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Neoadjuvant chemotherapy with or without nintedanib for advanced epithelial ovarian cancer: Lessons from the GINECO double-blind randomized phase II CHIVA trial

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HIGHLIGHTS

- CHIVA assessed nintedanib integrated into a neoadjuvant strategy for ovarian cancer.
- Nintedanib was associated with worse progression-free survival (primary endpoint).
- Nintedanib was associated with an increase in typical chemotherapy adverse effects but not surgical complications.
- Nintedanib is not recommended as part of neoadjuvant therapy for ovarian cancer.

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ABSTRACT

Aim. The oral anti-angiogenic therapy nintedanib prolongs progression-free survival (PFS) when combined with chemotherapy after primary surgery for advanced epithelial ovarian cancer. The randomized phase II CHIVA trial evaluated the impact of combining nintedanib with neoadjuvant chemotherapy (NACT) for epithelial ovarian cancer.

Methods. Patients with newly diagnosed unresectable FIGO stage IIIC–IV epithelial ovarian cancer received 3–4 cycles of carboplatin plus paclitaxel every 3 weeks as NACT before interval debulking surgery (IDS), followed by 2–3 post-operative cycles. Patients were randomized 2:1 to receive either nintedanib 200 mg twice daily or placebo on days 2–21 every 3 weeks during NACT (omitting peri-operative cycles), and then as maintenance therapy for up to 2 years. The primary endpoint was PFS.

Results. Between January 2013 and May 2015, 188 patients were randomized (124 to nintedanib, 64 to placebo). PFS was significantly inferior with nintedanib (median 14.4 versus 16.8 months with placebo; hazard ratio 1.50, $p = 0.02$). Overall survival (OS) was also inferior (median 37.7 versus 44.1 months, respectively; hazard ratio 1.54, $p = 0.054$). Nintedanib was associated with increased toxicity (grade 3/4 adverse events: 92% versus 69%, predominantly hematologic and gastrointestinal), lower response rate by RECIST (35% versus 56% before IDS), and lower IDS feasibility (58% versus 77%) versus placebo.

Conclusions. Adding nintedanib to chemotherapy and in maintenance as part of NACT for advanced epithelial ovarian cancer cannot be recommended as it increases toxicity and compromises chemotherapy efficacy (IDS, PFS, OS).

ClinicalTrials.gov registration: NCT01583322.

1. Introduction

Until recently, standard treatment for women with advanced ovarian cancer (OC) comprised maximal cytoreductive surgery and carboplatin–taxane chemotherapy, with or without the anti-angiogenic agent bevacizumab. Neoadjuvant chemotherapy (NACT) represents an alternative strategy to upfront chemotherapy in patients with stage IIIC or IV OC not considered to be completely resectable at primary surgery [1–3]. Subset analyses of phase III trials suggested that front-line bevacizumab may offer the greatest progression-free survival (PFS) and overall survival (OS) benefit in patients with International Federation of Gynecology and Obstetrics (FIGO) stage III and residual disease after initial surgery, or FIGO stage IV OC [4–6]. In these patients with extensive and bulky disease, initial surgery is often delayed until patients have received 3–4 cycles of NACT [2]. However, peri-operative bevacizumab may be concerning given the long half-life (14–21 days) and potential interference with wound healing.

The anti-angiogenic agent nintedanib has a shorter half-life (10–15 h) [7], potentially representing an attractive alternative to neoadjuvant bevacizumab. Adding nintedanib to carboplatin–paclitaxel after upfront surgery and continuing as maintenance therapy improved PFS (but not OS) in the GCIG/ENGOT/AGO-OVAR 12 randomized phase III trial, although adverse events (AEs) were increased [8,9]. The neoadjuvant setting provides a valuable model to describe 'in vivo' biological effects on tumor cells and the microenvironment, and to understand whether intermediate endpoints can be used as surrogates for PFS and/or OS. We report efficacy and safety results from the CHIVA trial evaluating incorporation of nintedanib into a neoadjuvant strategy for advanced OC.

2. Patients and methods

CHIVA (ClinicalTrials.gov identifier: NCT01583322) was a double-blind placebo-controlled randomized phase II trial, sponsored by the Groupe dInvestigateurs National des Etudes des Cancers Ovariens et du sein (GINECO). CHIVA was designed to assess the efficacy and safety of nintedanib as part of neoadjuvant and adjuvant treatment in patients undergoing interval debulking surgery (IDS) for advanced OC. The protocol and related documents were approved by the French National Agency for Safety of Medicine and Health Products and the Committee on the Protection of Persons of Ile de France 1. Trial conduct complied with the International Conference on Harmonisation Guideline for Good Clinical Practice and all relevant laws and directives.

Eligible patients were aged ≥18 years with newly diagnosed epithelial ovarian, fallopian tube, or primary peritoneal cancer confirmed histologically by laparoscopy (or laparotomy), FIGO stage IIIC/IV, and Eastern Cooperative Oncology Group (ECOG) performance status ≤2. Eligible patients were not suitable for primary debulking surgery (i.e., considered unresectable after laparoscopic evaluation), and IDS with maximal cytoreductive effort aiming for no residual disease was planned. Prior systemic therapy for OC was not permitted. All patients provided written informed consent before undergoing any study-specific procedures. The Supplement details additional eligibility criteria.

All eligible patients received chemotherapy (carboplatin AUC 5 plus paclitaxel 175 mg/m^2) every 21 days for 3–4 cycles before surgery and 2–3 cycles after surgery (up to 8 cycles in total). Before initiating NACT, patients were stratified according to disease status at screening (non-measurable disease versus measurable disease <50 mm versus measurable disease ≥50 mm according to Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1), FIGO stage (IIIC versus IV), and treatment center, and randomized 2:1 to receive nintedanib 200 mg or placebo twice daily on days 2–21 of the first two neoadjuvant cycles (Fig. S1). All patients underwent IDS 3–4 weeks after the last chemotherapy administration, followed by adjuvant therapy starting 4 weeks after surgery (providing surgical wounds had healed completely) combined with either nintedanib or placebo on days 2–21, according to initial randomization. Nintedanib/placebo was continued as daily maintenance therapy for up to 2 years after completing chemotherapy, or until disease progression if earlier. Dose modifications for AEs are described in the Supplement.

The primary endpoint was PFS according to RECIST version 1.1, compared between treatment arms using a stratified log-rank test at one-sided alpha of 0.15. To provide 80% power, 130 PFS events (83 nintedanib, 47 placebo) were required, assuming a hazard ratio (HR) of 0.70 favoring nintedanib (median PFS increase from 10.0 to 14.2 months). The planned sample size was 188 patients, giving 162 evaluable patients assuming 10% drop out, 24 months accrual and 24 months'' follow-up. Median PFS was estimated using Kaplan-Meier methodology and reported with 95% confidence intervals (CIs).

Secondary endpoints included safety (operative and post-operative complications) and efficacy (response rate according to RECIST version 1.1 following two NACT cycles; complete resection rate according to the Peritoneal Cancer Index [PCI] [10] at IDS; best response to the overall treatment strategy according to RECIST version 1.1 at the end-of-treatment visit; and OS). Statistical tests were conducted two-sided with a significance level of 5%. A p-value <0.05 was judged as being statistically significant. AEs were graded using Common Terminology Criteria for Adverse Events version 4.0. Complications (wound-healing complications, bowel perforation or fistula, bleeding, infection or post-operative fever, and thromboembolic events) occurring during or within 30 days after surgery were graded using Clavien-Dindo classification [11].

Exploratory objectives included the identification of potential biomarkers predicting efficacy, toxicity, and surgical morbidity with nintedanib. Radiologic endpoints [12] and a substudy modeling CA-125 ELIMination rate constant K (KELIM) in surgical decision-making [13] were explored. Additional translational research will be reported separately.

A post hoc exploratory univariate analysis assessed potential surrogates for PFS and/or OS in NACT-treated patients. Covariates included RECIST-assessed response rate after NACT, PCI and its evolution at IDS, complete surgical resection at IDS, and clinical covariates (age, FIGO stage, ECOG performance status, tumor size, ascites, neutrophil:lymphocyte ratio, platelet count, hemoglobin, and CA-125 levels).

Efficacy and safety were analyzed using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA) in the intention-to-treat population (all randomized patients). Efficacy was also analyzed in the per-protocol population (all randomized patients with PFS data and no major protocol deviation). In three prespecified safety interim analyses, the independent data monitoring committee reviewed data after 30, 60, and 90 nintedanib-treated patients had completed NACT and IDS.

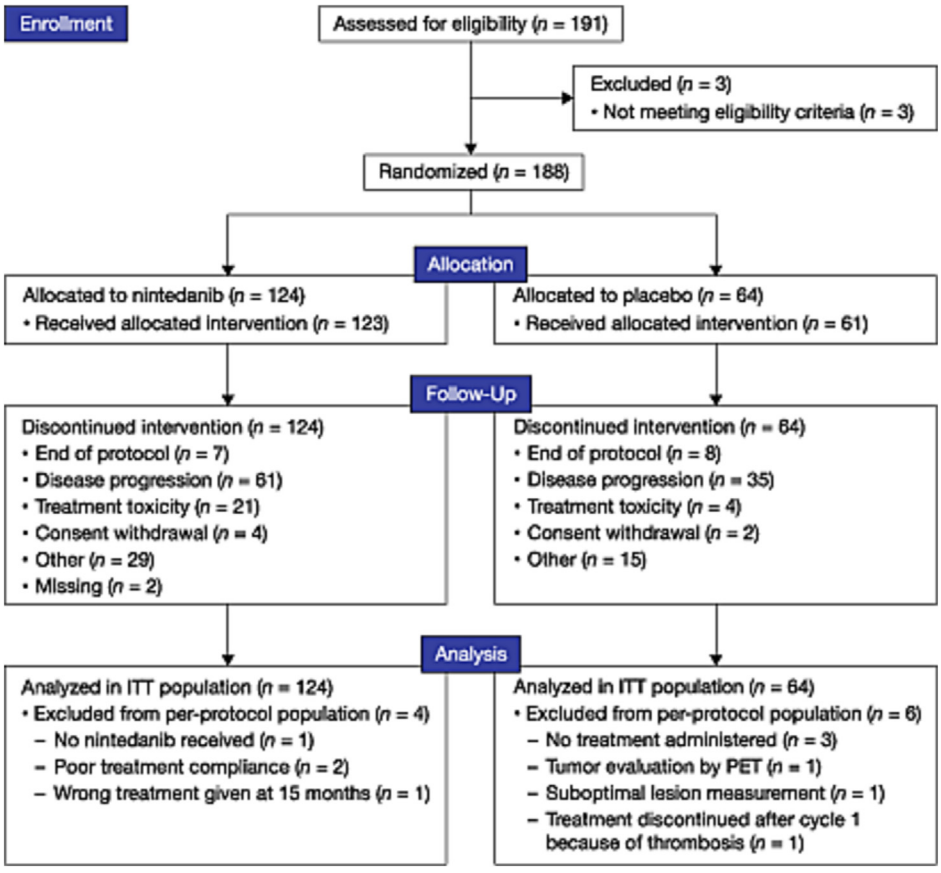

Fig. 1. CONSORT flow diagram. Four patients in the nintedanib arm and six in the placebo arm were excluded from the per-protocol population. ITT, intention-to-treat; PET, positron emission tomography.

Table 1
Baseline characteristics.

Characteristic	Nintedanib ($n = 124$)	Placebo ($n = 64$)
Median (range) age, years	64 (31–79)	63.5 (43–79)
ECOG performance status at baseline	($n = 122$)	($n = 63$)
0	49 (40%)	21 (33%)
1	63 (52%)	32 (51%)
2	10 (8%)	10 (16%)
Histology	($n = 124$)	($n = 63$)
Serous	108 (87%)	56 (89%)
Endometrioid	3 (2%)	0
Mucinous	1 (1%)	0
Clear cell	3 (2%)	0
Undifferentiated	4 (3%)	1 (2%)
Other	5 (4%)	6 (10%)
Histologic grade	($n = 124$)	($n = 63$)
1	2 (2%)	3 (5%)
2/3	95 (77%)	53 (84%)
Unknown	27 (22%)	7 (11%)
FIGO stage	($n = 124$)	($n = 63$)
IIIC	98 (79%)	47 (75%)
IV	26 (21%)	16 (25%)
Diagnosis		
Core biopsy	9 (7%)	2 (3%)
Laparoscopy	115 (93%)	62 (97%)
Reason for absence of surgical resection by laparoscopy[a]	($n = 115$)	($n = 62$)
Non-resectable disease localization	105 (91%)	57 (92%)
Patient's condition	4 (3%)	2 (3%)
Intraoperative morbidity	0	1 (2%)
Other reason	6 (5%)	2 (3%)
PCI at baseline	($n = 118$)	($n = 61$)
Median (IQR)	22.5 (19–27)	21 (15–25)
Hypertension at baseline	41 (33%)	19 (30%)
Ongoing anti-hypertensive therapy at baseline	38 (31%)	18 (28%)
Ongoing analgesic at baseline	23 (19%)	18 (28%)

ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; IQR, interquartile range; PCI, Peritoneal Cancer Index.
[a] Percentages calculated as a proportion of patients undergoing laparoscopy.

3. Results

Between 11 January 2013 and 13 May 2015, 191 patients were enrolled from 31 GINECO sites in France, of whom 188 were eligible and randomized: 124 to nintedanib and 64 to placebo (Fig. 1). Baseline characteristics were reasonably balanced between treatment arms (Table 1).

The data cut-off for the final analysis was 30 September 2017 (median follow-up 42.6 months). PFS was significantly worse with nintedanib than placebo (median PFS 14.4 versus 16.8 months, respectively; HR 1.50, 95% CI, 1.06–2.11; $p = 0.020$) (Fig. 2A). Results were similar in the per-protocol population (median 14.2 [95% CI, 12.2–15.4] versus 16.8 months [95% CI, 13.0–21.4], respectively; HR 1.50 [95% CI, 1.05–2.13]; $p = 0.024$). A sensitivity analysis of time to treatment failure (including treatment discontinuation due to toxicity as well as progression and death as events) showed consistent results (HR 1.67 [95% CI, 1.19–2.34]; median 12.4 vs 14.5 months, respectively).

Likewise, several secondary efficacy endpoints showed worse outcomes with nintedanib (Table 2). Median OS was 37.7 versus 44.1 months with nintedanib versus placebo, respectively (HR 1.54, 95% CI, 0.99–2.40; log-rank $p = 0.054$) (Fig. 2B). Response rate after 2 cycles of NACT was significantly inferior in the nintedanib arm. The proportion of patients achieving complete resection at IDS was similar in the two treatment arms, but fewer nintedanib-treated patients were candidates for IDS (58% vs 77%, respectively). The difference in best response across the entire treatment period was not statistically significant between treatments.

Median duration of treatment exposure was similar in the nintedanib and placebo arms (5.1 versus 5.2 months, respectively; Table 3). However, nintedanib-treated patients were more likely to require chemotherapy dose reduction or chemotherapy discontinuation before cycle 4.

Across the entire treatment period, nintedanib was associated with more grade 3/4 AEs (114/124 patients [92%] versus 44/64 [69%] in the placebo arm), more serious AEs (52% versus 47%), and more hospitalizations (29% versus 20%). Aspartate aminotransferase elevations occurred in 55 nintedanib-treated patients (44%) (grade 3/4 in 6%) and 17 placebo-treated patients (27%; all grade 1/2). Alanine aminotransferase elevations occurred in 58 nintedanib-treated patients (47%; grade 3/4 5%) and 21 placebo-treated patients (33%; all grade 1/2).

Table 4 presents AEs during NACT. Nintedanib was associated with an increased frequency of most AEs typical of chemotherapy. There were two fatal AEs during NACT: renal insufficiency at cycle 1 in one nintedanib-treated patient and intestinal occlusion at cycle 2 in one placebo-treated patient. Most patients required supportive therapy during NACT (94% of nintedanib-treated patients versus 91% of placebo-treated patients), and proportions for individual treatment classes were similar in the two arms, except for antibiotics (25% versus 20%, respectively), red blood cell transfusion (10% versus 5%), and anticoagulants (15% versus 20%).

Operative complications (serious or grade ≥ 3 AEs during surgery) were infrequent in both treatment arms (3/72 [4%] nintedanib-treated patients who underwent IDS versus 4/49 [8%] placebo-treated patients who underwent IDS). Post-operative complications (serious or grade ≥ 3 within 30 days after surgery) occurred in 7/72 (10%) nintedanib-treated versus 10/49 (20%) placebo-treated patients who underwent IDS. Data on the duration of surgery were available from 59 of 72 patients who underwent surgery in the nintedanib arm and 38 of 49 in the placebo arm. Among these patients, the mean (standard deviation) duration of surgery was 324 (123) minutes versus 371 (128) minutes, respectively. Among the 45 patients in the nintedanib arm and 32 in the placebo arm with data on blood loss during surgery, the median blood loss was 650 (range 0–6600) mL versus 500 (range 0–7600) mL, respectively. Peri-operative transfusions were required in 47% versus 41% of patients, respectively.

In exploratory analyses of endpoint surrogacy, neutrophil:lymphocyte ratio at baseline, RECIST-assessed objective response after 2 cycles of NACT, complete resection at IDS, and PCI at baseline and at IDS were prognostic for PFS and OS in univariate analysis at $p < 0.01$ (Table S1). Notably, change in PCI between baseline and IDS was not prognostic. In the multivariate Cox model, RECIST response after NACT ($p < 0.01$) and complete resection at IDS ($p < 0.01$) were the only independent variables predictive for PFS. Combining these two variables enabled identification of patients with good, intermediate, or poor prognosis for both PFS and OS (Fig. 3).

4. Discussion

In the randomized phase II CHIVA trial, adding nintedanib to NACT for advanced epithelial OC increased typical chemotherapy toxicities and compromised chemotherapy efficacy, leading to a reduced IDS rate and worse PFS and OS. The lack of efficacy improvement from adding anti-angiogenic therapy to NACT is consistent with previous experience. However, in CHIVA, nintedanib demonstrated a detrimental effect, contrasting with bevacizumab. In the GEICO 1205 trial, bevacizumab combined with chemotherapy was associated with less toxicity than chemotherapy alone and no difference in the primary efficacy outcome [14]. Similarly, subgroup results from MITO16A-MaNGO OV2A showed no detrimental effect of neoadjuvant bevacizumab on safety (or efficacy) [15], and in the ANTHALYA non-comparative phase II trial, neoadjuvant bevacizumab appeared to be tolerable and effective [16].

There are important lessons to learn from CHIVA to avoid deleterious effects in future neoadjuvant trials. When designing the trial and safety follow-up, given concerns about peri-operative bevacizumab, we focused the three interim safety analyses on monitoring surgical

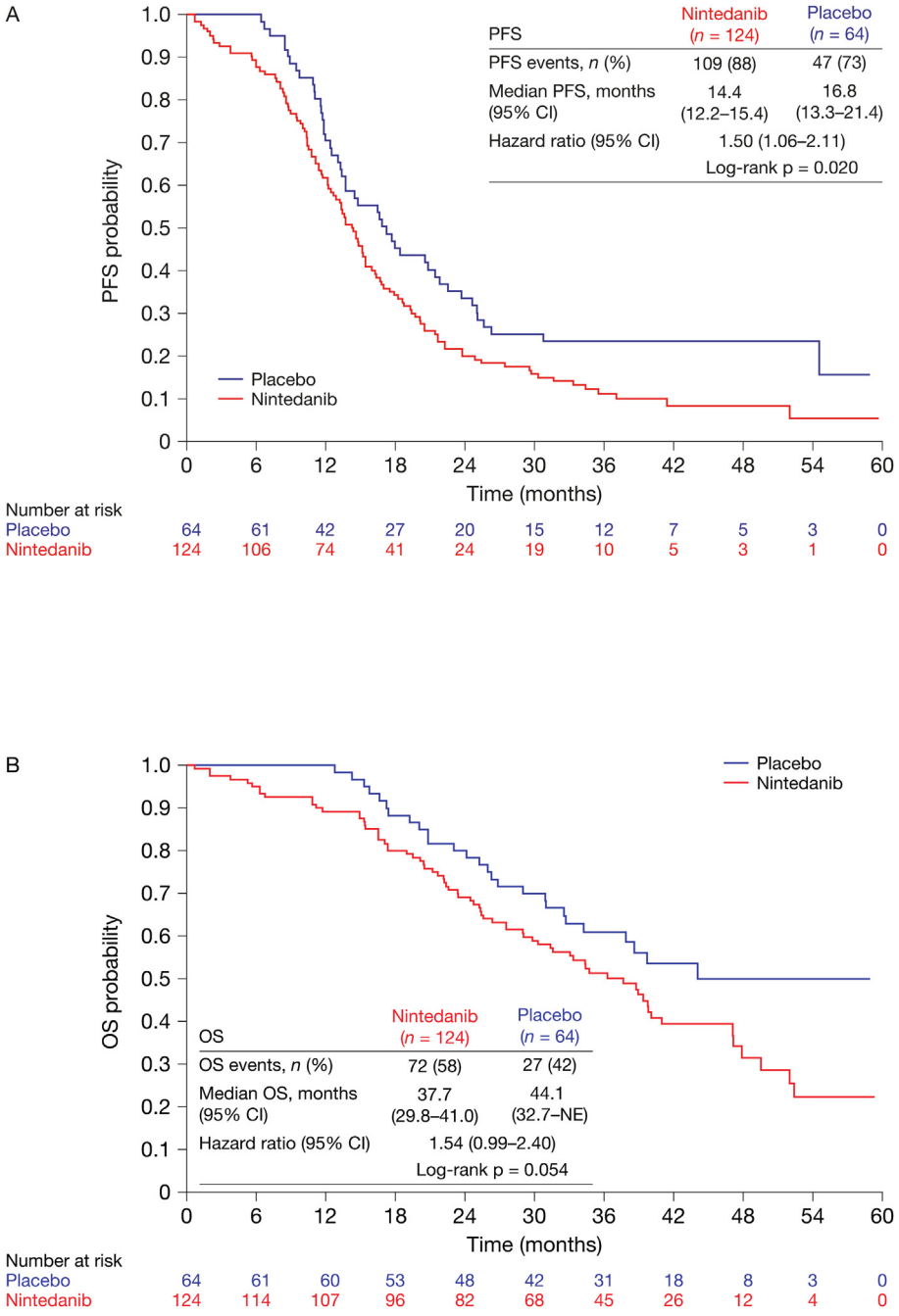

Fig. 2. Efficacy: (A) PFS. (B) OS. CI, confidence interval; NE, not evaluable; OS, overall survival; PFS, progression-free survival.

toxicities, underestimating the impact of nintedanib-induced chemotherapy toxicities on overall response and feasibility of IDS. The increased toxicity burden from a third agent has long been recognized. Furthermore, nintedanib increased toxicity, particularly gastrointestinal effects, in the AGO-OVAR12 front-line trial, leading to reduced dose intensity and chemotherapy completion [8]. In CHIVA, additional toxicity impaired chemotherapy delivery, potentially contributing to the lower efficacy and consequently to the low proportion of patients able to undergo IDS. Future trials investigating the addition of a drug to standard NACT must carefully monitor all toxicities and evaluate their impact on chemotherapy dose intensity, response rate, and IDS.

A second critical lesson is the timing of trial design and initiation. CHIVA began before definitive results were available from AGO-OVAR12 [8,9]. In AGO-OVAR12, the effect of nintedanib was seen almost exclusively in patients with stage IIB–III disease or low tumor burden, not in those with high disease burden as seen with bevacizumab. Thus, the population enrolled in CHIVA, many of whom were considered unresectable because of their disease burden, appears to represent the population least likely to benefit from nintedanib. The CHIVA study population also included a small yet distinct population of patients for whom NACT was preferred because of frailty, comorbidities, or performance status, but with potentially completely resectable disease. These patients may have had distinct outcomes, but robust subgroup analyses in such small sample sizes are not possible.

The third key lesson relates to the optimal criteria for accurately assessing efficacy in neoadjuvant trials. When CHIVA was initiated, it was unclear whether tumor response to NACT and/or complete surgical resection would be the most relevant parameter. We anticipated that

Table 2
Secondary endpoints (intention-to-treat population; consistent results were seen in the per-protocol analysis).

Endpoint	Nintedanib ($n = 124$)	Placebo ($n = 64$)	Chi-squared p-value
RECIST response rate after two cycles of NACT, n/N (%)	39/111 (35)	33/59 (56)	0.009
PCI decrease, n/N (%)	52/79 (66)	42/50 (84)	0.024
Surgical debulking at IDS, n (%)[a]	72 (58)	49 (77)	–
Complete resection before or after surgical debulking, n/N (%)	56/75 (75)	38/49 (78)	0.71
Total patients achieving complete resection, n (%)	56 (45)	38 (59)	–
CR or PR as best response across the entire treatment period, n (%)	84 (68)	49 (77)	0.35
Patients died, n (%)	72 (58)	27 (42)	–
Median overall survival, months (95% CI)	37.7 (29.8–41.0)	44.1 (32.7–NE)	–

CI, confidence interval; CR, complete response; IDS, interval debulking surgery; NACT, neoadjuvant chemotherapy; NE, not evaluable; PCI, Peritoneal Cancer Index; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.
[a] Among nintedanib-treated patients who did not undergo IDS, the most common reason was the non-resectable disease localization.

PFS or OS improvement through enhanced NACT efficacy may be attributable primarily to the increased likelihood of achieving complete resection. Indeed, complete resection was a key prognostic factor in both univariate and multivariate analyses. However, in patients with high tumor burden as in CHIVA, response to chemotherapy also yields important prognostic value. To assess tumor response to NACT, we evaluated two different criteria: PCI and RECIST response. CHIVA included rigorous surgical tumor burden scoring at baseline and at IDS. The PCI, which divides the abdomen into 13 regions and is scored from 0 to 39, is highly dependent on diffusion of the disease and correlates with tumor burden, whereas RECIST focuses on the size of up to five lesions, but also considers non-measurable disease including ascites or pleural effusion and localization outside the abdomen. PCI assessment depends on visual examination by the same surgeon at initial laparoscopy and IDS, whereas RECIST depends on CT scan interpretation by one or more radiologists. In univariate analysis, PCI score at initial surgery was a highly significant predictor of both PFS and OS. By including both diffusion and size of the tumor, the PCI score appears to provide a better reflection of the prognostic value of tumor burden than provided by tumor measurement solely by CT scan (Table S1). PCI score at IDS was also prognostic, but the evolution of PCI score from baseline to IDS was not, highlighting difficulties in evaluating change in tumor burden during surgery after chemotherapy without complementary pathologic assessment. Ultimately, both RECIST response to NACT and complete resection were independently predictive for PFS and OS. Several scenarios can be proposed to understand how response to chemotherapy and surgical complete resection can be dissociated. At one end of the spectrum, patients with high tumor burden and potentially resectable disease may be offered NACT to reduce the adverse effects of surgery. In this case, complete resection may still be achievable even if chemotherapy is minimally effective. At the other extreme, patients with high disease burden at baseline may remain inoperable despite a RECIST response because of insufficient reduction in tumor mass, persistence of diffuse small lesions, or lesions in a location that makes them inoperable. CHIVA revealed that it is the combination of both RECIST response and complete resection that influences patient outcome, which could be considered as a surrogate marker for PFS and OS. In future neoadjuvant trials, the primary endpoint could be the proportion of patients achieving both a RECIST response and complete resection at IDS.

Despite the negative outcome, CHIVA brings important insights that should be incorporated into future trial design and conduct to avoid compromising patient outcomes. Additionally, the rich CHIVA dataset enables improved understanding of disease biology. Ongoing translational research is exploring the potential role of biological or radiologic biomarkers predicting chemotherapy efficacy [12,13] and other biological factors, such as primary tumor chemosensitivity assessed by the modeled CA-125 kinetic parameter KELIM™ [17], which may help to identify subsets in which neoadjuvant anti-angiogenic therapy potentially improves outcomes.

Table 3
Treatment exposure (intention-to-treat population).

Treatment exposure	Nintedanib ($n = 124$)	Placebo ($n = 64$)
Nintedanib/placebo		
Median (IQR) No. of cycles	6 (3–8)	8 (5–10)
<4 cycles administered	42 (34%)	12 (19%)
≥6 cycles administered	65 (52%)	44 (69%)
Dose reduction during neoadjuvant therapy	15 (12%)	5 (8%)
Treatment interruption during neoadjuvant therapy[a]	39 (31%)	12 (19%)
Carboplatin		
Median (IQR) No. of cycles	6 (5–7)	6 (6–7)
<4 cycles administered	23 (19%)	5 (8%)
≥6 cycles administered	88 (71%)	54 (84%)
Dose reduction during neoadjuvant therapy	20 (16%)	0
Treatment interruption during neoadjuvant therapy[b]	29 (23%)	5 (8%)
Paclitaxel		
Median (IQR) No. of cycles	6 (5–7)	6 (6–7)
<4 cycles administered	23 (19%)	6 (9%)
≥6 cycles administered	87 (70%)	51 (80%)
Dose reduction during neoadjuvant therapy	12 (10%)	3 (5%)
Treatment interruption during neoadjuvant therapy[b]	28 (23%)	5 (8%)

IQR, interquartile range.
[a] Interruption of >7 days between two visits.
[b] Dose delayed by >7 days.

Table 4
Main adverse events (worst grade) during neoadjuvant therapy.

Adverse event	Nintedanib ($n = 124$)		Placebo ($n = 64$)	
Grade	Any	3/4	Any	3/4
Any	124 (100%)	104 (84%)	62 (97%)	39 (61%)
Anemia	94 (76%)	14 (11%)	40 (63%)	5 (8%)
Neutropenia	68 (55%)	42 (34%)	29 (45%)	15 (23%)
Febrile neutropenia	6 (5%)	6 (5%)	1 (2%)	1 (2%)
Thrombocytopenia	65 (52%)	22 (18%)	16 (25%)	6 (9%)
Bleeding	13 (10%)	1 (1%)	3 (5%)	0
Fatigue	91 (73%)	12 (10%)	45 (70%)	3 (5%)
Diarrhea	78 (63%)	22 (18%)	15 (23%)	1 (2%)
Nausea	75 (60%)	4 (3%)	30 (47%)	1 (2%)
Alopecia	72 (58%)	NA	44 (69%)	NA
Pain	70 (56%)	7 (6%)	38 (59%)	4 (6%)
Arterial hypertension	40 (32%)	23 (19%)	18 (28%)	6 (9%)
Vomiting	36 (29%)	4 (3%)	13 (20%)	1 (2%)
Sensory neuropathy[a]	26 (21%)	1 (1%)	27 (42%)	3 (5%)
Constipation	21 (17%)	1 (1%)	24 (38%)	1 (2%)
Thromboembolism	10 (8%)	8 (6%)	3 (5%)	3 (5%)
GI perforation	2 (2%)	2 (2%)	0	0
Fistula	2 (2%)	1 (1%)	1 (2%)	1 (2%)

GI, gastrointestinal; NA, not applicable.
[a] Paresthesia/dysesthesia.

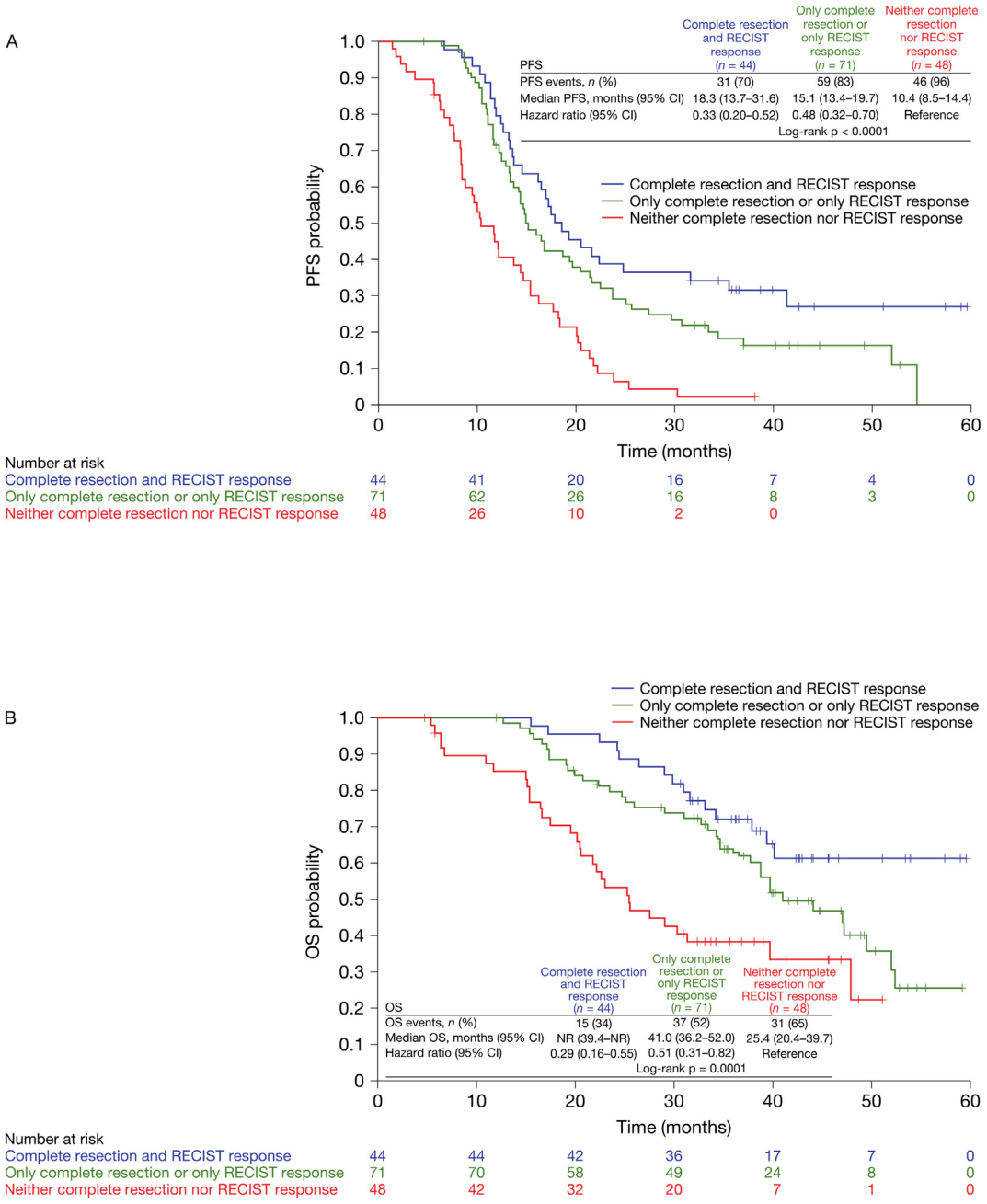

Fig. 3. Surrogate markers of PFS and OS at the time of IDS. (A) PFS. (B) OS. CI, confidence interval; IDS, interval debulking surgery; NR, not reached; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

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BI reviewed the study design but had no involvement in collection, analysis, or interpretation of the data, manuscript writing, or the decision to submit for publication. BI had the opportunity to review the manuscript for medical and scientific accuracy regarding the BI substance as well as intellectual property considerations.

CRediT authorship contribution statement

Gwénaël Ferron: Conceptualization, Methodology, Investigation, Resources, Writing – original draft, Writing – review & editing. **Gaëtan De Rauglaudre:** Resources, Writing – review & editing. **Stéphanie Becourt:** Resources, Writing – review & editing. **Nicolas Delanoy:** Resources, Writing – review & editing. **Florence Joly:** Resources, Writing – review & editing. **Alain Lortholary:** Resources, Writing – review & editing. **Benoît You:** Resources, Writing – review & editing. **Patrick Bouchaert:** Resources, Writing – review & editing. **Emmanuelle Malaurie:** Resources, Writing – review & editing. **Sebastien Gouy:**

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Data availability statement

Currently no mechanism is in place to allow sharing of individual deidentified participant data. Requests sent to ARCAGY–GINECO (bvotan@arcagy.org) will be considered on a case-by-case basis.

Declaration of Competing Interest

Gwénaël Ferron: Advisory boards (Clovis, AstraZeneca, GSK, MSD, Roche, RanD Biotech, Olympus), lectures/symposia (AstraZeneca, Clovis, GSK, MSD, PharmaMar). Nicolas Delanoy: Advisory boards/honoraria (GSK, AstraZeneca, MSD, Clovis Oncology). Florence Joly: Advisory boards (Clovis, AstraZeneca, GSK, MSD, Seagen), lectures/symposia (AstraZeneca, Clovis, GSK, MSD); non-gynecology: Ipsen, Janssen, Sanofi, Bayer, Astellas, Pfizer, Amgen. Alain Lortholary: Advisory board fees (AstraZeneca, MSD Tesaro), speaker honoraria (Clovis Oncology, Roche), congress participation (Novartis, Pfizer, MSD, Lilly, Roche), member of CS3 sein UNICANCER. Benoît You: Consulting (MSD, AstraZeneca, GSK–Tesaro, Bayer, Roche/Genentech, ECS Progastrin, Novartis, LEK, Amgen, Clovis Oncology, Merck Serono, BMS, Seagen, Myriad). Nadine Dohollou: Consulting/expert (Daiichi, Lilly, Roche, Seagen), conferences/training (Daiichi, Lilly, Roche, Seagen), research grants/clinical trials (AstraZeneca, BMS, Boehringer Ingelheim, Genomic Health, Lilly, MSD, Novartis, Pfizer, Roche). Anne Floquet: Advisory boards (MSD, AstraZeneca, GSK, Clovis Oncology), congress participation (AstraZeneca, GSK, MSD, PharmaMar, Roche). Michel Fabbro: AstraZeneca, GSK, Clovis. Jérôme Alexandre: AstraZeneca, GSK, Clovis, MSD, Eisai, Novartis. Isabelle Ray-Coquard: Advisory/consultancy (Amgen, AstraZeneca, Clovis Oncology, Genmab, GSK, ImmunoGen, Mersana, Deciphera, Novocure, Eisai, Sutro Pharma, Merck Sharp & Dohme, Pfizer/Merck Serono, PharmaMar, Roche), research grant/funding (Roche, BMS, MSD, GSK), travel/accommodation/expenses (AstraZeneca, Roche, GSK, Clovis).

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Appendix A. Supplementary data

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