Prognostic factors of overall survival for patients with FIGO stage IIIc or IVa ovarian cancer treated with neo-adjuvant chemotherapy followed by interval debulking surgery: A multicenter cohort analysis from the FRANCOGYN study group

L. Vincent, C. Jankowski, Lobna Ouldamer, M. Ballester, S. Bendifallah, P.A. Bolze, C. Akladios, H. Costaz, V. Lavoué, G. Canlorbe, et al.

Credit author statement

Study concepts: LV, CJ, CC

Study design: LV, CJ, CC

Data acquisition: LV, CJ, SD

Quality control of data and algorithms: LV, CJ, SD

Data analysis and interpretation: LV, CJ, SD

Statistical analysis: LV, CJ

Manuscript preparation: LV, CJ, CC

Manuscript editing: LV, CJ, LO, MB, SB, PAB, CA, HC, VL, CU, PC, CT, CH, AB, SD, MMP, JF, LB, LA, CC

Manuscript review: LV, CJ, LO, MB, SB, PAB, CA, HC, VL, CU, PC, CT, CH, AB, SD, MMP, JF, LB, LA, CC

Prognostic factors of overall survival for patients with FIGO stage IIIc or IVa ovarian cancer treated with neo-adjuvant chemotherapy followed by interval debulking surgery: a multicenter cohort analysis from the FRANCOGYN study group.

Vincent L[a,b*], Jankowski C[a], Ouldamer L[c,d,] Ballester M[e], Bendifallah S[f], Bolze PA[g], Akladios C[h], Costaz H[a], Lavoué V[i], Canlorbe G[j,k], Collinet P[l], Touboul C[m], Huchon C[n], Bricou A[o], Dridi S[a,b], Padéano MM[a], Bengrine L[p], Arnould L[q], Coutant C[a,b] ; Groupe de Recherche FRANCOGYN

*Corresponding author: Laura Vincent, Department of Surgical Oncology Georges-Francois Leclerc Cancer Center, 1 Professor Marion's street, Dijon, France; lvincent@cgfl.fr, 03 80 73 75 09, fax: 03 80 73 75 29

[a] Department of Surgical Oncology, Georges-Francois Leclerc Cancer Center, 1 Professeur Marion street, 21000 Dijon, France

[b] University of Burgundy, 7 Jeanne d'Arc boulevard, 21000 Dijon, France

[c] Department of Gynecology, Centre Hospitalier Universitaire de Tours, 2 Tonnelé boulevard, 37000 Tours, France,

[d] INSERM U1069 Université François-Rabelais, 10 Tonnelé boulevard, 37000 Tours, France

[e] Department of Gynecologic and Breast Surgery, Groupe Hospitalier Diaconesses Croix Saint Simon, 125 Avron street, 75020 Paris, France

[f] Department of Gynaecology and Obstetrics, Tenon University Hospital, Assistance Publique des Hôpitaux de Paris (AP-HP), 4 Chine street, 75020 Paris, France

[g] Gynecological Surgery Service, CHU Lyon-Sud, 165 Grand Revoyet road, 69495 Pierre-Bénite, France

[h] Department of Surgical Gynecology, University Hospital of Strasbourg, Molière avenue 67200 Strasbourg, France

[i] Department of Gynecological Surgery, Rennes University Hospital, 16 Bulgarie boulevard 35200 Rennes, France

[j] Department of Gynecologic and Breast Surgery and Oncology, AP-HP, Pitié-Salpêtrière University Hospital, 47-83 Hopital boulevard, 75013 Paris, France

[k] INSERM,UMR S 938, Sorbonne University, 75005 Paris, France

[l] Department of Gynecological Surgery, Jeanne de Flandre University Hospital, Eugéne Avinée avenue 59000 Lille, France

[m] Department of Obstetrics and Gynaecology, Centre Hospitalier Intercommunal, 40 Verdun avenue 94010 Créteil, France

[n] Department of Gynecology, Centre Hospitalier de Poissy, 10 Champ Gaillard street 78300 Poissy, France

[o] Department of Gynaecology, Bobigny University, AP-HP, Hôpital Jean-Verdier, 14 Juillet avenue, 93140 Bondy, France

[p] Department of Medical Oncology, Georges-Francois Leclerc Cancer Center, Dijon, 1 Professeur Marion street, 21000 France

[q] Department of Anatomopathology, Georges-Francois Leclerc Cancer Center, 1 Professeur Marion street, 21000 Dijon, France

1 **ABSTRACT**

2 **Introduction.** The aim of this study was to identify prognostic factors of overall survival in

3 patients with FIGO stage IIIc or IVa ovarian cancer (OC) treated by neo-adjuvant

4 chemotherapy (NAC) followed by interval debulking surgery.

5 **Materials and Methods.** Data from 483 patients with ovarian cancer were retrospectively

6 collected, from January 1, 2000 to December 31, 2016, from the FRANCOGYN database,

7 regrouping data from 11 centers specialized in ovarian cancer treatment. Median overall

8 survival was determined using the Kaplan-Meier method. Univariate and multivariate analysis

9 were performed to define prognostic factors of overall survival.

10 **Results.** The median overall survival was 52 after a median follow up of 30 months. After

11 univariate analysis, factors significantly associated with decreased overall survival were; no

12 pelvic and/or para-aortic lymphadenectomy (p=0.002), residual disease (CC1/CC2/CC3) after

13 surgery (p<0.001), positive cytology after NAC (p<0.001), omental disease after NAC

14 (p=0.002), no pathologic complete response (pCR) (p=0.002). In multivariate analysis, factors

15 significantly associated with decreased overall survival were; residual disease after surgery

16 (HR=1.93; CI95% (1.16-3.21), p=0.01) and positive cytology after NAC (HR=1.59; CI95%

17 (1.01-2.55), p=0.05). Patients with no residual disease after surgery had a median overall

18 survival of 64 months versus 35 months for patients with residual disease. Patients with

19 negative cytology after NAC had a median overall survival of 71 months versus 43 months

20 for patients with positive cytology after NAC.

21 **Conclusion.** In this first and largest French based retrospective study, complete cytoreductive

22 surgery in ovarian cancer remains the main prognostic factor of overall survival.

23

24 **KEYWORDS**: ovarian cancer, neoadjuvant chemotherapy, interval debulking surgery,

25 overall survival.

1 **ABBREVIATIONS:**

2 BMI: Body Mass Index

3 CCS: Complete Cytoreductive Surgery

4 HE4: Human Epididymal protein 4

5 IDS: Interval Debulking Surgery

6 LVSI: Lymphovascular Space Invasion

7 NAC: Neo-adjuvant chemotherapy

8 OC: Ovarian cancer

9 OS: Overall survival

10 pCR: pathologic Complete Response

11 PFS: Progression Free Survival

12

13

14

15

16

17

18

19

20

21

22

23

24

25

26 Declarations of interest: none

27

1. INTRODUCTION

In France, ovarian cancer (OC) is the eighth leading cause of cancer in women. Incidence in France in 2018 was 4985 cases and mortality rate was 3927 deaths/year (1).

In approximately 70% of cases, patients with OC are diagnosed at an advanced stage, stage IIIc International Federation of Gynecology and Obstetrics (FIGO) or higher, and have peritoneal carcinomatosis (2,3). The prognosis of advanced OC (stage IIIc or IVa FIGO) remains poor, with a median overall survival (OS) estimated at 30 months according to the European Organization for the Research and Treatment of Cancer (EORTC) (4).

OC management is based on a complete resection surgery, preceded or not by neo-adjuvant platinum-based chemotherapy. Complete resection is a prognostic factor of survival, but excision of peritoneal carcinomatosis lesions might be impossible (5). Performing a neo-adjuvant chemotherapy (NAC) followed by an interval debulking surgery (IDS) decrease surgical resection and thus surgical morbidity without affecting patient survival. A randomized study conducted by the EORTC comparing primary surgery to NAC followed by IDS, demonstrated no significant difference in terms of recurrence-free survival and OS. NAC followed by complete resection surgery became the standard of care in patients with unresectable epithelial OC (4,6,7).

Residual tumors in the operative specimens are evaluated by pathological examinations, allowing histological response definitions. Studies have shown a prognostic impact of complete histological response or pathologic complete response (pCR) on progression-free survival (PFS) and OS. Petrillo *et al*., studied the prognostic impact of pCR after NAC in unresectable OC. In this study, pCR was significantly associated with longer PFS and OS (8). However, pCR is a rare event in these advanced OC receiving NAC (approximately 6%) (9). Therefore it is interesting to identify other factors associated with OS in OC, receiving NAC to optimize patient management, in particular regarding adjuvant treatments after IDS. In fact,

1   identifying subgroups with worse OS could allow us to adapt adjuvant treatment. Two three-

2   phase randomized studies (ICON 7 and GOG-218) have demonstrated a progression free

3   survival (PFS) benefit of adding bevacizumab as adjuvant therapy in poor prognosis sub

4   group's patients (10,11).

5   The objectives of this study are to identify prognostic factors of OS in patients with stage IIIc

6   or IVa OC treated with taxane/platinum-based NAC and IDS and to evaluate the prognostic

7   impact of pCR.

8

9

10   **2.   MATERIALS AND METHODS**

11   *2.1.   Population*

12   Data from 483 patients with OC, stage IIIc or IVa treated by NAC followed by IDS were

13   retrospectively collected, from January 1, 2000 to December 31, 2016, from the

14   FRANCOGYN database regrouping data from 11 French centers specialized in OC treatment:

15   "Georges-François Leclerc Cancer Center" Dijon, "International Hospital" Créteil,

16   "University hospital Lyon Sud", "Jean Verdier Hospital" Bondy, "La Pitié-Salpêtrière

17   Hospital" Paris, "Jeanne de Flandre University Hospital" Lille, "Hospital of Poissy",

18   "University Hospital" Rennes, "University Hospital", Strasbourg, "Hôpital Tenon" Paris and

19   "University Hospital", Tours. NAC was decided after a diagnostic laparoscopy. The research

20   protocol was approved by the Institutional Review Board of the French College of Obstetrics

21   and Gynecology (CEROG 2014-GYN-020). The inclusion criteria were: inoperable initial

22   stage FIGO IIIc or IVa OC, treated by taxane/platinum-based NAC followed by IDS.

23   *2.2.   Clinical and pathological variables*

24   The clinical and pathological variables studied were: age, body mass index (BMI), CA125

25   serum level during evaluation and after NAC, FIGO stage, menopause, BRCA mutation, and

5

1 histological type. Concerning chemotherapy, the variables studied were: number of NAC

2 cycles, NAC protocol, and bevacizumab treatment.

3 Surgery variables studied were: Fagotti score, digestive resection, pelvic lymphadenectomy or

4 para-aortic lymphadenectomy, macroscopic residual tumor, and intraoperative capsular

5 rupture.

6 Pathology variables studied were: peritoneal cytology, lymphovascular space invasion

7 (LVSI), omentum invasion, grade of serous tumors, differentiation, involvement of pelvic and

8 para-aortic nodes and histological response.

9 *2.3.   Definition of the histological response*

10 At the end of IDS, an anatomopathological examination of the surgical specimens was carried

11 out to define histological response in three types: complete response, partial response and no

12 response. Pathologic complete response (pCR) was defined by the absence of invasive

13 residual tumor in operative specimens. Partial histological response was defined by the

14 presence of degenerative changes of the tumor cells. Absence of a histological response was

15 defined by the absence of anatomopathological response to NAC. An expert in gynecological

16 pathology performed histology in all cases.

17 *2.4.   Statistical analysis*

18 Univariate and multivariate analysis were performed to identify clinical, pathological,

19 chemotherapy and surgery variables significantly associated with OS. To identify factors

20 associated with OS, each variable was tested in univariate analysis using the log-rank test.

21 Survival medians were defined according to the Kaplan-Meier method. Variables included in

22 multivariate analysis had a *p* value equal or inferior to 0.10, a significant confidence interval

23 (CI) in univariate analysis and less of 20% missing data.

6

1   Multivariate analysis was performed according to a Cox model. Results were considered

2   significant when *p* value was equal or inferior to 0.05. Survival curves obtained using the

3   Kaplan-Meier method and compared according to the log-rank test. Patients were censored at

4   death or at 137 months if alive.

5   Data were managed with an Excel database (Microsoft Corporation, Redmond, WA, USA)

6   and analyzed using R 3.3.1 software (R Foundation, Vienna, Austria), available online

7   (http:/lib.stat.cmu.edu/R/CRAN/). The research protocol was approved by the institutional

8   review board of the French College of Obstetricians and Gynecologists (CEROG 2016-GYN-

9   1003).

10

11 **3. RESULTS**

12 *3.1.   Population characteristics at initial evaluation*

13 Data from 483 patients with NAC-treated OC followed by IDS were retrospectively collected

14 from 11 French expert centers.

15 Population characteristics are summarized in Table 1. The average age was 61.5 years (+/- 11

16 years). BMI was in average 25.1 kg/m^2 (+/- 5.3 kg/m^2). 83.2% patients were menopausal.

17 Thirty-eight patients had a germline mutation BRCA gene (7.9%) but the BRCA gene status

18 was unknown for 72.9% of patients. Three hundred and fifty-eight patients had FIGO stage

19 IIIc (74.1%) and 97 FIGO stage IVa (20.1%). The majority of patients had a serous ovarian

20 tumor (81.6%).

21 Of the NAC protocols used, 442 patients received taxane/platinum-based chemotherapy

22 (91.5%). Ninety-eight patients received adjuvant therapy with bevacizumab (20.3%).

23 The mean CA125 serum level was 2181 U/ml (+/- 4499 U / ml), 247 patients had a CA125

24 level ≤1000 U/ml (51.2%), 115 patients had a CA125 between 1000 and 3000 U/ml (23.8%),

25 and 87 patients had a CA125 ≥3000 U / ml (18%).

1 Three hundred and sixty-one patients underwent exploratory surgery, of which 291 had

2 exploratory laparoscopy (80.6%), 44 had exploratory laparotomy (12.2%) and 4 had a

3 conversion to laparotomy (1.1%). In this surgical evaluation, sixty-nine patients had a Fagotti

4 score lower than 8 (14.3%) and 199 patients had a Fagotti score ≥ 8 (41.2%). Initial peritoneal

5 cytology was positive in 179 patients (69.8%).

6 *3.2. Evaluation after NAC*

7 Regarding the number of NAC cycles, 195 patients received 2 or 3 or 4 cycles (40.4%), 200

8 patients received 5 or 6 cycles (41.4%), 170 patients received 6 cycles (35.2 %) and 47

9 patients had more than 6 cycles (9.7%) (table 2).

10 Regarding radiological evaluation after NAC, 238 patients had a TAP scan (49.3%) and 35

11 patients underwent a PET scan (7.2%). In this radiological evaluation, 56 patients had ascites

12 (11.6%) and omentum invasion was found in 70 patients (14.5%). With respect to lymph node

13 assessment, 36 patients had suspicious pelvic nodes (7.5%) and 33 patients had suspicious

14 para-aortic nodes (6.8%). Eight patients seem to have small bowel involvement (1.7%) and 22

15 patients seem to have colon involvement (4.6%).

16 *3.3. Characteristics of IDS and histological response after NAC*

17 The Characteristics of IDS and histological response after NAC are summarized in table 2.

18 After NAC, the average CA125 level was 152U/ml (+/- 316U/ml). One hundred and thirty

19 patients had a CA125 level ≤35 U/ml (26.9%) and 120 patients had a CA125 level >35 U / ml

20 (24.8%).

21 During IDS, Fagotti score was less than 8 for 105 patients (21.7%) and ≥ 8 for 65 patients

22 (13.5%). Bowel resection was performed in 140 patients (28.9%). Three hundred and

23 seventeen patients underwent pelvic and para-aortic lymphadenectomy (65.6%), 14 patients

24 had only pelvic lymphadenectomy (2.9%) and 8 patients received a para-aortic

8

1   lymphadenectomy only (1.7%). Among 36 patients with positive pelvic lymph nodes on

2   imaging, 24 patients had a pelvic lymphadenectomy and 22 had a para-aortic

3   lymphadenectomy. Among patients with negative nodes on imaging, 114 patients had a pelvic

4   lymphadenectomy and 110 patients had a para-aortic lymphadenectomy. Among 33 patients

5   with positive para-aortic lymph nodes on imaging, 23 had a para-aortic lymphadenectomy.

6   After IDS, three hundred and fifty-five patients had no visible residual tumor CC0 (73.5%)

7   and 106 had a CC1 or CC2 or CC3 macroscopic residual tumor (21.9%).

8   After histopathological analysis, 31 patients had a pCR (6.4%), 403 patients had a partial

9   histological response (83.4%) and 8 patients showed no response to NAC (1.7%). Capsular

10 rupture was found in 100 patients (20.7%). Peritoneal cytology was positive for 230 patients

11 (47.6%), omentum was invaded for 281 patients (58.2%). One hundred and nineteen patients

12 had positive pelvic lymph nodes (24.7%) and para-aortic lymph nodes were metastatic in 258

13 patients (53.4%).

14 *3.4.   Univariate and multivariate analysis of OS*

15 Univariate analysis of OS is summarized in table 1 and 2. Median follow-up was 30 months

16 and median OS was 52 months.

17 In univariate analysis, age, BMI, menopausal status, germline BRCA mutation, FIGO stage,

18 histological type, NAC protocol, CA 125 at evaluation, Fagotti's score before NAC, and

19 adjuvant bevacizumab didn't significantly affected OS (table 1). At the contrary, positive

20 peritoneal cytology at evaluation was associated with worse OS (p=0.04).

21 Regarding the characteristics of IDS, the absence of pelvic and/or para-aortic

22 lymphadenectomy, and the absence of complete cytoreductive surgery (CCS); CC1/CC2/CC3

23 was associated with worsen OS (respective p value: 0.002 and <0.001). There was no

24 significant difference of OS regarding patients with surgical resection (p=0.23).

9

1 Concerning pathological analysis after IDS, variables significantly associated with a decrease

2 in OS were positive peritoneal cytology at evaluation (p=0.04) and after NAC (p<0.001),

3 omentum invasion at evaluation (p=0.02) and after NAC (p=0.002), para-aortic

4 lymphadenectomy after NAC (p=0.01), presence of LVSI (p=0.04), absence of pCR

5 (p=0.002) and capsular rupture (p=0.03).

6 Among significant variables in univariate analysis (p≤0.10), only those with less than 20%

7 missing data were studied in multivariate analysis. These variables were: absence of pelvic

8 and /or para-aortic lymphadenectomy, presence of residual tumor during interval surgery,

9 positive peritoneal cytology after NAC, omentum invasion after NAC and absence of pCR.

10 After multivariate analysis, the presence of residual tumor (CC1/CC2/CC3) and positive

11 peritoneal cytology after NAC were significantly associated with a decrease in OS

12 (respectively HR = 1.93, 95%CI (1.16-3.21), p=0.01 and HR = 1.59, 95%CI (1.01-2.55),

13 p=0.05) (figure 1).

14 The median OS of patients with no visible residual tumor (CC0) was 64 months, while that of

15 patients with a CC1, CC2 and CC3 was 35 months. The median OS of patients with a positive

16 peritoneal cytology after NAC was 43 months, and 71 months for patients with negative

17 peritoneal cytology after NAC. Survival curves according to residual tumor and peritoneal

18 cytology results are shown in figure 2.

19

10

1 **4. DISCUSSION**

2 This is the first and largest French based retrospective study examining the outcome for

3 patients with stage IIIc or IVa OC treated with NAC. It confirms that CCS remains the main

4 prognostic factor. In our study, 73.5% of patients underwent macroscopically complete

5 resection (CC0) during IDS, and 106 were CC1/CC2/CC3. This rate is relatively high

6 compared to literature data where this level varies between 30 and 85% (2,12–15). We have

7 also shown that the presence of residual tumor after ICS is one of the major prognostic factors

8 of decreased OS of stage IIIc or IVa OC treated with NAC. The median OS of patients with

9 no visible residual tumor (CC0) was 64 months, while that of patients with a CC1, CC2 and

10 CC3 was 35 months. The importance of residual tumor has been shown in many studies (16).

11 Indeed, in 2009, Du Bois *et al*. demonstrated in an analysis of 3 randomized studies (AGO-

12 OVAR 3, 5 and 7) that CCS for stage IIb to IV OC was associated with significant

13 improvement in OS: the median OS was 99 months for patients with no residual tumor, 36

14 months for patients with a residual tumor of 1 to 10 mm and 29 months for patients with a

15 residual tumor strictly larger than 10 mm (*p*<0.0001) (17). Similarly, Bristow *et al.* showed

16 that the 24.5 months median OS was significantly associated with CCS (*p*=0.027). Indeed, a

17 10% increase in CCS rate, increased median survival by 1.9 months (18). However, it is

18 sometimes difficult to compare data from literature as the definition of CCS varies according

19 to studies, that often define CCS as residual tumor of less than 1 cm (4,9,15,19–21). In our

20 study, CCS was not defined by a residual tumor less than 1 cm but by absence of residual

21 tumor (CC0), limiting the biases associated to this factor. Obtaining no residual tumor after

22 surgery is increased by NAC as demonstrated by Lee *et al.*(22). Similarly, the EORTC-NCIC

23 study demonstrated that obtaining a residual tumor of less than 1 cm concerned 41.6% of

24 patients during primary surgery and 80.6% after IDS (23). In addition, the CHORUS study

25 conducted by Kehoe *et al*., showed the non-inferiority of the NAC compared to the primary

1 surgery, therefore it seemed interesting to perform a NAC in patients with major peritoneal

2 dissemination to reduce peri-operative morbidity/mortality and to increase CCS rate (13).

3 However, Hacker *et al.* demonstrated that primary CCS remained the gold standard for

4 patients with OC immediately resectable. In fact, inflammation after NAC can make surgery

5 complicated and ovarian tumors sensitivity to platinum salts can't be predicted (24).

6 In the present study, residual tumor seems to predominate over pCR, that does not appear to

7 be significantly associated with OS in multivariate analysis (p=0.5). Furthermore, pCR rate is

8 6%, similar to what has been previously reported (9). This low rate can be explained by the

9 peritoneal diffusion of OC. However, many studies have demonstrated the importance of

10 histological response after NAC, since NAC is significantly associated with PFS. Rose *et al.*

11 showed that pCR rate was 19.9%. In this study, PFS was 16.1 months in a pCR, 13.5 months

12 in a partial response and 11.7 months when no response was observed (p=0.018) (25).

13 Therefore, Petrillo *et al.*, searched for predictors of pCR. Only the FIGO stage was

14 significantly associated with pCR (p=0.21) (8).

15 Taking in consideration the previously described data, it seemed important to identify other

16 prognostic factors of OS and PFS of IIIc or IVa ovarian stage cancers, to adapt neoadjuvant

17 and adjuvant therapies to subgroups at risk. Scores for predicting OS could be created and

18 implemented using different variables such as the CA125 marker, the presence of BRCA

19 mutation, omental disease. Indeed, Rutten *et al.,* created a nomogram based on clinical-

20 pathological variables, to estimate the 5-year survival of patients with OC treated by primary

21 surgery or IDS. The variables used in this nomogram were age, primary surgery or IDS, post-

22 surgical residual tumor, histological type, FIGO stage, WHO performance status, ascites

23 amount and BRCA status. The total number of points resulting from all variables analysis

24 allowed defining 1-year, 3-year and 5-year survival (26).

1   In our study, a CA125 serum level higher than or equal to 3000 U/ml at evaluation was

2   significantly associated with decreased OS in univariate analysis (p=0.08). As missing data

3   rate was higher than 20%, this marker was not studied in multivariate analysis. Nevertheless,

4   several authors have shown interesting results with this marker. Mahdi *et al.*, showed that a

5   CA125 level of less than 20 U/ml was a predictor of progression-free survival (HR = 0.37,

6   95%CI (0.20-0.66), p<0.001) but not OS (HR = 0.64, 95%CI (0.34-1.21), p=0.17) (27). Other

7   markers could also be used for their prognostic value. The human epididymal protein 4 (HE4)

8   is overexpressed in serous and endometrioid-type OC and can be used for both diagnosis and

9   follow-up of these cancers (28). Thus, Chudecka *et al*. demonstrated that post-treatment

10   normalization or a 50% reduction in HE4 was significantly associated with increased

11   recurrence-free survival and OS (29). Similarly, a meta-analysis performed by Yuang *et al.*,

12   showed that a high pre-operative HE4 level had a negative impact on OS (HR=1.91, 95%CI

13   (1.40-2, 61), p<0.001) (30).

14   Pathological variables such as omental disease could also be implemented in these scores. In

15   our study, omentum invasion after NAC was significantly associated with decreased OS in

16   univariate analysis but was no longer in multivariate analysis. On the other hand, Le *et al.*

17   demonstrated that omentum involvement and its response to NAC were prognostic factors of

18   PFS (20). Given these different data, the combination of biological and pathological criteria

19   could be helpful to identify subgroups with poor prognosis.

20   In our study, the presence of BRCA1/2 mutation was not significantly associated with OS, in

21   contrast with previously reported data but there were missing data for 72.9% of patients. The

22   prognostic value of a BRCA1/2 mutation was assessed in a large number of retrospective

23   cohorts and a recent meta-analysis involving 34 studies concluded that patients with a

24   BRCA1/2 mutation had a benefit in terms of PFS (HR = 0.62, 95%CI (0.53-0.73), p=0.261)

25   and OS (HR = 0.67, 95%CI(0.57-0.78), p=0.001) and this benefit was more important in

13

1 patients with a BRCA2 mutation (31). In another study, the presence of a BRCA1/2 mutation

2 was associated with a better prognosis in the short term (*p*=0.03) but was not found after 10

3 years of follow-up (32). These data might be explained by a higher sensitivity of patients with

4 a BRCA mutation to platinum-based chemotherapy, as demonstrated by Gorodnova *et al.*

5 (33).

6 In recent years, the development of molecular biology and genomics has revolutionized the

7 treatment and understanding of neoplasic diseases, particularly breast cancer. This is still not

8 the case for OC. Mendiola *et al.* demonstrated that 5 overexpressed genes found in malignant

9 ovarian tumors (ANGPT1, CD34, CD44, MMP7, PDGFB) were favorable prognostic factors

10 of OS of high-grade serous OC (34). Mutation identification or new biomarkers associated

11 with survival will be necessary to define subgroups of patients with poor prognosis leading to

12 treatment intensification. In fact, the use of bevacizumab as an adjuvant is still not consensual

13 and is depended on the benefit/risk balance in patients with stage IIIc/IVa OC treated with

14 NAC. Thus, no prognostic score objectively defines patients belonging to high-risk

15 subgroups, who require this adjuvant treatment. Finally, identifying new biomarkers may lead

16 to the development of new therapies such as targeted therapies that may improve the bad

17 prognosis of this pathology.

18

19 **5. CONCLUSION**

20 This is the first and largest French based retrospective study about prognostic factors of OS in

21 stage IIIc or IVa OC treated with NAC. It confirms that CCS remains the main prognostic

22 factor (HR = 1.93, 95%CI (1.16-3.21), *p*=0.01) and residual tumor after IDS seems to

23 predominate over pCR (*p*=0.5). At the time of personalized medicine in oncology, identifying

24 clinical, pathological, surgical, molecular or genomic factors, prognosis of OS and PFS would

14

1 optimize patient management leading to treatment intensification in subgroups with poor

2 prognosis.

3

4 **6. REFERENCES**

5 1.   Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer

6 statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers

7 in 185 countries. CA Cancer J Clin. nov 2018;68(6):394‑424.

8 2.   Heintz APM, Odicino F, Maisonneuve P, Quinn MA, Benedet JL, Creasman WT, et

9 al. Carcinoma of the ovary. FIGO 26th Annual Report on the Results of Treatment in

10 Gynecological Cancer. Int J Gynaecol Obstet. nov 2006;95 Suppl 1:S161‑92.

11 3.   Prat J, FIGO Committee on Gynecologic Oncology. Staging classification for cancer

12 of the ovary, fallopian tube, and peritoneum. Int J Gynaecol Obstet. janv 2014;124(1):1‑5.

13 4.   Vergote I, Tropé CG, Amant F, Kristensen GB, Ehlen T, Johnson N, et al.

14 Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J

15 Med. 2 sept 2010;363(10):943‑53.

16 5.   Peiretti M, Zanagnolo V, Aletti GD, Bocciolone L, Colombo N, Landoni F, et al. Role

17 of maximal primary cytoreductive surgery in patients with advanced epithelial ovarian and

18 tubal cancer: Surgical and oncological outcomes. Single institution experience. Gynecol

19 Oncol. nov 2010;119(2):259‑64.

20 6.   European Society of Gynaecological Oncology. Ovarian Cancer Surgery Guidelines,

21 Advanced stage. guidelines.esgo.org; 2016 oct.

22 7.   Conduites à tenir initiales devant des patientes atteintes d'un cancer épithélial de

23 l'ovaire/Synthèse. e-cancer.fr; 2018 nov.

24 8.   Petrillo M, Zannoni GF, Tortorella L, Pedone Anchora L, Salutari V, Ercoli A, et al.

25 Prognostic role and predictors of complete pathologic response to neoadjuvant chemotherapy

26 in primary unresectable ovarian cancer. Am J Obstet Gynecol. déc 2014;211(6):632.e1‑8.

27 9.   Muraji M, Sudo T, Iwasaki S, Ueno S, Wakahashi S, Yamaguchi S, et al.

28 Histopathology predicts clinical outcome in advanced epithelial ovarian cancer patients

29 treated with neoadjuvant chemotherapy and debulking surgery. Gynecol Oncol. déc

30 2013;131(3):531‑4.

31 10.   Oza AM, Cook AD, Pfisterer J, Embleton A, Ledermann JA, Pujade-Lauraine E, et al.

1 Standard chemotherapy with or without bevacizumab for women with newly diagnosed
2 ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. Lancet Oncol.
3 août 2015;16(8):928‑36.

4 11. Burger RA, Brady MF, Bookman MA, Fleming GF, Monk BJ, Huang H, et al.
5 Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med. 29
6 déc 2011;365(26):2473‑83.

7 12. Onda T, Satoh T, Saito T, Kasamatsu T, Nakanishi T, Nakamura K, et al. Comparison
8 of treatment invasiveness between upfront debulking surgery versus interval debulking
9 surgery following neoadjuvant chemotherapy for stage III/IV ovarian, tubal, and peritoneal
10 cancers in a phase III randomised trial: Japan Clinical Oncology Group Study JCOG0602. Eur
11 J Cancer. 2016;64:22‑31.

12 13. Kehoe S, Hook J, Nankivell M, Jayson GC, Kitchener H, Lopes T, et al. Primary
13 chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer
14 (CHORUS): an open-label, randomised, controlled, non-inferiority trial. Lancet. 18 juill
15 2015;386(9990):249‑57.

16 14. Fagotti A, Ferrandina G, Vizzielli G, Fanfani F, Gallotta V, Chiantera V, et al. Phase
17 III randomised clinical trial comparing primary surgery versus neoadjuvant chemotherapy in
18 advanced epithelial ovarian cancer with high tumour load (SCORPION trial): Final analysis
19 of peri-operative outcome. Eur J Cancer. 2016;59:22‑33.

20 15. Eisenkop SM, Friedman RL, Wang HJ. Complete cytoreductive surgery is feasible and
21 maximizes survival in patients with advanced epithelial ovarian cancer: a prospective study.
22 Gynecol Oncol. mai 1998;69(2):103‑8.

23 16. Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ. Survival effect of
24 maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a
25 meta-analysis. J Clin Oncol. 1 mars 2002;20(5):1248‑59.

26 17. du Bois A, Reuss A, Pujade-Lauraine E, Harter P, Ray-Coquard I, Pfisterer J. Role of
27 surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined
28 exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the
29 Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-
30 OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire
31 (GINECO). Cancer. 15 mars 2009;115(6):1234‑44.

32 18. Bristow RE, Chi DS. Platinum-based neoadjuvant chemotherapy and interval surgical
33 cytoreduction for advanced ovarian cancer: a meta-analysis. Gynecol Oncol. déc

1 2006;103(3):1070‑6.

2 19.   Vermeulen CKM, Tadesse W, Timmermans M, Kruitwagen RFPM, Walsh T. Only
3 complete tumour resection after neoadjuvant chemotherapy offers benefit over suboptimal
4 debulking in advanced ovarian cancer. Eur J Obstet Gynecol Reprod Biol. déc
5 2017;219:100‑5.

6 20.   Le T, Williams K, Senterman M, Hopkins L, Faught W, Fung-Kee-Fung M. Omental
7 chemotherapy effects as a prognostic factor in ovarian cancer patients treated with
8 neoadjuvant chemotherapy and delayed primary surgical debulking. Ann Surg Oncol. sept
9 2007;14(9):2649‑53.

10 21.   Sørensen SM, Schnack TH, Høgdall C. Impact of residual disease on overall survival
11 in patients with FIGO stage IIIB-IIIC vs. stage IV epithelial ovarian cancer after primary
12 surgery. Acta Obstet Gynecol Scand. 31 août 2018;

13 22.   Lee YJ, Chung YS, Lee J-Y, Nam EJ, Kim SW, Kim S, et al. Impact of increased
14 utilization of neoadjuvant chemotherapy on survival in patients with advanced ovarian cancer:
15 experience from a comprehensive cancer center. Journal of Gynecologic Oncology [Internet].
16 26   mars   2018   [cité   8   juin   2018];29(4).   Disponible   sur:
17 https://doi.org/10.3802/jgo.2018.29.e63

18 23.   Vergote I, Amant F, Kristensen G, Ehlen T, Reed NS, Casado A. Primary surgery or
19 neoadjuvant chemotherapy followed by interval debulking surgery in advanced ovarian
20 cancer. Eur J Cancer. sept 2011;47 Suppl 3:S88‑92.

21 24.   Hacker NF, Rao A. Surgery for advanced epithelial ovarian cancer. Best Pract Res
22 Clin Obstet Gynaecol. mai 2017;41:71‑87.

23 25.   Rose PG, Java JJ, Morgan MA, Secord AA, Kesterson JP, Stehman FB, et al. Disease
24 Extent at Secondary Cytoreductive Surgery is Predictive of Progression-free and Overall
25 Survival in Advanced Stage Ovarian Cancer: an NRG Oncology/Gynecologic Oncology
26 Group study. Gynecol Oncol. déc 2016;143(3):511‑5.

27 26.   Rutten MJ, Boldingh JHL, Schuit E, Trum H, van Driel W, Mol BWJ, et al.
28 Development and internal validation of a prognostic model for survival after debulking
29 surgery for epithelial ovarian cancer. Gynecol Oncol. oct 2014;135(1):13‑8.

30 27.   Mahdi H, Maurer KA, Nutter B, Rose PG. The Impact of Percent Reduction in CA-
31 125 Levels on Prediction of the Extent of Interval Cytoreduction and Outcome in Patients
32 With Advanced-Stage Cancer of Müllerian Origin Treated With Neoadjuvant Chemotherapy.
33 Int J Gynecol Cancer. juin 2015;25(5):823‑9.

1   28.   Drapkin R, von Horsten HH, Lin Y, Mok SC, Crum CP, Welch WR, et al. Human
2   epididymis protein 4 (HE4) is a secreted glycoprotein that is overexpressed by serous and
3   endometrioid ovarian carcinomas. Cancer Res. 15 mars 2005;65(6):2162‑9.

4   29.   Chudecka-Głaz A, Cymbaluk-Płoska A, Wężowska M, Menkiszak J. Could HE4 level
5   measurements during first-line chemotherapy predict response to treatment among ovarian
6   cancer patients? PLoS ONE. 2018;13(3):e0194270.

7   30.   Yuan C, Li R, Yan S, Kong B. Prognostic value of HE4 in patients with ovarian
8   cancer. Clin Chem Lab Med. 27 juin 2018;56(7):1026‑34.

9   31.   Biglia N, Sgandurra P, Bounous VE, Maggiorotto F, Piva E, Pivetta E, et al. Ovarian
10   cancer in BRCA1 and BRCA2 gene mutation carriers: analysis of prognostic factors and
11   survival. Ecancermedicalscience. 2016;10:639.

12   32.   McLaughlin JR, Rosen B, Moody J, Pal T, Fan I, Shaw PA, et al. Long-term ovarian
13   cancer survival associated with mutation in BRCA1 or BRCA2. J Natl Cancer Inst. 16 janv
14   2013;105(2):141‑8.

15   33.   Gorodnova TV, Sokolenko AP, Ivantsov AO, Iyevleva AG, Suspitsin EN,
16   Aleksakhina SN, et al. High response rates to neoadjuvant platinum-based therapy in ovarian
17   cancer patients carrying germ-line BRCA mutation. Cancer Lett. 28 déc 2015;369(2):363‑7.

18   34.   Mendiola M, Redondo A, Heredia-Soto V, Herranz J, Berjón A, Hernández A, et al.
19   Predicting Response to Standard First-line Treatment in High-grade Serous Ovarian
20   Carcinoma by Angiogenesis-related Genes. Anticancer Res. sept 2018;38(9):5393‑400.

21

Table 1 : Univariate analysis of prognostic factors of OS in population characteristics

Variables	Values (n = 483)	Median overall survival (months)	p
Age at diagnosis (mean ± SD, years)	61.5±11		
≤ 50 (reference)	78 (16.1%)	60	
50 to 70	284 (58.9%)	54	0.75
≥ 70	120 (24.8%)	43	0.13
Unknown	1 (0.2%)		
BMI (mean ± SD, years)	25,1±5.3		
≤ 25	252 (52.2%)	46	
>25	187 (38.7%)	53	0.15
Unknown	44 (9.1%)		
Menopause			
Yes	402 (83.2%)	50	
No	47 (9.7%)	69	0.22
Unknown	34 (7.1%)		
BRCA mutation			
Yes	38 (7.9%)	73	
No	93 (17.1%)	67	0.28
Unknown	352 (72.9%)		
FIGO stage			
IIIc	358 (74.1%)	54	
IVA	97 (20.1%)	46	0.08
Unknown	28 (5.8%)		
Histological type			
Serous (reference)	394 (81.6%)	54	
Endometrioid	22 (4.6%)	48	
Clear cells	11 (2.3%)	42	
Other	22 (4.6%)	46	0.7
Unknown	34 (7%)		
NAC protocol			
Taxane/platinum-based chemotherapy	442 (91.5%)	53	
Others	41 (8.5%)	41	0.3
CA125 at evaluation (U/ml)			
≤ 1000 (reference)	247 (51.2%)	55	
1000 to 3000	115 (23.8%)	46	0.61
≥ 3000	87 (18%)	41	0.08
Unknown	34 (7%)		
Fagotti score before NAC			
< 8 (reference)	69 (14.3%)	69	
≥ 8	199 (41.2)	46	0.1
Unknown	215 (44.5%)		
Peritoneal cytology at evaluation			
Positive (reference)	176 (69.8%)	46	
Negative	31 (12.3%)	74	**0.04**
Unknown	276		
Adjuvant bevacizumab			
Yes (reference)	98 (20.3%)	46	
No	255 (52.8%)	54	0.87
Unknown	130 (26.9%)		

Abbreviations : BMI = body mass index; FIGO = International Federation of Gynecology and Obtsetrics, NAC = neo-adjuvant chemotherapy

Table 2: Univariate analysis of prognostic factors of OS after IDS

Variables	Values (n = 483)	Median overall survival (months)	*p*
Fagotti score after NAC			
< 8	105 (21.7%)	43	0.1
≥ 8	65 (13.5%)	49	
Unknown	313 (64.8%)		
CA125 post NAC (mean±SD, U/ml)	152±317		
≤ 35	130 (26.9%)	54	0.22
> 35	120 (24.8%)	46	
Unknown	233 (48.3%)		
Surgical resections			
Digestive resections			
Yes	140 (28.9%)	54	0.23
No	342 (70.8%)	46	
Unknown	1 (0.2%)		
Pelvic and para-aortic lymphadenectomy			
Yes	317 (65.6%)	60	**<0.001**
No	151 (31,3%)	44	
Unknown	1 (0,2%)		
Residual tumor after IDS			
CC1/CC2/CC3	106 (21.9%)	64	**<0.001**
CC0	355 (73.5%)	35	
Unknown	22 (4.6%)		
Peritoneal cytology after NAC			
Positive	230 (47.6%)	43	
Negative	153 (31.7%)	51	**<0.001**
Unknown	100 (20.7%)		
Pathological response to NAC			
None (reference)	8 (1.7%)	24	
Partial	403 (83.4%)	49	0.2
Complete	31 (6.4%)	66	**0.002**
Unknown	41 (8.5%)		
Capsular rupture			
None	113 (23.4%)	72	**0.03**
Yes	100 (20.7%)	42	
Unknown	270 (55.9%)		
Invaded omentum after NAC			
Yes	281 (58.2%)	44	**0.002**
No	101 (20.9%)	73	
Unknown	101 (20.9%)		
Invaded pelvic nodes after NAC			
Yes	113 (35.6%)	53	0.073
No	180 (56.8%)	65	
Unknown	24 (7.6%)		
Invaded para-aortic nodes after NAC			
Yes	125 (39.4%)	49	**0.01**
No	139 (43.8%)	74	
Unknown	53 (16.8%)		
Embolus			
Yes	47 (9.7%)	41	**0.04**
No	80 (16.6%)	72	
Unknown	356 (73.7%)		

Abbreviations : NAC = Neo-adjuvant chemotherapy; CC0 = no visible residual tumor; CC1/CC2/CC3 = macroscopic residual tumor
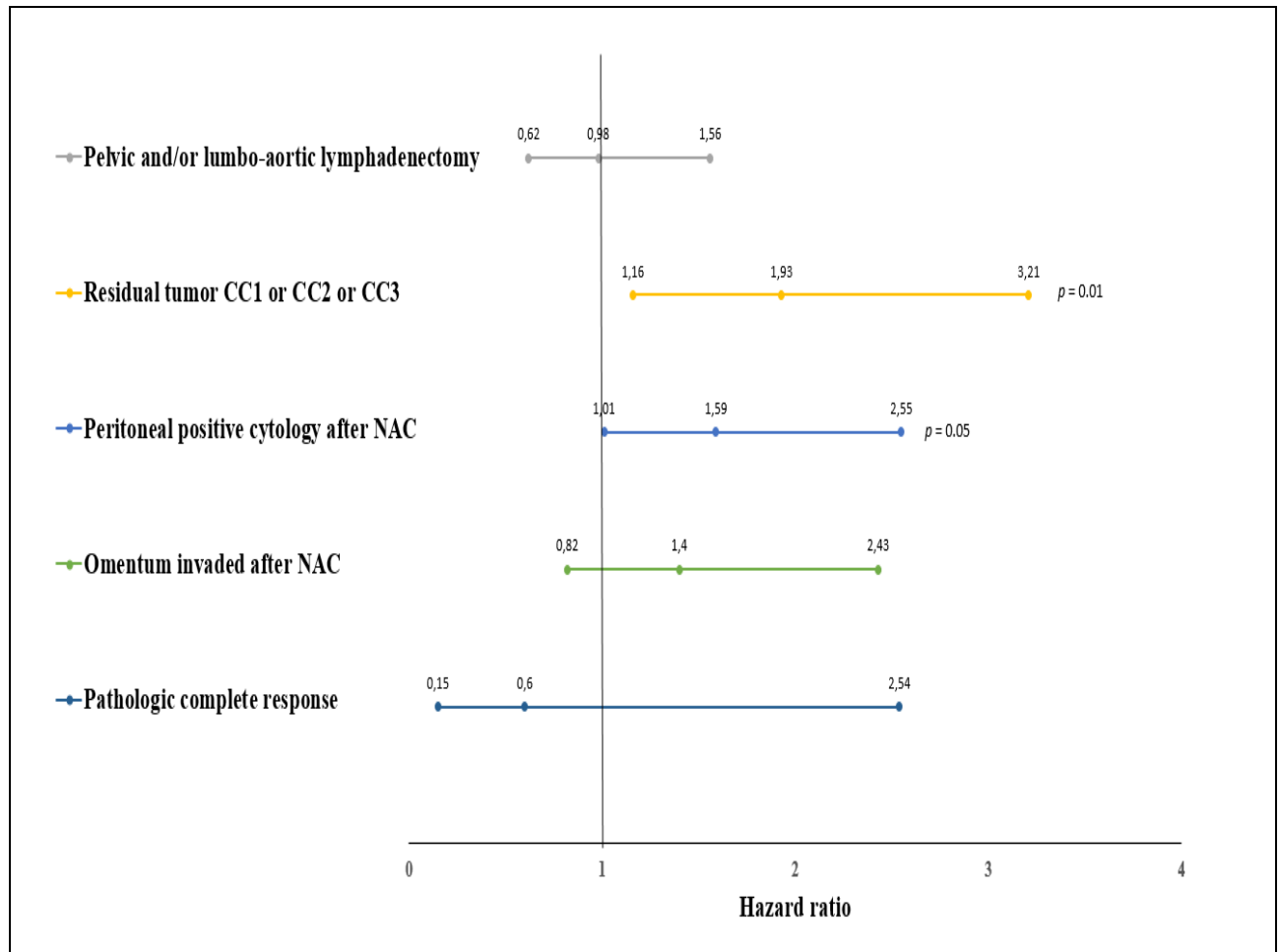
Fig 1. Prognostic factors of overall survival in multivariate analysis.

NAC = neo-adjuvant chemotherapy; CC0 = no visible residual tumor; CC1 or CC2 or CC3= macroscopic residual tumor.
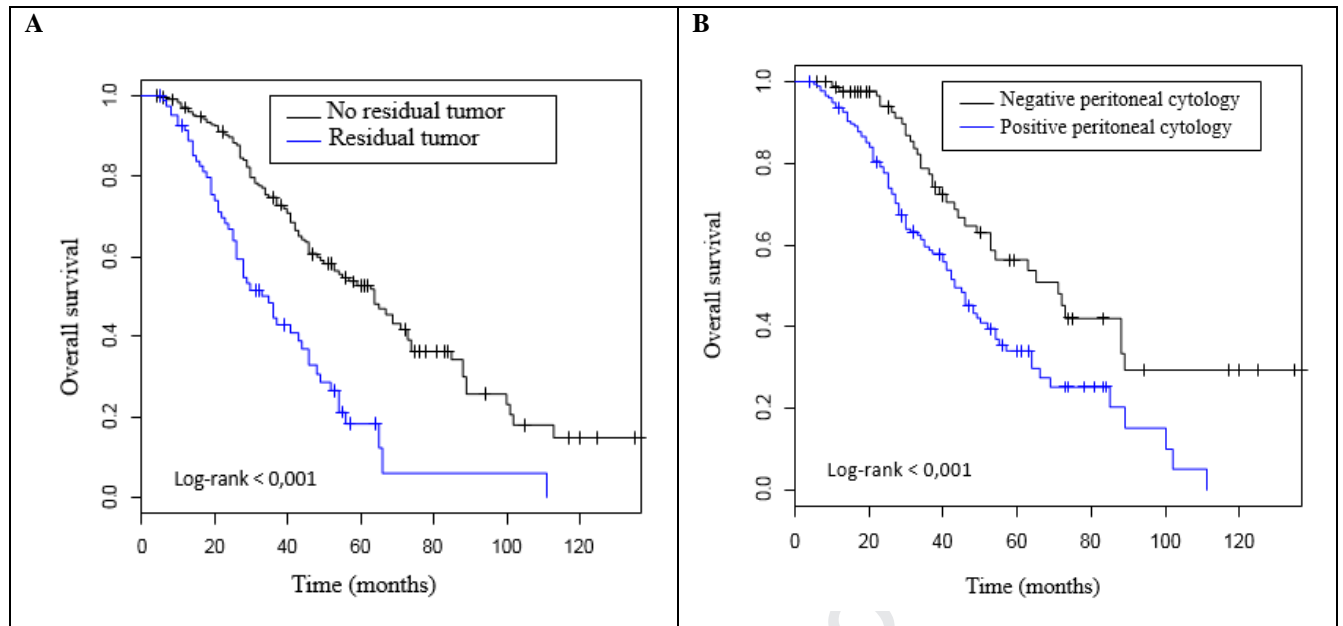
Fig 2. Estimation of overall survival according to residual tumor (A) and peritoneal cytology (B) after interval debulking surgery in Stage IIIc or IVa ovarian cancer patients treated with NAC.

CONFLICTS OF INTEREST

None.

ACKNOWLEDGEMENTS