

The Oncogramme[®] Predicts the Response of Metastatic Ovarian Cancer to Chemotherapeutic Treatment: Link with Patient Care Pathway Through Peritoneal Cancer Index, RECIST Criteria 1.1 and Resective Surgical Operability: A Pilot Study

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Abstract

Objective: Although surgical advances and the success of chemotherapeutic drugs (carboplatin and paclitaxel) have improved outcomes for patients, Ovarian Cancer (OC) remains one of the deadliest cancers worldwide. Indeed, first line treatment is weakly efficient. Rapid, reliable, and adapted tests are thus needed to help clinicians provide personalized chemotherapeutic treatments.

Methods: A pilot study was conducted on 15 patients to evaluate the ability of the Oncogramme® (an innovative ex vivo assay) to predict tumor responses to chemotherapies (sensitivity/resistance). Carbohydrate Antigen 125 (CA125) levels and the Peritoneal Cancer Index (PCI) score were measured to monitor patients. Oncogramme® responses were compared to PCI interpretation, the RECIST 1.1 criteria (the reference used by clinicians to monitor tumor responses to treatment), and patient operability (or suitability for resective surgery).

Results: For the majority of the patients, CA125 levels switch from abnormal to normal during the study period and evolution of PCI scores was favorable. In terms of sensitivity, the Oncogramme® capacity of identification of an efficient treatment reaches 75% if PCI interpretation is used as a marker of response, 75% with the RECIST 1.1 criteria, and 91% with the patient operability as the ultimate proof of the patient's response.

Conclusion: This pilot study demonstrates potential benefits and utility of the Oncogramme® for predicting the responses of patient tumors to improve patient care. A larger-scale trial is needed to fully validate this test as a new tool for helping clinicians make rapid decisions regarding treatment of these patients.

Keywords: Functional assay; Ovarian cancer; Oncogramme®; Precision medicine; primary culture.

Introduction

Ovarian cancer (OC) is the third most common gynecologic tumor worldwide, with the highest mortality rate of all cancers in women [1]. Several factors increase the risk of developing OC. Among them, germline mutations in the *BRCA1* or *BRCA2* genes are responsible for 20–25% of high-grade serous carcinoma (HGSC) cases (which represent the most common hereditary condition) [2]. Other known risk factors are age, post-menopausal hormonal therapy, infertility, and null parity.

According to the International Federation of Gynecology and Obstetrics (FIGO) classification, OC has 4 tumor stages defined in function of the tumor spread. OC is insidious; often, it is silent and asymptomatic. It is also heterogeneous (subdivided into at least 5 different histologi-

cal subtypes, with HGSC being the most common) and frequently diagnosed at an advanced stage [3] as it does not require blood or lymph for metastasis [4]. For all stages combined, the 5-year survival rate is <50%.

To determine the extent of disease, diagnostic assessment is based on imaging methods [i.e., ultrasound, Computed Tomography (CT), Magnetic Resonance Imaging (MRI), and (Positron Emission Tomography (PET)-scans [5], and confirmed by histologic criteria and blood analysis of serum molecular tumor markers, of which Carbohydrate Antigen 125 (CA125) is the most common. Indeed, the level of CA125 is a biochemical tool used for management of advanced OC patients who receive first-line paclitaxel/platinum-based chemotherapy [6]. Although CA125 is thought to be rather nonspecific, a recent study shows that levels are related to development and progression of OC,

making it useful for early diagnosis, disease development monitoring, and evaluation of prognosis [7]. Furthermore, the RECIST (Response Evaluation Criteria in Solid Tumors) criteria are determined to establish the treatment response of each patient while taking into account the presence of metastasis, their number and their evolution. Defined as the gold standard [8], the latest revised version is RECIST 1.1 [9]. Finally, the Peritoneal Cancer Index (PCI; first described by Sugarbaker) is also useful for disease monitoring. It is measured during operative times (biopsy and surgery ones), and provides an assessment of the local, regional, and general extent of OC [10].

Adequate cancer staging and optimal cytoreduction (either by laparotomy or debulking) are the main goals of the surgical treatment for OC [11,12]. Before surgery, neoadjuvant chemotherapy can be prescribed to allow surgical intervention or increase optimal cytoreduction. After surgery, adjuvant chemotherapy is considered [13]. The backbone chemotherapeutic strategy is a combination of platinum analogs (either cisplatin or carboplatin) plus a taxane (either paclitaxel or docetaxel) [15-17]. Patients that suffer of therapeutic failure can undergo Hyperthermic IntraPeritoneal Chemotherapy (HIPEC) that is the delivery of intraperitoneal chemotherapy (cisplatin) during surgery under hyperthermic conditions [18]. Nearly all patients experience recurrence, leading to the use of the term “Platinum-Resistant Ovarian Cancer” (PROC) [19].

For this reason, developing *ex vivo* assays destined to individualize treatment, and reducing the gap between clinical assays and “the real life”, is a challenge. These tools should be rapid and provide data that can be used to improve responses to treatment (i.e., the patient prognosis by suggesting better therapeutic options earlier in the disease course), while at the same time avoiding multiple cycles of ineffective drugs that show notable toxicity, thereby reducing the cost of patient care.

The first test was set up in 1977 [20]. Among available tools, companion diagnostic 2D- and 3D-cultures have been developed (for a review, see [21]). Such diagnostic tests were initially named Chemo-Response Assays (CRAs), with the most famous being the MiCK (MicroCulture-Kinetics [22]) and ChemoFx assays [23,24]. Today, those tests are

referred to “functional assays” [25]. More recently, and because OC is a heterogeneous malignant tumor, investigations have focused on 3D-culture approaches. Thus, development of organoids and spheroids (non-adherent culture conditions) has increased. These culture systems retain the characteristics of the parental tumor (good genetic stability and high homology [26]), with a complex cellular organization. However, their heterogeneity is also their weakness to use them as an *In Vitro* Diagnosis Medical Device (IVD-MD). As each fragment of tumor sent for a functional analysis may have a ratio of stromal and tumor cell which did not reflect the real tumor ratio of the global tumor, standardization is impossible and the reliability of the results obtained can be subject to wide variations (sometimes excellent, sometimes unsatisfactory). Moreover, their experimental analysis stays complex and they remain expensive.

Developed by the company Oncomedics, the Oncogramme® is an IVD-MD that possesses numerous advantages over the above assays, as (i) cultured cells keeping characteristics of the parental tumor, ii) a time frame of 15 days maximum, (iii) the use of cancer-specific-defined media, and (iiii) reliable results due to highly sensitive analyses. The Oncogramme® has already been developed for other cancers (colon [27-29] and breast [30,31]). Moreover, technical approval for OC has been undertaken and published [32]. Therefore, we decided to drive a pilot study aiming at evaluating its predictive effectiveness in a small cohort of patients suffering from advanced OC. The aim was to demonstrate the potential of the Oncogramme® as a decision support tool that facilitates decision-making by clinicians to identify patients with tumors likely to be chemo-sensitive/resistant.

Neo-adjuvant chemotherapy is administered to facilitate surgical intervention (linked to PCI determination and operability). Patients were treated accordingly to the standard of care (a combination of platinum analogs plus a taxane). They were monitored using complementary imaging (CT, MRI, and PET-scan), histology characteristics, CA125 levels and PCI scores. Although useful, these markers stay unspecific and need to be completed. Finally, the surgery stays the only curative treatment.

The aim of our study was to determine benefits of

Oncogramme® sensitivity in neo-adjuvant conditions compared with usual markers as PCI interpretation, RECIST criteria and patient operability. Data from the Oncogramme® profiles (based on tumor chemo-responses) was analysed for predicting if a treatment i) induce tumor size evolution (based on PCI scores), ii) reduce the tumor progression measured by the RECIST 1.1 criteria, iii) and allow patient operability (or feasibility of surgical cytoreduction). Those criteria are essential for clinicians.

Material and Methods

Study Design

This study was carried out according to The Code of Ethics of the World Medical Association (Declaration of Helsinki). Informed consent was obtained from all participants. The study was approved by the author's institutional board and was performed under regulatory authorization (ClinicalTrials.gov database, registration number: NC-T02910622) on 22th September 2016.

Demographics and Description of the Study Population

Quantitative variables [age (years), body mass index (kg/m²), determination of disease characteristics (by CT, MRI, and/or PET-scan), histology data and CA125 levels (IU/mL and interpretation), determined by clinicians, were obtained from Case Report Forms.

Inclusion/Exclusion Criteria

OC specimens, obtained from included patients during primary tumor resection at University Hospital and private institute from June 2012 to June 2016, were anonymized.

Inclusion criteria were as follows: consent to use tumor samples; aged ≥ 18 years with operable stage IIIc or IV (with pleural effusion) cancer (based on the FIGO classification); OC requiring induction treatment, with disease measurable according to the RECIST 1.1 criteria by MRI or CT, or evaluable by PET-scan (PCI score); patients without cancer within 5 years (with the exception of basal cell carcinoma, spino cell carcinoma, or treated cervical cancer *in situ*); and patients not included in a therapeutic trial involv-

ing an investigational compound.

Non-inclusion criteria were as follows: lack of contraception for women of childbearing age; receipt of targeted therapy, hormone therapy, or concurrent radiation therapy; inability to attend follow-ups for geographical, social, or psychological reasons; deprivation of liberty by administrative or judicial decision; a person under guardianship; difficulty in understanding the study protocol; and lack of coverage by social security insurance.

The Oncogramme® Process and Profiles

Tissue samples collect, preparation, primary culture, and Oncogramme® analysis were conducted as described previously [32] using stock solutions of chemotherapeutics (Calbiochem, Saint-Quentin-Fallavier, France). The carboplatin/paclitaxel (termed as Carbo/Taxol) ratio was determined as follows: %cytotoxicity (Carbo/Taxol) / %cytotoxicity Control.

The quartile method (median, minimum, maximum, 25th, and 75th quartiles) was applied to categorize samples as sensitive (Carbo/Taxol ratio > the 75th quartile), intermediate (Carbo/Taxol ratio between the 75th and 25th quartiles), or resistant (Carbo/Taxol ratio < the 25th quartile), as described previously [28].

PCI Scores and Interpretation

PCI scores give information on invaded areas observed during operative times (biopsy and surgery ones). They were determined at the time of biopsy and then again, at the time of surgery [10,33]. Three independent analyses were made by surgeons.

Results are explained in terms of PCI categorization based on the difference between PCI scores at the time of biopsy and at the time of surgery. The quartile method was applied to classify TA, TB and TC categories as Favorable (PCI evolution > the 75th quartile), and TD category as Unfavorable (PCI evolution < the 25th quartile).

RECIST 1.1 Criteria and Surgical Process

The RECIST 1.1 criteria [9,34] categorize patients based on their complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD).

With respect to therapeutic care, “responders” were defined with a complete/partial response as a stable disease, *versus* “non-responders” having a progressive disease.

The clinicians decided whether a patient was suitable for surgical resection (laparotomy and debulking) or for observational examination (by coelioscopy).

Statistical Analysis

Contingency tables were constructed by matching results observed on patients (PCI interpretation, RECIST 1.1 criteria and operability) and Oncogramme® categorizations. It allows determination of *true positives* (A, patients termed as sensitive/intermediate by Oncogramme® and who have answered positively to the analyzed criteria) and *true negatives* (D, patients termed as resistant by Oncogramme® and who have answered negatively to the analyzed criteria). In the Tables, (B) corresponds to patients identified as sensitive/intermediate by Oncogramme® and who answered negatively to the analyzed criteria (false positive), and (C) corresponds to patients identified as resistant by Oncogramme® and who answered positively to the analyzed criteria (false negative). These different values permit calculation of indicative data (see below) using the formula described before [28,35]:

Sensitivity is defined as the capacity of the test to predict a positive result (sensitive or intermediate) when a patient answers positively to the analyzed criteria (responder); it is calculated by the formula $A/(A+C)$.

Specificity is defined as the capacity of the test to predict a negative result (resistant) when a patient answers negatively to the analyzed criteria (non-responder); it is calculated by the formula $D/(B+D)$.

Positive Predictive Value (PPV) is defined as the probability that the tumor is sensitive to chemotherapy when the test predicts it; it is calculated by the formula $A/(A+B)$.

Negative Predictive Value (NPV) is defined as the probability that the tumor is resistant to chemotherapy

when the test predicts it; it is calculated by the formula $D/(C+D)$.

Predictive Capacity (PC) is the capacity of the test to predict tumor responses to chemotherapy; it is calculated by the formula $(A+D)/(A+B+C+D)$.

The 95 % confidence intervals (CIs) were calculated with the exact method. To quantify concordance between Oncogramme® results following categorization and results observed on patients, Kappa coefficient, ranging from -1 to 1, was also estimated with a 95 % confidence interval. For its interpretation, categories from Landis and Koch were used: Poor, Slight, Fair, Moderate, Substantial and Almost Perfect agreement for coefficient values ranging between -1 and 0, 0 and 0.2, 0.21 and 0.4, 0.41 and 0.6, 0.61 and 0.8 and 0.81 and 1.0, respectively.

Results

Patient Characteristics

Twenty-two OC samples corresponding to operable stage IIIc or IV pleural IFGOs were suitable for Oncogramme® analysis. Three of them were excluded because inclusion number was achieved. Moreover, 4 samples not usable for cell culture (1 with bacterial contamination and 3 with too few cells) were excluded, leaving 15 patients and 16 samples for analysis (Oncogramme® realized on 2 different samples from one same patient; **Figure 1**). Disease was characterized by CT, MRI, and PET scans that identified peritoneal carcinosis (**Table 1**). Histology confirmed cellular characteristics of OC (i.e., HGSC).

CA125 Levels and PCI Scores

CA125 levels were measured by different laboratories during the preoperative and post-therapeutic period (**Table 2a**). During the post-therapeutic period, 6/15 patients (40%) had normal values, 7/15 (46.7%) had abnormal values, and 2/15 patients (patients 24 and 59; 13.3%) had non-determined data. For the majority of included patients (13/15, 86.7%), CA125 levels post-treatment were lower than those of pretreatment.

Table 1: Clinical characteristics of the patients included in the study.

Disease characteristics determination						
Patient ID	Age (years)	BMI (kg/m ²)	With CT-scan	With MRI	With PET-scan	Histology
05	62	18.2	Peritoneal carcinosis	Peritoneal carcinosis	Peritoneal carcinosis	Ovarian adenocarcinoma
06	65	19.8			Supra-diaphragmatic adenopathy	Serous papillary adenocarcinoma/peritoneal carcinosis
11	63	32.7	Ovarian mass	Ovarian mass	Peritoneal carcinosis	Ovarian adenocarcinoma
12	72	28.2	Right ovarian mass		Diffuse peritoneal carcinosis	Ovarian adenocarcinoma/peritoneal carcinosis
17	70	21.5	Pelvic mass with ascites	Peritoneal carcinosis with ascites	Ovarian lesion with peritoneal carcinosis	Ovarian adenocarcinoma
19	69	17.7	Ascites	Endometrial cancer		Ovarian papillary carcinoma
21	76	27.1		Cystic mass with peritoneal carcinosis		Ovarian adenocarcinoma
22	69	27.7	Mass with peritoneal carcinosis	Bilateral ovarian lesion with ascites and peritoneal carcinosis	Pelvic evolution and peritoneal carcinosis	Ovarian carcinoma
23	58	23.4		Suspected mixed ovarian cysts	Ovarian cystic evolution with peritoneal carcinosis and doubts on hepatic damage	High grade serous ovarian adenocarcinoma with localized peritoneal carcinosis
24	66	19.5			Peritoneal carcinosis	Ovarian serous adenocarcinoma
52	62	21.3	Peritoneal carcinosis			Serous type adenocarcinoma
54	66	24.6	Peritoneal carcinosis with ascites and depot on the diaphragm			Serous invasive carcinoma

55	79	35.8	Multiple peritoneal nodules with ascites			Serous carcinoma
57	66	24.7	Left ovarian mass with ascites and left pleural effusion			Serous papillary ovarian carcinoma
59	74	35.2	Peritoneal carcinosis with epiploic lesion and lymph nodes disease			Adenocarcinoma poorly differentiated

BMI, body mass index; CT, Computed Tomography; MRI, Magnetic Resonance Imaging; PET, Positron Emission Tomography.

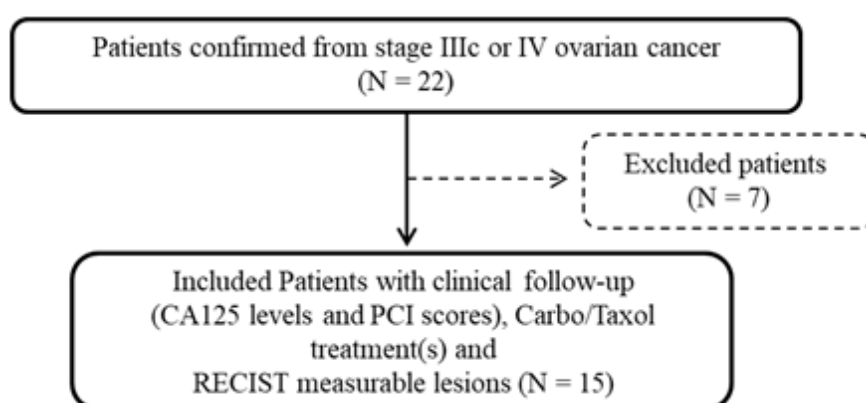


Figure 1: Flow chart showing the patient selection process.

PCI scores were determined by clinicians during biopsy and surgery that allows determination of patient evolution (as PCI interpretation; **Table 2b**). Only four patients experienced unfavorable evolution (patients 21, 23, 54 and 55).

For the majority of included patients, CA125 levels and the PCI interpretation are in accordance with the favorable evolution of OC (**Table 2 a and b**), as described by CA125 monitoring [7].

Oncogramme® Results

Sixteen fresh OC specimens from resected primary tumors were anonymized and analyzed by the Oncogramme® (2 samples from the same patient were obtained; patient 12; **Table 3a**). Data were expressed as percentage of cell death for the non-treated (termed as Control) and treated (termed as Carbo/Taxol) conditions. The results were used to determine the Carbo/Taxol ratio, which allows categorization of OC as sensitive/intermediate/resistant, using the quartile method (**Table 3b**).

Table 2: a) Preoperative and post-therapeutic CA125 levels; **b)** PCI categorization and interpretation.

a)

Patient ID	Preoperative time	Post-therapeutic treatment time
05	413; A	15.6; N
06	963; A	15.1; N
11	533; A	29; N
12	77; A	9.41; N
17	2400; A	18.1; N
19	1103; A	117; A
21	19,900; A	2900; A
22	1180; A	27; N
23	205; A	46.7; A
24	444; A	ND
52	897; A	131; A
54	3340; A	150; A
55	>1800; A	651; A
57	2040; A	235; A
59	437.2; A	ND

IU, International Units; A, abnormal; N, normal; ND, non-determined.

The preoperative condition corresponds to the time of hospital admission. The post-therapeutic treatment condition corresponds to the time following chemotherapy and surgery.

b)

Patient ID	PCI categorization	PCI interpretation
05	TB	Favourable
06	TA	Favourable
11	TA	Favourable
12	TC	Favourable
12	TC	Favourable
17	TB	Favourable
19	TC	Favourable
21	TD	Unfavourable
22	TA	Favourable
23	TD	Unfavourable
24	TC	Favourable
52	TB	Favourable

54	TD	Unfavourable
55	TD	Unfavourable
57	TC	Favourable
59	TA	Favourable

PCI, Peritoneal Cancer Index.

Table 3: a) Sample sensitivity/resistance to Carbo/Taxol treatment based on the Oncogramme® categorization; **b)** Main Oncogramme® results following determination of cytotoxicity based on primary cultures from individual patients.

a)

Sample ID	% Cytotoxicity (control)	% Cytotoxicity (Carbo/Taxol)	Carbo/Taxol ratio	Oncogramme® categorization
05	6.8	33.3	4.879	S
06	11.6	45.7	3.945	S
11	8.3	11.1	1.340	I
12	19.4	16.7	0.862	R
12	47.9	36.3	0.758	R
17	15.4	40.9	2.665	I
19	3	9.6	3.266	I
21	7.4	10.9	1.463	I
22	6.3	18	2.843	I
23	7.6	19.8	2.613	I
24	7.4	21.1	2.858	I
52	13.9	29.9	2.161	I
54	1.7	7.5	4.470	S
55	13.1	15	1.147	R
57	3.8	3.7	0.968	R
59	8	29.4	3.686	S

S, sensitive; R, resistant; I, intermediate.

Cells were treated with Carbo/Taxol [Carboplatin (50 µg/mL) and Paclitaxel (7 µg/mL)]. Carbo/Taxol ratios were calculated as follows: % Cytotoxicity Carbo/Taxol / % Cytotoxicity Control.

The Oncogramme® results were categorized according to percentile: R = resistant < 25th percentile < I = intermediate < 75th percentile < S = sensitive.

b)

	Median	Minimum	Maximum	25 th quartile	75 th quartile
Carbo/Taxol ratio	2.639	0.758	4.897	1.291	3.371

Table 4: Table matching PCI interpretation with the Oncogramme® categorization.

PCI interpretation Oncogramme categorization	Favourable 12/16	Unfavourable 4/16
Sensitive or Intermediate 12/16	9 (A)	3 (B)
Resistant 4/16	3 (C)	1 (D)

Sensitivity 75%; Specificity 25%; PPV 75%; NPV 25%; Predictive Capacity 63%.

Table 5: a) The RECIST 1.1 criteria for patients included in the study; b) Table matching patient RECIST 1.1 criteria with the Oncogramme® categorization.

a)

Patient ID	RECIST 1.1 criteria	RECIST classification
05	2	PR
06	3	CR
11	2	PR
12	2	PR
17	2	PR
19	2	PR
21	2	PR
22	2	PR
23	3	CR
24	2	PR
52	2	PR
54	2	PR
55	1	SD
57	1	SD
59	2	PR

RECIST, Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

b)

RECIST criteria Oncogramme categorization	Responder 16/16	Non-responder 0/16
Sensitive or Intermediate 12/16	12 (A)	0 (B)
Resistant 4/16	4 (C)	0 (D)

Sensitivity 75 %; PPV 100%; Predictive Capacity 75%; Specificity and NPV were undetermined because none patient was Non-responder according to RECIST criteria.

Table 6: a) Surgical intervention for patients included in the study; **b)** Table matching patient operability (suitable for surgery) with the Oncogramme® categorization.

a)

Patient ID	Surgical intervention
05	Laparotomy
06	Laparotomy
11	Laparotomy
12	No; evaluative coelioscopy
17	Debulking
19	No; interval exploratory coelioscopy
21	No; exploratory coelioscopy
22	Laparotomy
23	Debulking
24	Debulking
52	Laparotomy
54	Laparotomy
55	N/A
57	Laparotomy
59	Laparotomy

N/A, not applicable.

b)

Oncogramme categorization \ Patient operability	Yes 11/16	No 5/16
	10 (A)	2 (B)
Sensitive or Intermediate 12/16		
Resistant 4/16	1 (C)	3 (D)

Sensitivity 91%; Specificity 60%; PPV 83%; NPV 75%; Predictive Capacity 81%.

Among the 16 analyzed samples, 4 were sensitive (25%), 8 were intermediate (50%), and 4 were resistant (25%). Sensitive and intermediate samples were grouped together (12/16; 75%) for the rest of the study.

Matching Between the Oncogramme® Profiles and the PCI Interpretation

Using the quartile method, **Table 4** matches the PCI interpretation with the Oncogramme® categorization: sensitivity was 75% [9/12, 95 % CI (43; 95)], with 9 true positive patients. Specificity was 25% [1/4, 95 % CI (01; 81)],

with one true negative patient. Moreover, PPV was 75% [9/12, 95 % CI (43; 95)], NPV was 25% [1/4, 95 % CI (01; 81)], and PC was 63% [10/16, 95 % CI (35; 85)]. The kappa coefficient, calculated at 0, indicates that there is no agreement between *ex vivo* and clinical results.

Matching Between the Oncogramme® Categorization and the RECIST 1.1 Criteria

The RECIST 1.1 criteria for each patient were analyzed by clinicians. As shown in **Table 5a**, 13/15 patients had a complete/partial response (86.7%) and 2/15 had a sta-

ble disease (13.3%). Because none had a progressive disease, all patients were considered as “responders” in term of RECIST 1.1 criteria.

For the 16 analyzed samples, patient clinical responses were cross tabulated with the Oncogramme® categorization (**Table 5b**). Sensitivity was 75% [12/16, 95 % CI (48; 93)], with 12 true positive patients. Specificity and NPV were undetermined because none true negative patients was observed. Moreover, PPV and PC were determined at 100% [12/12, 95 % CI (74; 100)] and 75% [12/16, 95 % CI (48; 93)] respectively. The kappa coefficient, calculated at 0, indicates that there is no agreement between *ex vivo* and clinical results.

Matching Between the Oncogramme® Profiles and the Patient Tumor Operability

As part of standard care, patients were treated as follows: cytoreductive surgery (laparotomy or debulking), 11/15 (73.3%); coeloscopy, 3/15 patients (20%); no surgery [death during the study period, 1/15 patient (6.6%); **Table 6a**].

Table 6b matches the patient operability with the Oncogramme® categorization. Sensitivity was 91% [10/11, 95 % CI (59; 99)], with 10 true positive patients. Specificity was 60% [3/5, 95 % CI (15; 95)], with 3 true negative patients. Moreover, PPV was 83% [10/12, 95 % CI (52; 98)], NPV was 75% [3/4, 95 % CI (19; 99)], and PC was 81% [13/16, 95 % CI (54; 96)]. The kappa coefficient, calculated at 0.54 [95 % CI (0.05; 1)].

Discussion

OC is one of the most worrying cancers in women due to its high mortality rate [1]. Often diagnosed at an advanced stage, it is a heterogeneous disease, difficult to treat. First-line therapy comprises a combination of surgery and chemotherapeutic drugs (platinum analogues plus a taxane [15]); however, sooner or later, the tumors become resistant [19], reinforcing the need to develop tests that predict tumor responses.

The main objective of this retrospective study was to analyze the predictive values of the Oncogramme® by con-

ducting a pilot study on 15 patients with OC (**Figure 1**) in order to obtain information regarding the effectiveness of the test so that a prospective clinical study can be launched on a large number of patients. This test is based on the results of our previous control study [32], which validated the technical application of the Oncogramme® in OC.

CT/MRI/PET images and histological findings show that the majority of patients had peritoneal carcinosis (**Table 1**) in accordance with inclusion criteria (advanced OC stage). However, it would have been interesting to i) include other OC types in the analysis, notably platinum-resistant tumors (or PROC), ii) to assess the mutational status of the *BRCA1* and *BRCA2* genes, and iii) to have the survival rate of patients.

Patients were monitored *via* measurement of CA125 levels. In most patients, CA125 levels decreased post-treatment in accordance with a favorable disease course. However, based on standards specific to each laboratory, abnormal levels were identified in 46.7% of cases (**Table 2a**), even after treatment. CA125 levels can fall even when OC progresses. In fact, a previous study showed that patients with low serum CA125 levels have the same clinical outcome as patients with high levels [36], demonstrating the non-specificity of this marker.

PCI scores were calculated to assess tumor invasion, and the vast majority of patients showed a clear decrease in the PCI score between biopsy and surgical intervention as noted as favorable PCI interpretation (**Table 2b**).

However, while used in hospital practice, results obtained with CA125 and PCI demonstrate that it is still necessary to search more specific markers to gain a more accurate picture of disease behavior. While non-invasive methods such as imaging improve patient monitoring [5], helping clinicians to predict the efficacy of treatment before treating would be of great value, notably to benefit of effective surgery [11]. Here, we show that the Oncogramme® could meet this need.

Oncogramme® analysis (**Table 3a and b**) allowed samples to be classified into 2 groups: sensitive or intermediate (12/15; 80%) and resistant (3/15; 20%). Moreover, sensitivities of the Oncogramme® were of 75% for PCI interpreta-

tion (**Table 4**), 75% for RECIST criteria (**Table 5b**) and 91% for patient operability (**Table 6b**).

For PCI interpretation (**Table 4**), the test shows a sensitivity of 75% [9/12, 95 % CI (43; 95)] because it was able to identify 9 patients among the 12 patients for whom Oncogramme® tests were sensitive to treatment and whom disease evolution was favorable based on PCI interpretation. With a PC of 63% [10/16, 95 % CI (35; 85)], the Oncogramme® is able to predict PCI evolution (favorable or unfavorable) for almost two out of three times before the start of the treatment. The kappa coefficient in this case is very weak, this probably being related to the fact that the specificity is low 25% [1/4, 95% CI (01; 81)].

The RECIST 1.1 criteria provide a practical method for evaluating global tumor responses (primary tumor and metastasis) [9,34]. All patients enrolled in the present study were classified as responders according to the RECIST 1.1 criteria (**Table 5a**), thanks to the effectiveness of chemotherapeutic treatment. Although the RECIST classification was revised in 2018, major limitations continue to persist, including variability of tumor size measurements and tumor heterogeneity [37]. The criteria did not take three-dimensional tumor volume into account, nor imaging intensity, nor tumor growth rate. For these criteria, the Oncogramme® assay demonstrates the characteristics of a reliable test (**Table 5b**). The sensitivity is 75% [12/16, 95 % CI (48; 93)] (due to detection of 12 sensitive/intermediate patients among 16 responders), that is essential for a test designed to predict responses to treatment. Moreover, the high PPV (100%) demonstrates the ability of the Oncogramme® to identify responders among sensitive/intermediate patients, and the adequate PC (75%) highlights its ability to predict patients' response to treatment. However, these results should be interpreted with caution, as no patient was classified as having a progressive tumor according to RECIST criteria. Therefore, specificity and NPV could not be calculated. The PC of the Oncogramme® according to RECIST criteria will thus need to be recalculated on a larger number of patients, including those whose tumors will be assessed as progressive. Nevertheless, sensitivity and PPV, which are not impacted by this absence of patients with progressive tumors, remain promising.

For patient tumor tissue operability (**Table 6b**), the specificity of the test was 60% [3/5, 95 % CI (15; 95)], which means that it correctly identified the 3 resistant patients among the 5 patients who were too resistant to the treatment chosen empirically that they did not have a resection surgery. Sensitivity was 91% [10/11, 95 % CI (59; 99)] because the test correctly identified 10 patients sensitive/intermediate among the 11 patients who underwent resection surgery. These data are reflected in the PPV score of 83% [10/12, 95 % CI (52; 98)] and the NPV score of 75% [3/4, 95 % CI (19; 99)]. Finally, the PC score of 81% [13/16, 95 % CI (54; 96)] illustrates the capacity of the Oncogramme® to predict operability (suitability for surgery) of patients in function of the *ex vivo* response of their tumor. The kappa coefficient, calculated at 0.54 [95 % CI (0.05; 1)], indicates that there is a moderate agreement between *ex vivo* and clinical results. Compared with patient tumor tissue operability, the Oncogramme® shows good overall performance, with large CI being related to the small sample size of the study.

The data presented herein are broadly consistent with those for ATP-based functional assays on OC reported in the literature (sensitivity 95%, specificity 44%, PPV 66% and NPV 89%) [38]. Differences can be explained by the characteristics of the patient group (only IFGO stage III OC; N = 38) and drug associations used in the ATP-based assay.

Numerous clinical studies have validated *ex vivo* assays for analyze treatment responses. For example, the response rate of PROC patients included in the ATP-based Tumor Chemosensitivity Assay (ATP-TCA) arm (for whom treatment was based on chemotherapy-sensitivity analysis) was superior to that in the physician's-choice arm (40.5% *versus* 31.5% [39]). Moreover, the ATP-TCA showed favorable response rates (59% with 33/56 patients who undergo chemotherapy based on *in vitro* ATP-TCA responses) when used to predict responses of patients with recurrent epithelial OC to individualized chemotherapy [40]. Finally, another study demonstrated improved survival rates in patients treated with chemotherapy regimens selected thank to *ex vivo* drug testing: 38 *versus* 21 months for the overall survival (P=.005) and 15 *versus* 7 months for the progression-free median survival (P=.0002) in the assay group compared with the control group [41].

Previously, Oncomedics' searchers validated the Oncogramme® using different tumor models: for colorectal cancer, the initial technical description of the assay [27], a pilot study of 19 patients [28], and a multicenter/prospective trial of 256 patients [29]. Moreover, the method was validated in breast cancer to analyze data from 40 patients [30], and the assay was used to assess 10 patients expressing Human Epidermal Growth Factor Receptor-2 treated with Herceptin (a monoclonal antibody) [31]. With respect to OC, a study of 28 patients demonstrated the usefulness of the Oncogramme® [32]. Thus, Oncogrammes® are more than just a proof of concept: they are useful tools for clinicians that should be used routinely in the clinic.

This study demonstrated that the ability of the Oncogramme® to predict tumor response in first-line treatment is very promising. Thereby, it could 1) avoid treating patients with ineffective molecules, 2) avoid secondary effects from inefficient treatment combination, and 3) reduce the treatment cost. After relapse which occurs frequently, it could permit to adapt the second-line treatment (notably Caelyx, Topotecan, Vepeside... [32]). Indeed, today, the quantity of available drugs has increased the number of their possible associations. Because the Oncogramme® has the capacity to test numerous drugs and drug associations, the possibilities are endless to adapt future therapies and to improve patient cures.

Conclusion

Following on its technical validation [32], the results of this pilot study which establish the diagnosis performances of the Oncogramme® for OC are encouraging. Sensitivity, PPV and PC of the assay are consistent with the clinical responses of the tumor tissues according to the RECIST 1.1 criteria, while specificity and NPV could not be calculated due to the absence of patients whose tumor was resistant

to treatment. More importantly, Oncogramme® is in accordance with the patient outcomes regarding tumor tissue operability, which is the most important prognosis impact factor. This new personalized tool could help clinicians rapidly (turnaround time, 15 days for all the Oncogramme® process) distinguish sensitive/resistant patients, thus allowing efficient personalized therapeutic management for each patient. At any rate, although the Oncogramme® can assist clinicians, this test remains an investigational method with respect to OC. Further clinical studies with more participants, including platinum-resistant patients, are now needed to fully validate the test.

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Ethical Considerations

SG (General and Scientific Director) and CL (President and Chief Operating Officer) are employees of Oncomedics SAS. OPC is an employee of Oncomedics SAS. TG, RM, VF, SL, PMP, ED, NTM, LV, AF, FG, JM, and AP have no conflicts of interest to declare.

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