Adding nintedanib to neo-adjuvant chemotherapy (NACT) is deleterious for advanced epithelial ovarian cancer (EOC) patients: The CHIVA double-blind randomized phase II GINECO study

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Background

Neoadjuvant chemotherapy represents an alternative strategy for patients with stage IIIC or IV who are considered not to be optimally resectable at primary surgery.

Subset analyze of ICON7 and GOG 218 have suggested that patients with FIGO stage III and residual disease after initial surgery or FIGO stage IV are those who might most benefit from the addition of bevacizumab to first-line chemotherapy both in terms of PFS and OS. There are some concerns to administer bevacizumab during the chemotherapy surrounding the interval debulking surgery due to its long half life (14-21 days) and its interference with wound healing.

Nintedanib, an oral inhibitor of VEGF/FGF/PDGF receptors with a short half-life (7-19 hours), might offer a better alternative to bevacizumab in the neo-adjuvant setting. The addition of nintedanib to carboplatin–paclitaxel in the adjuvant setting after up-front surgery was investigated in the AGO-OVAR12 trial and showed a prolonged PFS but was associated with more adverse events (du Bois et al. Lancet Oncol 2016).

CHIVA is a randomized (2:1) double blinded placebo-controlled phase II trial was conducted to compare PFS and surgical complications of patients with FIGO stage IIIC/IV treated in first line with 3 to 4 cycles (cy) of carboplatin (AUC 5) and paclitaxel (175 mg/m²) (CP) before interval debulking surgery (IDS) followed by 2 to 3 cy of CP for a total of 6 cy, plus either 200 mg of nintedanib (arm A) or placebo (arm B) twice daily on days 2–21 q3week at cy 1&2, 5&6 and maintenance therapy for up to 2 years.

Main eligibility criteria

- First diagnosis obtained by laparoscopy (or by laparotomy) of histological confirmed adenocarcinoma of ovary, fallopian tube or primary peritoneal cancer. Non-epithelial or mixed mullerian malignant tumor, and borderline were excluded.
- FIGO 2014-Stage IIIC – IV
- ECOG performance status < 2
- Primary debulking surgery denied and maximum surgical effort of cytoreduction with the goal of no residual disease planned as interval debulking surgery
- Interval between diagnosis and enrolment (informed consent) ≤ 8 weeks
- Adequate hepatic, renal and bone marrow functions

Main endpoints

Primary endpoint: Progression-free Survival (PFS).

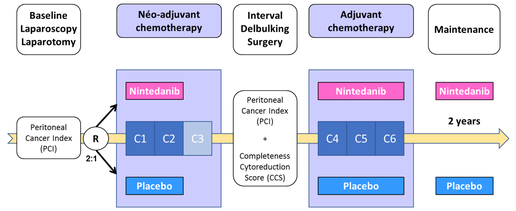
Secondary endpoints :

- Safety including operative complications rate. 3 planned safety interim analyses were run by the IDMC after 30, 60 and 90 patients in the experimental arm had completed the neo-adjuvant and IDS phase.
- Efficacy: Response rate (using RECIST 1.1) to neoadjuvant treatment; Complete debulking rate (CC0) at interval debulking surgery; Best response to the global strategy; Biological progression-free interval by serum Ca125; Overall survival; Quality of life

Patients Characteristics

	Arm A Nintedanib	Arm B Placebo
Age (median/ y)	64	63.4
Histological type (%)		
Serous	87.1	88.9
Endometrioid	2.4	-
Mucinous	0.8	-
Clear cells	2.4	-
Undifferenciated	3.2	1.6
Other	4.0	9.5
Histological Grade (2 & 3) (%)	76.6	84.2
FIGO staging (%)		
III	79	77.5
IV	21	22.5
Diagnostic surgery by lapararoscopy (%)	92.7	94.7
Peritoneal cancer index (PCI) at baseline		
Median (IQR)	22.5 (19-27)	21 (15-25)

Study design



Paclitaxel: 175mg/m2, I.V Carboplatin: AUC 5 or AUC 6 (6 to 8 cycles)
Nintedanib: (oral TKI inhibiting VEGFR/PDGFR/FGFR): 400 mg/day
IDMC run 3 planned safety interim analyses after 30, 60 and 90 patients had completed the neo-adjuvant and IDS phase

Neo-adjuvant treatment compliance

	Arm A Nintedanib	Arm B Placebo
Dose reduction (%)		
Carboplatin	13.7	0
Paclitaxel	4.0	1.6
Dose interruption (%)		
Nintedanib/Placebo	45.9	29.7
Early stopping (< 4 cy) (%)		
Carboplatin	18.5	7.9
Paclitaxel	14.5	6.2
Nintedanib/Placebo	33.9	18.8

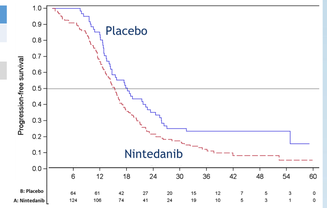
Results

Between Jan. 2013 to May 2015, 188 patients were included (124 arm A, 64 arm B) with a median Peritoneal Cancer Index of 22 (range 19-27).

Survival

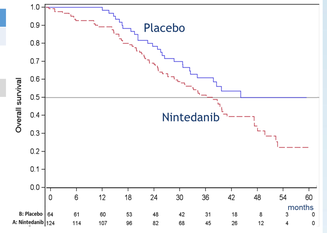
Progression Free Survival

Arm	Events/Total	Median (95% CI)	HR
Nintedanib	109/124	14.4 (12.2-15.4)	1.50
Placebo	47/64	16.8 (13.3-21.4)	Reference
Logrank P-value: 0.02			



Overall survival

Arm	Events/Total	Median (95% CI)	HR
Nintedanib	72/124	37.7 (29.8-41.0)	1.54
Placebo	27/64	44.1 (32.7-not reached)	Reference
Logrank P-value: 0.053			



Response to neo-adjuvant chemotherapy

	Arm A Nintedanib	Arm B Placebo	p-value
Response after 2 cy (RECIST) (%)			
Complete response	2.7	3.4	
Partial response	32.4	52.5	
Stable	59.5	42.4	
Progression	2.7	-	
Not evaluable	2.7	1.7	
Overall response after 2 cy (RECIST), n (%)	39 (35.1)	33 (55.9)	0.0090
Interval debulking surgery performed, n (%)	72 (69.9)	49 (81.7)	
Response at IDS (PCI Decrease) (%)	65.8	84	0.0237
Complete Cytoreductive surgery (CC0) (%)	74.7	77.6	0.7139

Toxicity

Arm A was associated with more toxicity compared to arm B respectively (grade 3&4 adverse events: 92 versus 71 %)

During neo-adjuvant therapy

	Arm A Nintedanib		Arm B Placebo	
Grade (NCI-CTCAE v4)	1 or 2	3 or 4	1 or 2	3 or 4
Hematological (%)				
Neutropenia	20.4	13.5	21.7	6.7
Anemia	53.8	3.3	53.3	0
Thrombopenia	26.2	5.9	10.0	0
Non-hematological (%)				
Nausea	41.1	2.4	32.3	0
Vomiting	19.3	1.6	14.6	0
Diarrhea	37.9	9.7	19.3	1.6
Constipation	5.0	0.8	21.6	0
Fatigue	52.1	2.5	46.6	0
High Blood Pressure	13.5	12.6	18.4	0
Venous Thrombosis	1.7	4.2	0	3.3
Bleeding	5.6	0.8	3.2	0
Fistula	-	3.2	-	0

Operative and post-operative toxicity

	Nintedanib	Placebo
Grade (NCI-CTCAE v4)	3 or 4	3 or 4
Interval Debulking Surgery		
n / Total	72 / 124	49 / 64
%	69.9	81.7
Operative complication (%)	4.2	8.2
Post-operative complication (%)	9.7	20.0

During whole treatment

	Nintedanib		Placebo	
Grade (NCI-CTCAE v4)	1 or 2	3 or 4	1 or 2	3 or 4
Transaminase increase (%)				
AST	42.7	5.6	27.0	0
ALT	46.0	4.8	33.3	0

Conclusions

The addition of nintedanib to neoadjuvant chemotherapy for advanced epithelial ovarian cancer patient increases toxicity and compromise chemotherapy efficacy leading to a reduced rate of Interval Debulking Surgery and worse PFS and OS.

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