72 (90.0%)
Human epidermal growth factor 2		
IHC (0,1 +)	70 (85.4%)	76 (95.0%)
IHC 2 + and FISH-	8 (9.8%)	3 (3.8%)
IHC missing and FISH-	4 (4.9%)	1 (1.3%)
Number of organs involved, *N* (%)		
1	29 (35.4%)	21 (25.9%)
2	25 (30.5%)	29 (35.8%)
3	12 (14.6%)	17 (21.0%)
≥ 4	16 (19.5%)	14 (17.3%)
Metastatic sites		
Lymph nodes	40 (48.8%)	35 (43.2%)
Lungs	36 (43.9%)	48 (59.3%)
Liver	31 (37.8%)	34 (42.0%)
Bone	22 (26.8%)	15 (18.5%)
Brain	9 (11.0%)	6 (7.4%)
Skin	5 (6.1%)	6 (7.4%)
Prior chemotherapy for metastatic disease, *N* (%)		
0 lines	35 (42.7%)	33 (40.7%)
1–2 lines	47 (57.3%)	48 (59.3%)
Advanced only	8 (10.0%)	3 (4.1%)
Adjuvant/neoadjuvant only	48 (60.0%)	48 (64.9%)
Adjuvant/neoadjuvant plus advanced	24 (30.0%)	23 (31.1%)
Time in months from last therapy to randomization, median (range)	7.44 (0.4–77.2)	7.77 (−0.1[a] to 50.3)

GC+*w-iniparib* iniparib weekly with gemcitabine/carboplatin, GC+*tw-iniparib* iniparib twice-weekly with gemcitabine/carboplatin

[a]One patient was randomized 3 days after the end of last therapy

previous adjuvant/neo-adjuvant treatment or prior chemotherapy for metastatic TNBC. Approximately two-thirds of the patients (69.3%) had at least two organs involved at baseline, including the primary site. Lung metastases were 15% more frequent in patients in the GC+tw-iniparib arm (59.3% vs. 43.9%, respectively).

Thirty-three patients (40.7%) in the GC+tw-iniparib arm and 35 (42.7%) in the GC+w-iniparib arm were randomized into the strata "no prior chemotherapy for metastatic disease". Prior neo-adjuvant/adjuvant systemic therapy was considered prior chemotherapy for metastatic disease if the first relapse occurred within 1 year after the last treatment, and was reported in 36 patients in the GC+tw-iniparib arm and 31 patients in the GC+w-iniparib arm. Eight (9.9%) patients in the GC+tw-iniparib arm and nine (11.0%) in the GC+w-iniparib arm were randomized into the wrong strata. Approximately 25% of patients in each arm had received prior bevacizumab.

A total of 134 (82.2%) patients discontinued treatment due to disease progression. Nine patients discontinued due to an AE, five (6.1%) in the GC+w-iniparib arm and four (4.9%) in the GC+tw-iniparib arm. Other reasons for treatment discontinuation included withdrawal of consent (three GC+w-iniparib, one GC+tw-iniparib), clinical disease progression (three GC+tw-iniparib), complete response (three GC+tw-iniparib) or stable disease (one GC+tw-iniparib), no benefit (two GC+w-iniparib), maximal gemcitabine–carboplatin effect observed (one GC+tw-iniparib), investigator decision (one GC+tw-iniparib), and poor compliance (one in each arm).

Efficacy

Response and survival data are presented in Table 2. The median follow-up was 12.2 months. In the ITT population, the ORR was 34.1% (95% CI 23.9–44.4%) in the GC+w-iniparib arm and 29.6% (95% CI 19.7–39.6%) in the GC+tw-iniparib arm. As expected, ORR by randomization stratum was higher in the no previous chemotherapy compared with

Table 2 Efficacy response, ITT patients

	GC+w-iniparib	GC+tw-iniparib
Best overall response	***N* = 82**	***N* = 81**
Complete response, *N* (%)	1 (1.2%)	2 (2.5%)
Partial response, *N* (%)	27 (32.9%)	22 (27.2%)
Stable disease, *N* (%)	38 (46.3%)	36 (44.4%)
Progressive disease, *N* (%)	13 (15.9%)	20 (24.7%)
Not evaluable/missing data, *N* (%)	3 (3.7%)	1 (1.2%)
Overall response, *N* (%)	28 (34.1%)	24 (29.6%)
95% CI[a]	23.9–44.4%	19.7–39.6%
Clinical benefit[b], *N* (%)	34 (41.5%)	26 (32.1%)
95% CI[a]	30.8–52.1%	21.9–42.3%
No prior chemotherapy for mTNBC	*N* = 35	*N* = 33
Overall response, *N* (%)	16 (45.7%)	12 (36.4%)
95% CI[a]	29.2–62.2%	20.0–52.8%
Clinical benefit[b], *N* (%)	20 (57.1%)	13 (39.4%)
95% CI[a]	40.7–73.5%	22.7–56.1%
1–2 prior lines of chemotherapy for mTNBC	*N* = 47	*N* = 48
Overall response *N* (%)	12 (25.5%)	12 (25.0%)
95% CI[a]	13.1–38.0%	12.8–37.3%
Clinical benefit[b], *N* (%)	14 (29.8%)	13 (27.1%)
95% CI[a]	16.7–42.9%	14.5–39.7%
Progression-free survival (PFS)	***N* = 82**	***N* = 81**
Patients with PFS event, *N* (%)	57 (69.5%)	57 (70.4%)
Documented disease progression, *N* (%)	55 (67.1%)	56 (69.1%)
Death without progression, *N* (%)	2 (2.4%)	1 (1.2%)
Patients censored, *N* (%)	25 (30.5%)	24 (29.6%)
No progression and no death, *N* (%)	7 (8.5%)	8 (9.9%)
New anti-cancer treatment, *N* (%)	16 (19.5%)	14 (17.3%)
Death or progression after > 1 missed tumor assessment, *N* (%)	2 (2.4%)	2 (2.5%)
Median PFS in months (95% CI)	5.5 (4.2–5.7)	4.3 (3.0–5.8)
Overall survival (OS)	***N* = 82**	***N* = 81**
Patients with OS event, *N* (%)	51 (62.2%)	50 (61.7%)
Patients censored, *N* (%)	31 (38.3%)	31 (38.3%)
Median OS in months (95% CI)	12.6 (10.6–17.2)	12.4 (10.6–16.0)

GC+*w-iniparib* iniparib weekly with gemcitabine/carboplatin, GC+*tw-iniparib* iniparib twice-weekly with gemcitabine/carboplatin

[a]95% confidence intervals estimated by normal approximation

[b]Complete + partial responses + stable disease ≥ 24 weeks

the one or two previous lines of chemotherapy setting. For patients with no previous chemotherapy, ORR was 45.7% (95% CI 29.2–62.2%) in the GC+w-iniparib and 36.4% (95% CI 20.0–52.8%) in the GC+tw-iniparib. For patients in second or third-line setting, ORR was lower, being approximately 25% in both arms.

For CBR, the difference between the two arms was 17.7% favoring the GC-w-iniparib arm. Overall, 70% of patients had a PFS event. Median PFS was 5.5 months (95% CI 4.2–5.7 months) and 4.3 months (95% CI 3.0–5.8 months) in the GC+w-iniparib and GC+tw-iniparib arms, respectively (Table 2, Fig. 2). OS was similar in the two arms at cutoff, with 62.2% and 61.7% deaths, and median OS of 12.6 months (95% CI 10.6–17.2) and 12.4 months (95% CI 10.6–16.0 months) in the GC+w-iniparib and GC+tw-iniparib arms, respectively (Table 2).

Pharmacokinetics

Summary pharmacokinetic parameters for iniparib, IABM and IABA are shown in Table 3. Mean AUC of IABM was < 1% of iniparib AUC and of IABA was ≤ 2.5%. C_{max} and exposure for iniparib and its metabolites increased approximately two-fold with the dose of 11.2 mg/kg once-weekly compared to the 5.6 mg/kg dose twice-weekly. There was no accumulation in exposure on day 8 or day 11, and for the twice-weekly arm, the plasma concentrations at end of the infusion on day 4 were similar to those on day 1. Total exposure did not differ between the schedules at each cycle. Maximum plasma concentrations of iniparib were generally reached between 30 and 60 min after the infusion start and decreased rapidly when the infusion stopped. The terminal elimination half-life for iniparib as measured by the geometric mean was generally a little shorter than that observed with the arithmetic mean, at 0.32 h and 0.61 h for cycle 1, day 1 of the twice-weekly cohort and 0.43 h and 0.62 h for the once-weekly cohort. The arithmetic and geometric means of the terminal half-lives for the metabolites were similar, and approximately 1 h for IABM and 1 h 50 min for IABA. Iniparib pharmacokinetic parameters for cycle 2 (first and last day) as well as cycle 1 day 4 (twice-weekly) were similar to those of cycle 1 day 1. The plasma concentrations of both inactive metabolites were generally less than 1% of the parent drug (data not shown).

Safety

Safety was analyzed in the 162 treated patients. A median of six cycles were administered in both arms (range: 1–40 for GC+w-iniparib, and 1–31 for GC+tw-iniparib). For both arms, relative drug intensity for gemcitabine was > 69%, > 71% for carboplatin, and > 92% for iniparib and there were no clinically meaningful differences in exposure between the two arms for any drug.

Toxicity profiles were similar for the two arms (Table 4). Most patients had at least one grade 3 or 4 event (86.6% of GC+w-iniparib and 93.3% of GC+tw-iniparib). Hematologic toxicity was widespread, with approximately 77%

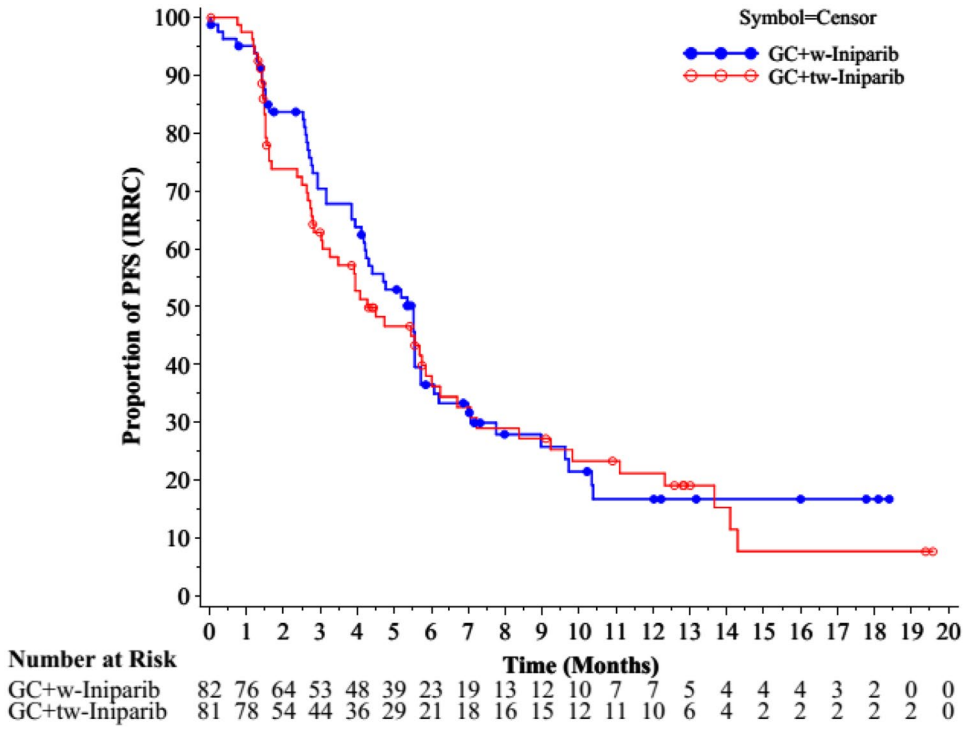

Fig. 2 Kaplan–Meier estimates of progression-free survival for the two iniparib schedules in the ITT population. GC+*w-iniparib* iniparib administered weekly in combination with gemcitabine/carboplatin. GC+*tw-iniparib* iniparib administered twice-weekly in combination with gemcitabine/carboplatin. At 3, 6, 9, 12 and 15 months, PFS probabilities (95% confidence intervals) were 0.7 (0.59–0.79), 0.36 (0.25–0.48), 0.26 (0.16–0.37), 0.17 (0.08–0.28) and 0.17 (0.08–0.28) with GC+w-iniparib, and 0.63 (0.51–0.73), 0.38 (0.26–0.49), 0.27 (0.17–0.39), 0.21 (0.12–0.32) and 0.08 (0.02–0.2) with GC+tw-iniparib

Table 3 Iniparib and metabolite pharmacokinetic parameters (cycle 1)

Schedule	Day	*N*	Iniparib, mean (CV%)			
			T_{max} (h)[a]	C_{max} (ng/mL)	AUC (ng h/mL)	$T_{1/2}$ (h)
Twice-weekly (5.6 mg/kg)	1	34	0.92	2190 (42%)	2060 (34%)	0.65 (146%)
	11	32	0.92	2410 (56%)	2420 (68%)	1.4 (139%)
Once-weekly (11.2 mg/kg)	1	34	0.69	3820 (41%)	4160 (119%)	0.92 (136%)
	8	33	0.58	3790 (44%)	3610 (36%)	1.32 (121%)
Schedule	Day	*N*	IABM, mean (CV%)			
			T_{max} (h)[a]	C_{max} (ng/mL)	AUC (ng h/mL)	$T_{1/2}$ (h)
Twice-weekly (5.6 mg/kg)	1	34	1.0	7.52 (49%)	14.1 (49%)	0.82 (26%)
	11	32	1.0	8.30 (51%)	15.9 (40%)	0.98 (33%)
Once-weekly (11.2 mg/kg)	1	35	1.0	16.0 (47%)	27.6 (32%)	0.84 (31%)
	8	33	1.0	15.9 (46%)	27.3 (37%)	0.85 (21%)
Schedule	Day	*N*	IABA, mean (CV%)			
			T_{max} (h)[a]	C_{max} (ng/mL)	AUC (ng h/mL)	$T_{1/2}$ (h)
Twice-weekly (5.6 mg/kg)	1	34	1.3	13.1 (63%)	38.9 (52%)	1.8 (22%)
	11	32	1.3	13.2 (58%)	41.4 (51%)	1.9 (36%)
Once-weekly (11.2 mg/kg)	1	35	1.3	30.9 (54%)	92.5 (62%)	1.8 (21%)
	8	33	1.3	31.8 (44%)	91.0 (43%)	1.8 (25%)

CV % coefficient of variation

[a]T_{max} presented as median values

patients having grade 3–4 events, in particular neutropenia (70% GC+w-iniparib patients, 72% GC+tw-iniparib) including four GC+w-iniparib and two GC+tw-iniparib patients with febrile neutropenia. Asthenia/fatigue and gastrointestinal toxicities were frequent. Nausea, fatigue, vomiting, decreased appetite, myalgia, and urinary tract infections were more frequent in GC+tw-iniparib patients, while asthenia was more frequent with GC+w-iniparib.

Fatal AEs were reported in three patients, one of which was considered treatment-related (acute respiratory distress syndrome in a GC+w-iniparib patient). AEs requiring treatment discontinuation were lung infection and anemia, acute respiratory distress syndrome, neutropenia, asthenia, and thrombocytopenia (GC+w-iniparib) and thrombocytopenia, acute generalized exanthematous pustulosis, tumor embolism, and paresthesia (GC+tw-iniparib).

Discussion

The twice-weekly iniparib schedule used in the initial phase II and phase III studies [14, 15] is very inconvenient, requiring four clinic visits for two weeks out of three. We thus decided to conduct the current study with a once-weekly regimen to determine if the same dose intensity of iniparib administered once weekly, gives a similar ORR without additional toxicity as the twice-weekly administration. The ORR was 34.1% and 29.6% in the once-weekly and twice-weekly iniparib arms, respectively, with the ORR in the once-weekly iniparib arm numerically superior to the twice-weekly iniparib arm. The pick-the-winner design was chosen to select between the two administration schedules, allowing statistical goals to be addressed while maintaining a relatively small sample size. Nonetheless this study design is not intended for formal hypothesis testing or endpoint comparison [18]. The ORRs observed in this trial are very similar to the 33.7% observed in the phase III trial with iniparib twice-weekly 5.6 mg/kg iniparib in a similar patient population [15]. However the ORR observed in the initial randomized phase II with twice-weekly iniparib was considerably higher [14]. This difference is difficult to explain since the patient populations appear similar. One possible explanation could be that in this and the phase III trials, response was centrally assessed whereas investigator assessment was used in the initial randomized phase II. Another possible explanation is the relatively small number of patients treated with iniparib in the initial phase II study ($N=61$).

Overall, AEs reported with the triplet iniparib combination were consistent with those of the backbone chemotherapy. The safety profile of iniparib combined with gemcitabine and carboplatin was similar across treatment arms in terms of severity (grade 3–4) and outcomes. A slight increase was noted in the frequency of grade 1 and 2 AEs with the twice-weekly iniparib regimen compared with the

Table 4 Main adverse events occurring in > 15% patients in at least one arm

	GC+w-iniparib (*N* = 82)		GC+tw-iniparib (*N* = 80)	
	All grades	Grade 3–4	All grades	Grade 3–4
Hematologic				
Neutropenia	51 (62.2%)	50 (70.4%)	55 (68.8%)	54 (72.0%)
Anemia	26 (31.7%)	10 (14.1%)	26 (32.5%)	10 (13.3%)
Leukopenia	23 (28.0%)	23 (32.4%)	26 (32.5%)	26 (34.7%)
Thrombocytopenia	23 (28.0%)	13 (18.3%)	24 (30.0%)	10 (13.3%)
Non-hematologic				
Nausea	44 (53.7%)	1 (1.2%)	57 (71.3%)	2 (2.5%)
Asthenia	39 (47.6%)	5 (6.1%)	34 (42.5%)	3 (3.8%)
Constipation	31 (37.8%)	0	35 (43.8%)	1 (1.3%)
Fatigue	23 (28.0%)	4 (4.9%)	35 (43.8%)	4 (5.0%)
Vomiting	22 (26.8%)	2 (2.4%)	30 (37.5%)	1 (1.3%)
Headache	24 (29.3%)	2 (2.4%)	24 (30.0%)	2 (2.5%)
Diarrhoea	18 (22.0%)	2 (2.4%)	22 (27.5%)	1 (1.3%)
Pyrexia	18 (22.0%)	0	16 (20.0%)	1 (1.3%)
Decreased appetite	11 (13.4%)	0	22 (27.5%)	0
Dyspnea	15 (18.3%)	4 (4.9%)	17 (21.3%)	2 (2.5%)
Alopecia	15 (18.3%)	0	17 (21.3%)	0
Cough	13 (15.9%)	0	15 (18.8%)	0
Back pain	11 (13.4%)	0	13 (16.3%)	1 (1.3%)
Dysgeusia	13 (15.9%)	0	10 (12.5%)	0
Myalgia	6 (7.3%)	0	17 (21.3%)	0
Dizziness	6 (7.3%)	0	12 (15.0%)	1 (1.3%)

GC+w-iniparib iniparib weekly with gemcitabine/carboplatin, *GC+tw-iniparib* iniparib twice-weekly with gemcitabine/carboplatin

once-weekly administration, although this could be attributed to the more frequent visit schedule in the former cohort.

Plasma concentrations of iniparib and its metabolites IABM and IABA increased dose proportionally with the once-weekly 11.2 mg/kg dose compared to the twice-weekly 5.6 mg/kg dose. Consistent with the short half-lives of iniparib and its inactive metabolites IABM and IABA, there was no drug accumulation. Plasma concentrations of both metabolites were low compared to iniparib concentrations. Iniparib is cleared extensively metabolically, mostly through glutathione de-activation [19]. The doubling of C_{max} due to the higher dose in the once-weekly arm compared to the twice-weekly arm, did not result in a difference in safety or efficacy endpoints between the two arms.

In summary, the equivalence of the efficacy and safety results for the two iniparib schedules that were observed in this study, combined with the clinically more logistically suitable weekly administration (with a consequently reduced visit frequency), support the use of once-weekly iniparib with a gemcitabine/carboplatin dosing regimen in any future clinical trials evaluating iniparib. This study shows the relevance of pharmacology-oriented clinical studies in support of the proper design of large clinical trials focusing on efficacy.

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Compliance with ethical standards

Conflicts of interest EC, GTE and IGR are current or former employees and have stock options of Sanofi. JG and JV have received remuneration and/or had an advisory/consultancy role for Sanofi. VD, EA, AA, JG, and JV have/had a consultancy/advisory role with and/or received remuneration from pharmaceutical companies other than Sanofi. All other authors declare no potential conflicts of interest (HB, BC, XP, AJ, SZ, GL, RP).

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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Affiliations

Véronique Diéras[1,2] · Hervé Bonnefoi[3] · Emilio Alba[4] · Ahmad Awada[5] · Bruno Coudert[6] · Xavier Pivot[7] · Joseph Gligorov[8] · Agnes Jager[9] · Stefania Zambelli[10] · Geoffrey J. Lindeman[11] · Eric Charpentier[12] · Gary T. Emmons[13] · Ignacio Garcia-Ribas[14] · Robert Paridaens[15] · Jaap Verweij[9]

Hervé Bonnefoi
H.Bonnefoi@bordeaux.unicancer.fr

Emilio Alba
ealbac@uma.es

Ahmad Awada
ahmad.awada@bordet.be

Bruno Coudert
BCoudert@cgfl.fr

Xavier Pivot
xpivot@strasbourg.unicancer.fr

Joseph Gligorov
joseph.gligorov@aphp.fr

Agnes Jager
a.jager@erasmusmc.nl

Stefania Zambelli
zambelli.stefania@hsr.it

Geoffrey J. Lindeman
lindeman@wehi.edu.au

Eric Charpentier
eric.charpentier@sanofi.com

Gary T. Emmons
Gary.Emmons@sanofi.com

Ignacio Garcia-Ribas
ignaciogarciaribas@googlemail.com

Robert Paridaens
paridaensrobert@hotmail.com

Jaap Verweij
j.verweij@erasmusmc.nl

[1] Department of Medical Oncology, Institut Curie, Paris, France

[2] Centre Eugène Marquis, Avenue de la bataille Flandres-Dunkerque, CS 44229, 35042 Rennes Cedex, France

[3] Institut Bergonié, Univ. Bordeaux, INSERM U1218, INSERM CIC1401, Bordeaux, France

[4] Department of Clinical Oncology, Hospital Clínico Universitario Virgen de la Victoria, Málaga, Spain

[5] Oncology Medicine Department, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium

[6] Medical Oncology Department, Centre Georges François Leclerc, Dijon, France

[7] Department of Medical Oncology, Centre Paul Strauss, Strasbourg, France

[8] Medical Oncology Dept Tenon Hospital, Inserm U938, Institut Universitaire de Cancérologie APHP-Sorbonne Université, Paris, France

[9] Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands

[10] Department of Medical Oncology, IRCCS OSR, San Raffaele, Milan, Italy

[11] Department of Medical Oncology, Peter MacCallum Cancer Centre and Royal Melbourne Hospital, The Walter and Eliza

Hall Institute of Medical Research, Melbourne, VIC, Australia

[12] Statistics Department, Sanofi, 640 Memorial Drive, Cambridge, MA 02139, USA

[13] Translational Medicine and Early Development, Sanofi, Bridgewater, NJ, USA

[14] Early Oncology Development, Sanofi, Madrid, Spain

[15] Department of Medical Oncology, University Hospital Gasthuisberg, Catholic University of Leuven, Leuven, Belgium