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Non-pegylated liposomal doxorubicin (NPLD, Myocet®) + carboplatin in patients with platinum sensitive ovarian cancers: A ARCAGY-GINECO phase IB-II trial

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HIGHLIGHTS

- Carboplatin + non-pegylated liposomal doxorubicin (NPLD) is effective in platinum-sensitive recurrent ovarian cancers.
- The disease control rate at 12 months was 30%.
- This combination is well tolerated but should be prescribed with G-CSF support.
- NPLD could be an alternative to pegylated liposomal doxorubicin in association with carboplatin.

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ABSTRACT

Background. Carboplatin and pegylated liposomal doxorubicin combination is a standard regimen in platinum-sensitive recurrent ovarian cancer patients. The pegylated liposomal doxorubicin shortage from 2011 to 2013 urged assessment of the efficacy and tolerance of non-pegylated liposomal doxorubicin in combination with carboplatin.

Methods. MYCA was a multicenter 2-step phase Ib-II single arm trial meant to assess the safety and efficacy of carboplatin AUC 5 mg/min.mL combined with non-pegylated liposomal (dose escalation from 40 to 50 mg/m^2

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during phase Ib step; and 50 mg/m2 during phase II step), every 4 weeks in patients with platinum-sensitive relapse. The primary objective was disease control rate (DCR) at 12 months.

Results. From 2012 to 2014, 87 patients were enrolled. They were treated as second (78%) or third line (22%) treatment. Total of 67 patients (78%) completed 6 cycles. G-CSF support was prescribed to 58% patients. The DCR at 12 months was 30.0% (95% CI, 20.3–39.7); the median PFS was 10.0 months (95% CI, 8.6–11.0). The median overall survival was 28.1 months (95% CI, 22.3–32.5); and the objective response rate was 58% (95% CI, 47–68). Grade 3–4 neutropenia, anemia and thrombocytopenia were observed in 17%, 13% and 1%, respectively; febrile neutropenia in 6%. One patient who did not receive GCSF support died from febrile neutropenia.

Conclusion. Non-pegylated liposomal doxorubicin-carboplatin combination exhibits an acceptable safety profile, with GCSF prophylaxis. Acknowledging the lack of direct comparison, efficacy in terms of 12 month DCR was comparable with standard treatments.

1. Introduction

Ovarian cancer is the leading cause of death from gynaecological malignancies with almost 239,000 new cases and 154,000 death every year worldwide [1]. In the case of platinum-sensitive (PtS) relapse, the standard therapeutic strategy is to re-challenge patients with a platinum-containing regimen. Carboplatin and pegylated liposomal doxorubicin (PLD) combination became a standard treatment after CALYPSO trial demonstrating significant improvement in progression-free survival (PFS; hazard ratio [HR], 0.82; 95% CI, 0.72–0.94; $P = 0.005$) in patients with PtS recurrent ovarian cancer patients (ROC) compared to conventional carboplatin paclitaxel (CP) regimen [2,3].

However PLD (Caelyx®) was not available due to international shortage from 2011 to 2013 [4]. An alternative treatment had to be considered.

Non-pegylated liposomal doxorubicin (NPLD, Myocet®) consists of doxorubicin complexed with citrate inside non-pegylated liposomes. Encapsulation of doxorubicin within liposomes is meant to minimize distribution of the active drug to healthy tissues, such as the heart, while increasing preferential distribution of the drug to the tumor site [5,6]. This drug is already approved for the treatment of metastatic breast cancers [7,8]. Although NPLD efficacy was assessed as a single agent in 20 patients with recurrent ovarian cancers in a small phase II trial (ORR 20%) [9], it has not been investigated in combination with carboplatin.

MYCA study was designed by ARCAGY-GINECO to assess the safety and efficacy of the NPLD-carboplatin combination, as an alternative to the PLD-carboplatin association in patients with PtS ROC.

2. Material and methods

2.1. Trial/study design

This multicenter prospective non-randomized two-step single arm phase Ib-II trial was conducted in France. It was designed to assess the efficacy and safety of carboplatin and NPLD combination in patients with PtS ROC (NCT01705158). It was approved by national and institutional research ethics committees. Patients provided written informed consent prior inclusion.

2.2. Eligibility criteria

Eligible patients were women ≥ 18 years old with a histologically confirmed diagnosis of epithelial ovarian cancer (EOC), Fallopian tube or peritoneal epithelial cancer, and had PtS recurrence after first- or second line platinum-based chemotherapy regimen. Platinum-sensitive relapse was defined as a clinical, biological or radiological recurrence occurring >6 months after the last platinum administration.

Patients were required to have a measurable tumor mass according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) or CA-125 assessable disease according to Gynecologic Cancer InterGroup (GCIG) criteria.

Other key eligibility criteria included a life expectancy of >12 weeks, satisfactory bone marrow [neutrophil count ≥ $1{,}5 \times 10^9$/l; platelet count ≥ 100×10^9/l; hemoglobin ≥ 9.0 g/dl], renal [calculated creatinine clearance by the Cockcroft and Gault formula or MDRD ≥ 50 ml/min] and hepatic [bilirubin ≤ 1.5 × upper norm; transaminases ≤ 2.5 × upper norm; alkaline phosphatase ≤ 2.5 × upper norm] functions, Eastern Cooperative Oncology Group performance status < 2.

The exclusion criteria were: benign or borderline tumor histology; malignant non-epithelial tumor; previous pelvic or abdominal radiotherapy; >2 previous lines of chemotherapy; antecedent of secondary malignancy in the past 5 years, with the exception of cervical intraepithelial neoplasia or basal cell carcinoma treated adequately or any solid tumor considered in complete remission without relapse for at least 5 years; bowel obstruction; symptomatic brain metastasis; cardiomyopathy contraindicating anthracyclines or left ventricular ejection fraction (LVEF) by MUGA or echocardiogram < 50%; acute infection; severe comorbidities not allowing cytotoxic treatment; non-menopausal women not using adequate contraceptive method.

2.3. Treatment plan

The first step of MYCA trial included a phase Ib dose escalation to determine the feasibility of 2 dose levels of 1 h intravenous infusion NPLD, 40 or 50 mg/m^2, followed by a 30 min intravenous infusion AUC 5 mg/min.ml carboplatin on day 1, every 4 week cycles. A standard 3 + 3 design was used to guide the dose escalation, and to determine the recommended dose for phase 2 trials (RP2D) of NPLD [10,11]. This dose was defined as the dose associated with a risk of dose-limiting toxicity (DLT) ≤ 1/6.

Once the NPLD RP2D was determined, additional patients were enrolled in the phase II step of MYCA trial in order to assess the efficacy and safety of the combination.

Using the NCI CTC for adverse events v4.0, DLTs were defined as ≥grade 3 non-haematological toxicity (except diarrhoea, alopecia, nausea/vomiting, hypersensitivity, asymptomatic reversible rise in hepatic transaminases); grade 4 thrombocytopenia; grade 4 neutropenia lasting >5 days; or febrile neutropenia.

Treatment was administered for 6 cycles, or less in the cases of disease progression or unacceptable toxicity, or consent withdrawal. After 6 cycles of chemotherapy, prescription of additional cycles was allowed upon local investigator decision. Although there is no data about the toxicity profile of carboplatin and NPLD regimen in the literature, we assumed the febrile neutropenia risk would be close to 10% to 15%. As a consequence, based on ASCO recommendations, prophylactic G-CSF support prescription was recommended as primary prophylaxis as a way of reducing the risk of febrile neutropenia and the risk of drug dose delay or reduction, but final decision was left to the investigator discretion.

2.4. Outcomes/patient assessments

The primary endpoint of the first step of MYCA trial (phase Ib) was the safety including the nature, number and grade of adverse events according to NCI-CTAE v.4 criteria [12] in order to determine the phase 2 trial recommended dose (RP2D).

The primary endpoint of the second step of MYCA trial (phase II) was the disease control rate (DCR) at 12 months. Secondary endpoints were objective response rate (ORR) according to RECIST 1.1 criteria [13]; progression-free survival (PFS) time; overall survival (OS) time and toxicity. Exploratory endpoints included assessment of the quality of life (QoL), as well as calculation of modeled CA125 kinetic parameters as potential predictive of prognostic factors [14]. Disease progression was defined according to GCIG criteria [15], including RECIST 1.1 criteria; CA125 growth; or clinical deterioration.

The DCR at 12 months was defined as the rate of patients with complete response or partial response, or with stable disease at 12 months. ORR was defined as the percentage of patients who achieved complete response or partial response, as best tumor responses. PFS was defined as the time from randomization to disease progression or recurrence, or to the date of death. OS was determined as time interval between randomization and death.

Clinical, haematological, biochemical and CA-125 assessments, including evaluation for toxic events were required at each cycle. QoL evaluations (well-being measured with visual analog scale) were required every 3 months, whilst tumor assessments by imaging were performed every 6 months or in the case of progression suspicion.

Toxicity and tolerability analyses were performed in all patients who completed ≥1 cycle of therapy.

2.5. Statistical analysis

This study was designed as a single-arm trial to determine the DCR at 12 months with carboplatin and NPLD combination. Statistical assumptions were based on results of the CALYPSO phase III trial demonstrating a 33% DCR at 12 months in the carboplatin + PLD arm [2]. With an acceptable 0.66 hazard ratio, the carboplatin + NPLD combination would be considering as clinically interesting if DCR at 12 months is ≥33% and not interesting if DCR at 12 months ≤ 22%.

Considering a 0.05 type I (alpha) error and an 80% statistical power, 71 patients had to be included in the phase II step trial.

Taking into account 6 expected evaluable patients in the phase Ib, and an estimated 10% lost-to-follow rate, the total number of patients to be enrolled in the study was 86.

All analyses were done on the ITT population. Sensitivity analyses were carried out on all of these criteria on the per protocol population.

Exploratory analyses examining the impact on PFS of age, platinum-free interval (PFI); primary tumor site; histology; grade; initial FIGO stage; ECOG performance score; treatment arm; and initial surgery with complete macroscopic resection status were performed using univariate Cox analysis. The outcomes of modeled CA-125 kinetic analysis and of quality of life are not presented here.

All data were collected and saved using the electronic documentation system SAS version 8.2 (SAS Institute, Inc., Cary, NC, USA). Statistical significance was considered to be indicated by $P < 0.05$. Data from toxicity analyses, PFS, OS were evaluated with descriptive statistics.

3. Results

3.1. Patients and treatments

From November 2012 to July 2014, 87 patients with PtS ROC were included in 28 French sites. One patient, who did not receive treatment, was excluded. As a consequence, 86 patients were assessed in the ITT analysis, including 98% patients assessable for safety and 91% for efficacy (Fig. 1).

The characteristics of the patients are presented in Table 1. All patients previously received platinum (100%), mostly in combination with paclitaxel (94%) and/or bevacizumab (32%). Most of patients had received one previous line of chemotherapy (78%). Of note, 31 (36%) patients had a 6–12 month PFI and 53 (62%) had a >12 month PFI. However 2 patients (2%) with a PFI< 6 months were incorrectly enrolled and included in the ITT assay. A total of 67 pts. (78%) completed 6 cycles, and 7 (8%) continued up to 9 cycles. Early discontinuation of therapy was decided in 28 cases (32%), mainly for progressive disease in 40% cases, for toxicity reasons in 40%, or for death in 7%. There were 15 cases (17%) of NPLD dose reductions, and 7 cases (8%) of carboplatin dose reductions. Forty patients (46%) experienced dosing delays ≥5 days, mainly due to hemato-toxicity.

3.2. Toxicity

Among 12 patients enrolled in the phase Ib step of the trial, 11 patients were actually treated. Among the first 3 patients treated at dose level 1 (40 mg/m^2), a suspicion of cardiomyopathy initially declared as a DLT, and eventually dispelled, led to inclusion of another patient. The latter one did however not receive any treatment, and an additional patient was enrolled. This patient experienced a DLT event (grade 4 thrombocytopenia) after cycle 2. As a consequence, 3 more patients were included on this dose level, and no DLT was reported. As per protocol, 3 patients received the treatment on dose level 2 at 50 mg/m^2. Because a patient experienced hypersensitivity reaction to NPLD on cycle 1 without being considered as a DLT, an additional patient was included. No DLT was subsequently reported, and further 75 patients were enrolled in the phase II step at dose level 2.

In total 84 patients were evaluable for toxicity, as 1 patient did not start treatment and 2 patients were excluded due to early discontinuation before the end of first cycle (Fig. 1). Table 2 summarizes the observed haematological and non-haematological toxicities.

Thirty-eight patients (45%) experienced at least one grade 3–4 adverse event, with a majority of haematological toxicities: neutropenia (17%) including febrile neutropenia in 6%; anemia (13%); and thrombocytopenia (1%). G-CSF supports were used in 58% of patients: 51% as primary prophylaxis and 7% after neutropenic event. Of note, a patient who did not receive prophylactic G-CSF support died from febrile neutropenia. Furthermore, two grade 3 cardiovascular events were reported: a pulmonary embolism; and a junctional tachycardia (JT) in a patient with previous JT history.

The most common non-haematological adverse events were fatigue (grade 1–2: 69%; grade 3: 13%) and nausea (grade 1–2: 61%; grade 3: 8%). Hand-foot syndrome (HFS) was uncommon (grade 1–2: 11%; grade 3: 1%). Alopecia grade 1–2 was observed in 51% patients.

3.3. Efficacy

Among the enrolled patients, 75 (87%) had tumor evaluations at 6 months and 48 (56%) at 12 months. Among the 38 patients (44%) who had no tumor assessments at 12 months, 30 had experienced disease progressions earlier, 2 had tumor evaluations performed ≥1 month after the theoretical date, and 6 patients were lost to follow-up (Fig. 1).

In ITT analysis, the DCR at 12 months was 30.0% (95% CI, 30.3–39.7). The 12 month DCR was 20.8% (95% CI, 4.6–37.0) in patients with 6–12 month PFI, and 33.9% (95% CI 22.8–45.7) in patients with PFI > 12 months.

The objective response rate was 58% (95% CI 47–68) in the overall population, including 17 patients (21%) with CR; 29 patients (36%) with PR; and 21 patients (26%) with SD, as best responses. As a consequence, the disease clinical benefit rate was 83%. The objective response rates were 50% (95% CI: 31.5–68.5) and 61% (95% CI: 47–74) in patients with 6–12 month or > 12 month PFI, respectively.

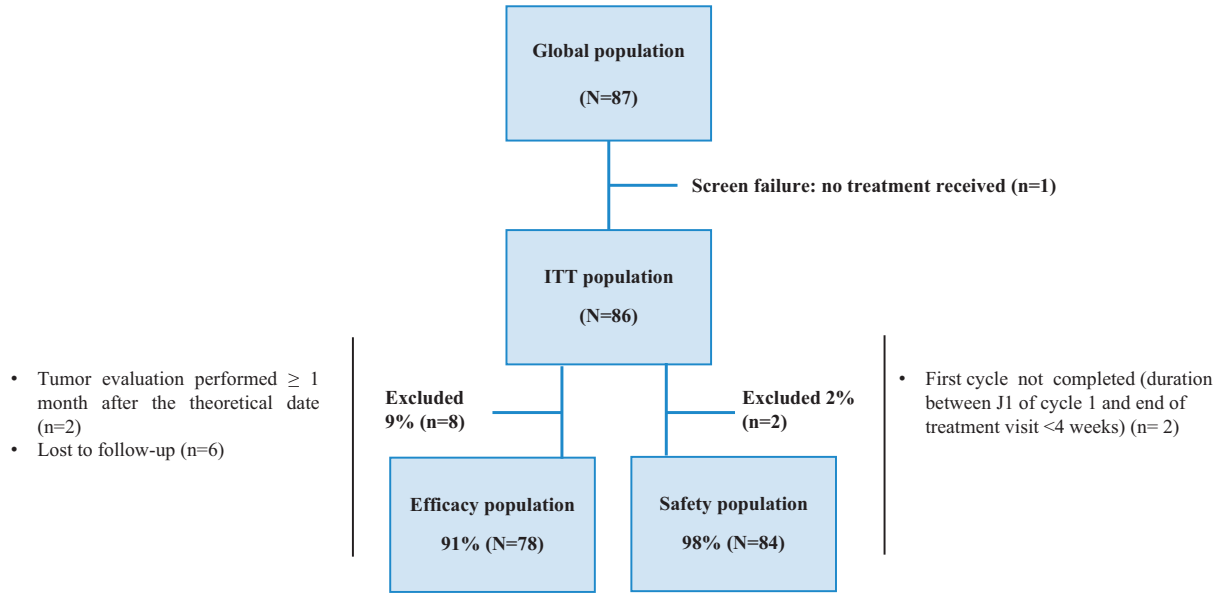

Fig. 1. Flow Chart for both phase Ib and phase II steps.

Regarding survival, the median follow-up was 24.5 months. In ITT analysis based on 79 PFS events, the median PFS was 10.0 months (95% CI 8.6–11.0), with no impact of PFI: 10.0 months for 6–12 months PFI, versus 9.9 months for PFI > 12 months; HR 0.74, 95%CI 0.45–1.21 (Table 3; Fig. 2).

Table 1
Patient characteristics.

		(*N* = 87)
Age (years)	Median	67.0 [44;84]
ECOG	0	41 (47.7%)
	1	40 (46.5%)
	Missing	5 (5.8%)
Initial FIGO stage	I	4 (4.6%)
	II	4 (4.6%)
	III	62 (71.3%)
	IV	10 (11.5%)
	Missing	7 (8.0%)
Primary tumor site	Ovary	79 (92.9%)
	Fallopian tube	2 (2.4%)
	Peritoneum	4 (4.7%)
	Missing	2
Tumor histology	Serous	77 (88.5%)
	Endometrioid	3 (3.4%)
	Clear cells	0
	Mucinous	0
	Undifferentiated	3 (3.4%)
	Others	4 (4.6%)
Histological grade	Low grade	5 (5.7%)
	High grade	61 (70.2%)
	Missing	21 (24.1%)
Initial surgery: complete macroscopic resection	No	37 (42.5%)
	Yes	47 (54.0%)
	Not performed	1 (1.1%)
	Not applicable	2 (2.3%)
Treatment history	Prior Platinum	87 (100%)
	Prior Taxane	82 (94%)
	1 previous line	68 (78.2%)
	2 previous lines	19 (21.8%)
Platinum free interval since last line	Median	14.2 [1.3;74.9]
	<6	2 (2.3%)
	[6–12]	31 (36.0%)
	>12	53 (61.6%)
Targeted therapies	No	53 (60.9%)
	Yes	34 (39.1%)
If yes		
	Bevacizumab	28 (32.2%)

Table 2
Adverse events during treatment – safety population in pooled patients treated at 40 and 50 mg/m^2.

	Grade	Patients (*N* = 84)
At least one AE with grade ≥ 2		76 (90.5%)
At least one AE with grade ≥ 3		38 (45.2%)
Non haematological toxicity		
Alopecia	1–2	43 (51.2%)
Nausea	1–2	51 (60.7%)
	3	7 (8.3%)
Vomiting	1–2	20 (23.8%)
	≥3	5 (6.0%)
Constipation	1–2	28 (33.3%)
	≥3	1 (1.2%)
Diarrhoea	1–2	12 (14.3%)
	≥3	3 (3.6%)
Fatigue	1–2	58 (69.0%)
	3	11 (13.1%)
Mucositis	1–2	16 (19.0%)
	≥3	0
Infection without febrile neutropenia	1–2	7 (8.3%)
	≥3	6 (7.1%)
Infection with febrile neutropenia	1–2	0
	≥3	5 (6.0%)
Sensitive neuropathy	1–2	18 (21.4%)
	≥3	0
Motor neuropathy	1–2	0
	≥3	0
Cardiovascular	1–2	2 (2.4%)
	≥3	2 (2.4%)
Allergic reaction	1–2	5 (6.0%)
	≥3	0
Hand-foot syndrome	1–2	9 (10.7%)
	3	1 (1.2%)
Arthralgia/Myalgia	1–2	10 (11.9%)
	3	1 (1.2%)
Pain	1–2	34 (40.5%)
	≥3	6 (7.1%)
Haematological toxicity		
Leucopenia	1–2	49 (62.8%)
	≥3	6 (7.7%)
Neutropenia	1–2	43 (55.1%)
	≥3	13 (16.7%)
Anemia	1–2	48 (61.5%)
	≥3	10 (12.8%)
Thrombocytopenia	1–2	10 (12.8%)
	≥3	1 (1.3%)

Table 3
Univariate Cox model on PFS – ITT population.

Variables		Hazard ratio [IC95%]	*P*-value	P-value globale
Age	≥70 vs <70 years	0.789 [0.493–1.263]	0.324	
Platinum-free interval	>12 vs [6–12] months	0.859 [0.522–1.415]	0.551	
Primary tumor site	Fallopian tube vs ovary	3.724 [0.866–16.014]	0.077	0.210
	Peritoneum vs ovary	1.012 [0.366–2.798]	0.981	
Tumor histology	Endometrioid vs serous/papillary	0.507 [0.124–2.073]	0.345	0.731
	Undifferentiated vs serous/papillary	0.631 [0.154–2.587]	0.522	
	Other vs serous/papillary	1.043 [0.379–2.871]	0.935	
Histological grade	2 vs 1	0.566 [0.217–1.473]	0.244	0.410
	3 vs 1	0.494 [0.184–1.326]	0.162	
Initial FIGO stage	II vs I	0.380 [0.084–1.716]	0.208	0.639
	III vs I	0.457 [0.162–1.285]	0.138	
	IV vs I	0.517 [0.158–1.695]	0.276	
ECOG	1 vs 0	1.443 [0.907–2.295]	0.121	0.206
Initial surgery: complete macroscopic resection	Yes vs no	0.765 [0.480–1.218]	0.259	

The outcomes of exploratory analyses examining the impact on PFS of age, PFI, primary tumor site, histology, grade, initial FIGO stage, ECOG performance status, and complete initial surgery using univariate Cox hazards regression are presented in Table 2. No covariate was statistically associated with PFS in ITT analysis. The median OS was 28.1 months (95% CI 22.3–32.5) with only 51 events reported (Supplementary Fig. S1).

4. Discussion

MYCA study is the first phase II trial demonstrating that NPLD and carboplatin association is feasible and active in patients with recurrent platinum-sensitive ovarian carcinomas.

In the context of PLD international shortage from 2011 to 2013, this trial was designed to assess the safety and efficacy profile of this combination, as an alternative to standard PLD-carboplatin regimen.

NPLD-carboplatin combination regimen was overall well tolerated, since 78% of patients completed the planned 6 cycles. The safety profile of this regimen was slightly different from those observed with PLD and carboplatin (Table 4), with a trend for more febrile neutropenia (6% vs 3%); grade 3–4 anemia (13% vs 8%) but less grade 3–4 neutropenia (1% vs 17%) and thrombocytopenia (16% vs 35%) than in CALYPSO trial [2,3]. Notably, a majority of patients (51%) received prophylactic G-CSF prescription, thereby suggesting that the rates of neutropenia and febrile neutropenia would have likely been higher without G-CSF prophylaxis. A patient who did not receive G-CSF died from febrile neutropenia. As a consequence, we believe NPLD-carboplatin regimen should be prescribed with G-CSF prophylaxis [16]. Regarding non-haematological toxicities, more patients experienced alopecia with NPLD in MYCA trial (51%), than with PLD in CALYPSO trial (34%) [2,3]. Reversely, HFS was less frequently observed with NPLD than with PLD prescribed at 30 mg/m^2: grade 1, 7% vs 27%; grade ≥ 2, 5% (including only 1% of grade 3) vs 12% (and no grade 3) [2,3]. In other studies, severe ≥ grade 3 HFS were reported in 15 to 20% patients treated with the standard monthly monotherapy 50 mg/m^2 PLD [17,18]. However PLD is now more frequently prescribed at 40 mg/m2 to reduce the risk of HFS, with no apparent efficacy reduction [19]. The 5% cardiotoxicity risk observed in MYCA trial was low, to be compared to 10% in CALYPSO trial.

In terms of efficacy, the 30% disease control rate at 12 months (primary endpoint) suggests comparable activity of this combination to the standard PLD-carboplatin combination acknowledging the lack of

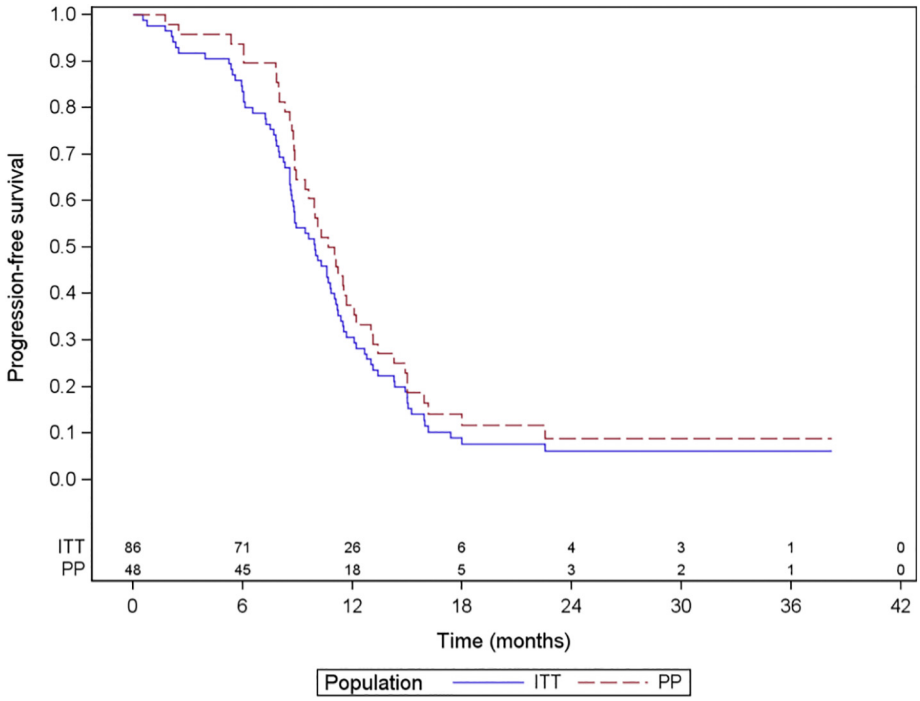

Fig. 2. Progression Free Survival (PFS) – Intention To Treat (ITT) and Per Protocol (PP) populations.

Table 4
Summary of main studies in platinum sensitive (PtS) recurrent ovarian cancer (ROC).

	MYCA	CALYPSO [2,3]	ICON-4 [20]	AGO-OVAR2.5 [21]	OVA 301 [22]	OCEANS [23]
	Carboplatin + NPLD	DLP-Carboplatin vs Paclitaxel + Carboplatin	Paclitaxel-Platinum vs Platinum	Gemcitabine Carboplatin vs Carboplatin	Trabectedine + DLP vs DLP	Gemcitabine + Carboplatin + Bevacizumab vs Gemcitabine-Carboplatin
Efficacy						
Patients	86	976	802	356	672	484
PFI > 12 (%)	62	65	77	60	33	58
PFI 6–12 (%)	36	35	23	40	32	42
PFI < 6 (%)	2	0	0	0	35	0
ORR (%)	58		66.0 vs 54.0 NS	47.2 vs 30.9 S	35.3 vs 22.6 S	78,5 vs 57,4 S
DCR at 12 months (%)	30	33				
Median PFS (months)	10.0	11,3 vs 9,4 S	12 vs 9 S	8,6 vs 5,8 S	9,2 vs 7,5 S	12,4 vs 8,4 S
Median OS (months)	28.1	30,7 vs 33,0 HR = 0,987 NS	29 vs 24 S	18 vs 17,3 NS	20,5 vs 19,4 NS	33,3 vs 35,2 NS
Toxicity						
Neutropenia (%)	72	80		89		
Grade 1–2 (%)	55	55		20		
Grade 3–4 (%)	17	35		69	63	22
Febrile neutropenia (%)						
Grade 3–4 (%)	6	3		1	7	2
Anemia (%)	74	66		87		
Grade 1–2 (%)	61	58		60		
Grade 3–4 (%)	13	8		27	12	
Thrombocytopenia (%)	14	68		79		
Grade 1–2 (%)	13	52		44		
Grade 3–4 (%)	1	16		35	18	
Hand-foot syndrome (%)	12	39				
Grade 1–2 (%)	7	27				
Grade ≥ 2 (%)	5	12				
Grade 3–4 (%)	1				4	
Alopecia (%)	51	34		49		
Grade 1–2 (%)	51					
Grade ≥ 2 (%)		7				
Grade 3–4 (%)	0			49		
Nausea (%)	69	78				
Grade 1–2 (%)	61					
Grade ≥ 2 (%)		35				
Grade 3–4 (%)	8				9	
Vomiting (%)	30	49		32		
Grade 1–2 (%)	24			29		
Grade ≥ 2 (%)		23				
Grade 3–4 (%)	6			3	10	
Constipation (%)	34	55				
Grade 1–2 (%)	33					
Grade ≥ 2 (%)		22				
Grade 3–4 (%)	1					
Diarrhoea (%)	18	23		14		
Grade 1–2 (%)	14			12		
Grade ≥ 2 (%)		5				
Grade 3–4 (%)	4			2		
Fatigue (%)	82	78		40		
Grade 1–2 (%)	69			37		
Grade ≥ 2 (%)		37				
Grade 3–4 (%)	13			3	6	
Cardiovascular events (%)	5	10.5				
Grade 1–2 (%)	2.5					
Grade ≥ 2 (%)		2				
Grade 3–4 (%)	2.5					
Sensitive neuropathy (%)	21	40		30		
Grade 1–2 (%)	21			29		
Grade ≥ 2 (%)		5				
Grade 3–4 (%)	0			1		

direct cross-trial comparison (Table 4). Indeed the 12 month DCR was 33% in CALYPSO trial [2], acknowledging that the populations were slightly different, and no direct comparison is possible. For example, more patients in MYCA trial (22%) had received 2 previous lines of chemotherapy, compared to 12% in CALYPSO trial. The other efficacy indicators (ORR, 58%; median PFS, 10.0 months and median overall survival, 28.1 months) suggest that NPLD-carboplatin association may be at least as effective as other standard treatments in PtS ROC patients (Table 4).

MYCA trial outcomes have however to be considered with caution. Indeed it was a single arm trial, with no randomized comparison to standard arm. It was meant to obtain preliminary data about the safety and efficacy of NPLD in combination with carboplatin. The population of patients enrolled in this trial is not fully representative of PtS ROC

patients treated nowadays. Indeed only 32% patients had previously received bevacizumab, although it is now approved as adjuvant treatment for stage III and IV diseases, and. in combination with carboplatin-based chemotherapy in platinum-sensitive recurrent ovarian cancer patients. Moreover, due to the small size, we could not find any impact on PFS of common prognostic factors such as PFI, histology, grade, initial FIGO stage, or complete initial surgery.

Despite these limitations, MYCA trial suggests that 50 mg/m^2 NPLD and AUC 5 mg/min.ml carboplatin combination given every 4 weeks is feasible and potentially effective in patients with PtS ROC. A phase III trial may be warranted to confirm our findings.

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Additional information

Previous presentation during congress

The results were presented in part during the EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY (ESMO) meeting in October 2016.

Ethics approval and consent to participate

This study (NCT01705158) was approved by Ethics Committee (CPP Sud Est IV) and Competent Authority (ANSM). The participants gave informed written consent.

Consent for publication

All authors provided consent for publication.

Availability of data and material

All data supporting the results reported in the article were obtained with permission from the Ethics committee and are stored in the Investigational Cancer Therapeutics department.

Conflict of interest

The authors have declared no conflicts of interest.

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Author's contributions

All the authors contributed to all stages of the study, read and approved the final manuscript.

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