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► To cite this version:

Patrick Robelin, Michel Tod, Olivier Colomban, Joel Lachuer, Isabelle Ray-Coquard, et al.. Comparative analysis of predictive values of the kinetics of 11 circulating miRNAs and of CA125 in ovarian cancer during first line treatment (a GINECO study). *Gynecologic Oncology*, 2020, 159, pp.256 - 263. 10.1016/j.ygyno.2020.07.021 . hal-03491450

HAL Id: hal-03491450

<https://hal.science/hal-03491450>

Submitted on 17 Oct 2022

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Comparative analysis of predictive values of the kinetics of 11 circulating miRNAs and of CA125 in ovarian cancer during first line treatment (a GINECO study).

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51 The authors declare no potential conflicts of interest.

52 **Running title:** Kinetics of miRNAs and of CA125 in ovarian cancer

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59

60 ***Electronic word count:***

61 Abstract: 243 words

62 Manuscript (excluding title page, abstract, translational relevance, references, tables, legends
63 to figures): 3270 words

64 2 Figures, 4 Tables, 7 Supplementary Figures

65 Number of references: 36

66 Abstract

67 **Objective:** MicroRNAs (miRNAs) are promising biomarkers in ovarian cancer. Their kinetics
68 during treatment might be useful for monitoring disease burden, and guiding treatments in
69 patients treated with peri-operative chemotherapy and interval debulking surgery (IDS).

70 **Methods:** Serial blood samples of patients enrolled in the randomized phase II CHIVA trial,
71 comparing first line carboplatin-paclitaxel +/- nintedanib (NCT01583322) and IDS, were
72 investigated to assess the kinetics of 11 relevant miRNAs. Their prognostic/predictive values
73 regarding the likelihood of complete IDS, and the patient survival, were assessed and
74 compared to those of CA125 kinetics. The selection of the miRNAs (miR-15b-5p, miR-16-5p,
75 miR-20a-5p, miR-21-5p, miR-93-5p, miR-122-5p, miR-150-5p, miR-195-5p, miR-200b-3p,
76 miR-148b-5p and miR-34a-5p) was based on the expression levels found with a large
77 explorative panel, and on the literature data.

78 **Results:** 756 serial blood samples from 119 patients were analyzed for a total of 8172 miRNA
79 assays, and 1299 CA125 values. The longitudinal kinetics of the miRNA expressions were
80 highly inconsistent, and were not related to CA125 dynamics. The miRNA changes during
81 neoadjuvant treatment were not found associated with RECIST tumor response or IDS
82 outcomes. Decreases of miR-34a-5p and miR-93-5p were associated with PFS benefit
83 ($p=0.009$) and OS benefits ($p<0.001$), respectively, using univariate tests.

84 **Conclusions:** The longitudinal kinetics of miRNA expressions during neo-adjuvant treatment
85 in ovarian cancer patients were inconsistent, and were not found to be associated with tumor
86 burden changes. Although some prognostic value could be discussed, no predictive value
87 regarding tumor responses or IDS quality could be identified.

88 Introduction

89 Ovarian cancer ranks fifth for mortality linked to female cancer in western countries [1]. In
90 2011, the Gynecologic Cancer Intergroup (GCIG) defined CA125 response as a $\geq 50\%$
91 reduction in CA125 levels from baseline, on a minimum 28 day period [2]. However, the
92 relevance of this specific criterion, has recently been questioned, since it was not found to
93 exhibit prognostic or predictive values regarding progression free survival (PFS) and overall
94 survival (OS) in several studies [3–6].

95 In first line setting, stage III or IV ovarian cancer patients with diseases considered to be not
96 amenable to primary cytoreductive surgery are usually treated with neoadjuvant
97 chemotherapy and interval debulking surgery (IDS) [7]. One of the main prognostic factors in
98 patients treated with such a strategy is the completeness of the cytoreductive surgery
99 (complete CC0 versus incomplete CC1-CC2) [8]. In this context, there are no validated
100 biomarkers prone to help predict the likelihood of complete IDS, or patient survival.

101 MicroRNAs (miRNAs) are small non-coding RNA molecules that bind specifically to their
102 target mRNAs for inhibiting the expression of genes after transcription [9]. Several studies
103 reported promising outcomes about the diagnostic [10–14], prognostic [10,12,13,15] or
104 predictive values [16–18] of miRNAs in ovarian cancer patients. Some data suggested that the
105 tumor burden changes observed during treatment correlated with the kinetics of some
106 circulating miRNAs in ovarian cancers patients [17,18].

107 We hypothesized that the kinetics of some miRNAs of interest may be more helpful than
108 CA125 for monitoring disease burden and guiding clinicians in decision making for ovarian
109 cancers patients. The aim of the present study was designed to assess the kinetics of 11
110 relevant miRNAs and of CA125 in first line treatment, as a way of comparing their prognostic
111 and predictive values regarding the likelihood of complete IDS.

112

113 Materials and methods

114 Patient population

115 Clinical and biological data were derived from the randomized phase II trial CHIVA
116 (NCT01583322). In this trial, patients with International Federation of Gynecology and
117 Obstetrics (FIGO) stage IIIC or IV ovarian carcinomas planned to be treated with peri-
118 operative chemotherapy and IDS, were randomly allocated to 1) the standard arm carboplatin
119 AUC 5 or 6 and paclitaxel 175mg/m² every 3 weeks with placebo, or 2) the experimental arm
120 with the same regimen combined to nintedanib at 200mg twice daily. The enrolled patients
121 received 3 to 4 cycles before cytoreductive surgery, and then 3 to 4 cycles after surgery,
122 followed by a maintenance treatment with nintedanib/placebo for up to 2 years [19].

123 Nintedanib (BIBF 1120, VARGATEFTM) is a receptor tyrosine kinase (RTK) inhibitor with
124 potential antiangiogenic and antineoplastic activities. The multitargeted tyrosine kinase
125 inhibitor BIBF 1120 selectively binds to and inhibits vascular endothelial growth factor
126 receptor (VEGFR), fibroblast growth factor receptor (FGFR) and platelet-derived growth
127 factor receptor (PDGFR) tyrosine kinases, which may result in the induction of endothelial
128 cell apoptosis; a reduction in tumor vasculature; and the inhibition of tumor cell proliferation
129 and migration.

130 Blood samples for miRNA, along with CA125 concentrations, were assayed at the 8
131 following times during the study: at screening, cycles 2, and 3; before IDS; the three cycles
132 after IDS; and at progression, if any. Moreover, the CA125 values were assayed every 3
133 months after the end of chemotherapy for follow-up. The following parameters were collected
134 for the present study: age, weight, height, pathology type, grade, FIGO stage, treatment arm,
135 post-operative disease residuals as judged by the surgeon (no macroscopic residual, tumor

residuals < 0.25cm, tumor residuals 0.25 to 2.5 cm, tumor residuals > 2.5 cm), and the radiological tumor objective response to treatment according to RECIST V1.1 criteria (complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD)).

The protocol was approved by an ethic committee and health authorities in 2012. Written informed consent was obtained from all patients before study entry.

Serum miRNAs quantification and analysis

The plasma samples were centrifuged, and stored at -80°C. MiRNAs were extracted with the Qiagen miRNeasy microkit. The targets miRNAs were quantified by qRT-PCR using the Qiagen kit custom miScript miRNA PCR assay. After performing the Qiazol lysis step, *C. elegans* miR-39 miRNA (cel-miR-39) was added as an external control for extraction efficiency and normalization.

Analysis were performed using the $2^{-\Delta\Delta C_t}$ method [20]. The ΔC_t is the difference of expression (expressed as cycle threshold (Ct)) between the target miRNA (miRNA being tested) and a housekeeping miRNA (external control, miRNA cel-miR-39) for each sample. The difference between the ΔC_t of the target sample and the ΔC_t of the reference sample (calibrator sample: first sample of the first patient) is the $\Delta\Delta C_t$. By calculating the $2^{-\Delta\Delta C_t}$, the relative quantification (RQ) of the target gene expression sample was compared to the reference sample. RQs greater or less than 1 were considered as over-expression or under-expressions, respectively. Samples with expressions lower than the limit of quantification (Ct result > 35 cycles) were excluded from the analyses and the graphics, because they were considered as non-significant expressions of miRNAs.

MiRNAs selection

More than 1000 cancer miRNAs have been reported in the literature [21]. Eleven miRNAs were selected for the present study. This number resulted from a selection performed in 2 steps. First, a large panel of 84 human circulating miRNAs (MIHS-106ZA, QIAGEN) were tested in 8 randomly selected patients in order to identify the 8 miRNAs which were the most relevant for our kinetic analysis with the following criteria: sufficient expression for replication (at least 75% of Ct lower than 35 cycles), and kinetics considered to be consistent during treatment (in the sense that the miRNA level should increase or decrease during treatment periods). Moreover, the selection was guided by the literature analysis with the requirement that these miRNAs had to be involved in the ovarian carcinogenesis, and they were shown to exhibit differential expressions in between ovarian cancer patients and control groups. The eight miRNAs selected from this step were: hsa-miR-15b-5p, hsa-miR-16-5p, hsa-miR-20a-5p, hsa-miR-21-5p, hsa-miR-93-5p, hsa-miR-122-5p, hsa-miR-150-5p and hsa-miR-195-5p (Supplementary Figure S1). In addition, three additional miRNAs were selected based on publications reporting relevant kinetics of miRNAs during chemotherapy: hsa-miR-200b-3p, hsa-miR-148b-5p, and hsa-miR-34a-5p [17,18,22].

The eleven selected miRNAs were quantified in the remaining 111 patients.

Kinetic analyses of longitudinal miRNAs and CA125 changes during CHIVA trial

The time changes of miRNA titers and of CA125 were assessed on the following time windows: 1) screening to pre-surgery timepoint; 2) pre-surgery timepoint to first cycle after surgery (cycle 4); and 3) third cycle after surgery to progression, if any. The differences in between plasma miRNA RQs and CA125 concentrations on these time periods were assessed using Wilcoxon signed-rank tests. The longitudinal changes in miRNAs RQ and in CA125 levels were graphically assessed for each patient, and for the global population.

182 Prognostic and predictive values of miRNA and of CA125 longitudinal time changes during
183 neo-adjuvant chemotherapy

184 As previously done for CA125 [2] and other serum biomarkers [23], the time changes of
185 miRNA RQs and of CA125 concentrations during neoadjuvant chemotherapy were calculated
186 using their percentage decreases from the baseline timepoint (screening value) to the pre-
187 operative timepoint (before IDS).

188 Receiver operating characteristic (ROC) curves were used to evaluate the discriminative
189 predictive ability of miRNA & CA125 percentage decreases regarding the likelihood of
190 complete CC0 IDS, and of radiological tumor response (assessed using RECIST V1.1
191 criteria).

192 PFS and OS were calculated as the time intervals from treatment start to the date of
193 progression or death, whichever occurred first, for PFS; and to the death only for OS.

194 The 5 following thresholds were arbitrarily chosen: the cutoffs maximizing 1) the prediction
195 ability of CC0 IDS (CC0 vs CC1-CC2); 2) the prediction ability of tumor response (complete
196 response and partial response (CR & PR) versus stable disease and progressive disease (SD &
197 PD), using the Youden index statistic criterion with ROC curves; along with 3) the 1st
198 quartiles of the biomarker percentage decrease distributions; 4) the cutoffs associated with a
199 decline of miRNA or CA125 by 25%; 5) the cutoffs associated with a decline of miRNA or
200 CA125 by 50%.

201 The predictive values of every miRNA and CA125 percentage variations, dichotomized by
202 the above thresholds, regarding PFS and OS were first investigated using c-index tests [24].
203 The prognostic values of CA125 and miRNA percentage variations found to be the most
204 significant with the c-index analyses, were subsequently assessed using Kaplan-Meier method
205 and log-rank tests.

206 All tests were two-sided with 5% alfa risks. All statistical analyses were performed using R
207 3.3.2 software with “survival”, "ROC" and "pec" packages.

208

209 Results

210 Patients characteristics

211 188 patients were included in the CHIVA trial from May 2013 to July 2015. The data from
212 119 of them (63%) could be analyzed for the present study, comprising 8 patients chosen for
213 the selection of 8 miRNAs from the large panel, and 111 remaining patients for the kinetic
214 analyses of 11 miRNAs (Supplementary Figure S2). The characteristics of the included
215 patients are presented in Table 1 and were similar for the 2 groups.

216 Total 8172 miRNAs concentrations were assayed. The concentrations were above the limits
217 of quantification for 6674 samples (82%), ranging from 23% to 98% depending of the
218 miRNA. All the 1299 CA125 measured values were above the limits of quantification (Table
219 2).

220 Kinetic analysis of miRNAs and CA125 longitudinal time changes in CHIVA trial

221 The kinetics of miRNAs were poorly assessable. No statistically significant changes of the
222 miRNAs expressions during treatment were found using Wilcoxon signed-rank tests.
223 However, statistically significant increases of miRNAs expressions were identified at disease
224 progressions for 6 mi-RNA (Table 2).

225 The comparative analyses of miRNA and CA125 kinetics during the disease managements
226 showed that the time-changes of CA125 were more homogeneous and rational, than those of
227 miRNAs (Table 2, Figure 1 and Supplementary Figures S3 to S7). Declines of CA125 by
228 50% or more during chemotherapy were found in 98% of patients (GCIG CA125 response

criterion), while such analyses were not assessable for the miRNAs, due to their hectic and irrational kinetics, with high inter-individual variability.

Predictive value of miRNAs regarding the tumor response rate or interval debulking cytoreductive surgery score

The predictive abilities of every miRNA expression percentage variation during neoadjuvant chemotherapy regarding the likelihood of complete IDS (yes vs no) using ROC area under the curve (AUC) are presented in Table 3. The ROC AUCs ranged from 0.51 to 0.88; none of them being statistically significant, except for the hsa-miR-200b-3p. The same lack of significant predictive value was found for the likelihood of tumor response (CR-PR vs SD-PD) with ROC AUCs ranging from 0.50 to 0.86; all of them being non-significant, except for hsa-miR-200b-3p (Table 3).

The same analyses done with CA125 percentage decrease showed a ROC AUC at 0.58 (95% CI 0.45-0.71) for prediction of CC0 IDS, and at 0.64 (95% CI 0.51-0.76) for prediction of tumor response (Table 3).

The values of the different thresholds maximizing the likelihood of complete surgery and of tumor response for miRNA and CA125 percentage decreases are presented in Table 3.

Predictive value of miRNA kinetics for survivals

The predictive values of miRNA and CA125 variations, dichotomized by the different cutoffs, regarding PFS and OS are shown in Table 4. The c-index values of miRNA time changes ranged from 0.47 to 0.67 for PFS; and from 0.44 to 0.81 for OS. The highest significant predictive values regarding PFS were observed with the hsa-miR-15b-5p (categorized by the threshold optimizing the tumor response likelihood) at 0.63 (95% CI 0.57-0.69), and with the hsa-miR-34a-5p (categorized by the cutoff associated with a decline by 25%) at 0.64 (95% CI 0.52-0.76).

For OS, the highest significant predictive values were obtained with the has-miR-15b-5p (categorized by the threshold optimizing the tumor response likelihood) at 0.63 (95% CI 0.53-0.73), and with the hsa-miR-93-5p (categorized by the threshold optimizing the prediction of complete IDS) at 0.66 (95% CI 0.56-0.76). The similar analyses done with the CA125 kinetics showed c-index values ranging from 0.50 to 0.54 for PFS, and 0.50 to 0.56 for OS.

The outcomes regarding the prognostic values of the most significant miRNAs using Kaplan-Meier survival curves and log-rank tests are presented in Figure 2. Hsa-miR-15b-5p and hsa-miR-34a-5p were associated with better PFS (median PFS = 13.2 vs 20.8 months and 13.7 vs 24.8 months, respectively, $p<0.01$), whilst hsa-miR-15b-5p and hsa-miR-93-5p were associated with better OS (median OS = 34.2 vs 52.0 and 34.3 vs NR months, respectively, $p<0.01$). CA125 kinetics assessed with the similar methodology were not significant, including with the 50% decrease cutoff recognized as the GCIg CA125 response criterion.

Discussion

This present study represents the first analysis on the actual predictive and prognostic values of miRNA longitudinal kinetics in cancer patients managed with medical-surgical treatments. MiRNAs have been recently reported as major actors in the tumorigenesis [25]. The miRNA expression time changes were expected to correlate with the tumor burden changes, thereby representing promising predictive biomarkers [17,18,26,27]. The ovarian cancer population was particularly adequate, since there is a need for reliable serum biomarkers to overcome the limitation of imaging, and also because miRNA kinetic value could be assessed with respect to the validated serum marker CA125 [2,28].

Several authors reported the prognostic or predictive values of miRNA expressions (e.g. miR-34a-5p level before treatment associated with CC0 cytoreductive surgery in 56 patients, ROC

AUC = 0.78) [22], or miRNA expression changes during treatments (e.g. miR-200b change from baseline to post-operative period regarding PFS in 33 patients) [17].

The innovative design of the randomized phase II trial CHIVA, in which serial blood samples were regularly performed during disease management, enabled us to assess the kinetics of 11 miRNAs measured in a properly conducted prospective trial. This miRNA selection was based on initial explorative analyses with a large panel of miRNAs in 8 patients, and based on the literature data. Our selection appeared adequate since the miRNAs were highly expressed in 82% of samples.

The kinetic analysis of miRNA demonstrates that no rational longitudinal profiles could be identified for any of them throughout the treatment. The large intra-individual and inter-individual variability of miRNA time-changes made any longitudinal assessment impossible with mathematical modeling. As a consequence, it was not adequate to search for relationships between tumor burden alterations and miRNA kinetics using mathematical modeling, contrarily to what was done with CA125 [3,29–32].

Our outcomes in favor a lack of predictive value of miRNA are not consistent with the data reported in the literature earlier [17,18,22,26,27,33]. This discrepancy could be understood by the methodology used by the other teams so far. In those studies, the kinetic analyses were performed on maximum two or three time points (contrarily to our approach based on 8 timepoints per patient), and it is possible that the limited numbers of time points would have induced biases in the outcomes given the high inter-individual variability of miRNA expressions. Moreover, the large inconsistency in the types of miRNAs reported in the literature assumed to exhibit prognostic or predictive values highlights the difficulty to identify miRNAs with reproducible prognostic/predictive values.

The present study present limitations prone to reduce the relevance of data. First, it was not possible to assess all miRNAs, and we had to select an affordable panel. We selected 11 miRNAs that appeared rational, based on an explorative analysis including a large panel of 84 miRNAs, and based on the literature. Our conclusions about the lack of assessable longitudinal prognostic or predictive kinetic profiles may not necessarily be transposable to other miRNAs. The selection of the best cut-offs for analyzing miRNAs kinetics in a way that would make the analyses helpful for clinical purpose was another difficulty. We chose to implement common statistical approaches, such as ROC curve tests and quartiles, but the relevance is questionable. None of the cutoffs that we assessed appeared superior. Moreover the expressions of the assessed miRNAs were below the lower limit of quantification in 18% of measurements, thereby making the kinetics analysis even more complicated, especially for miR-200b-3p. Furthermore, the impact of the tumor histological subtypes or BRCA status on miRNAs kinetics could not be assessed. Of note, recent data on the kinetics of CA125 assessed using mathematical modeling suggest that the modeled kinetic parameter KELIM could be a promising predictor of complete IDS likelihood, or of survival, in ovarian cancer patients [34–36]. However this parameter was not assessed here, because we thought that miRNA and CA125 kinetics had to be investigated with the same methodologies.

The present study is the largest work including serial assessment of a high numbers of miRNA, in cancer patients managed with multi-modal treatment in a properly conducted phase II trial. The outcomes indicate miRNA may not be adequate biomarkers for longitudinal kinetic analyses during treatment. Consistently with the inconsistent data of the literature on the prognostic or the predictive values of miRNA titers or time changes, we could not identify any miRNA prone to be reproducible predictors of IDS score, tumor response, or survivals in ovarian cancer patients.

324 Acknowledgements

325 We thank all the patients and their families, the investigators and study teams, Pharmacists,
326 Pathologists, Biologists, ARCAGY GINECO Project Manager and study teams and
327 ARCAGY GINECO biological resource center for their support of the study.

328 Conflict of interest statement

329 The authors declare no potential conflicts of interest.

330 Funding

331 This study was supported by the ARCAGY GINECO group.

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Figures Legends

Figure 1. Longitudinal time changes of the miR-195 expression and of CA125 concentrations. (A) Individual patient profiles of miR-195 and CA125 kinetics according to completeness of cytoreduction (green line: complete cytoreductive surgery; red: incomplete cytoreductive surgery); (B) Changes in populations values of blood miR-195 expressions and CA125 concentrations during management steps and at progression

Abbreviations: S: Screening; C: Pre-surgery; P: Progression.

Figure 2. Prognostic values of the expression changes of the most significant miRNAs and of CA125 regarding PFS and OS using Kaplan-Meier survival curves of patients. (A) PFS with miR-15b categorized by the threshold optimizing the tumor response likelihood and miR-34a categorized by the 25% decline threshold; (B) OS with miR-15b categorized by the threshold optimizing the tumor response and miR-93 categorized by the threshold optimizing the complete IDS likelihood; (C) PFS with CA125 categorized by the first quartile of the RV and OS with CA125 categorized the threshold maximizing the complete IDS likelihood.

IDS: interval debulking surgery; PFS: progression free survival; OS: overall survival.

485 **Tables**

486 **Table 1. Patient characteristics at inclusion**

487

488 **Table 2. Expressions of the 11 miRNA and of CA125. Statistical significances of the**
489 **comparisons of expressions on 3 different time windows using Wilcoxon signed-rank**
490 **tests: 1) from screening (baseline) to IDS; 2) from IDS to cycle 4; 3) from cycle 6 to**
491 **disease progression.**

492

493 **Table 3. Outcomes of the ROC curve AUC analyses on 1) Predictive ability of miRNA**
494 **and CA125 percentage decreases during neoadjuvant chemotherapy regarding the**
495 **likelihood of complete cytoreductive surgery (complete cytoreductive surgery with no**
496 **macroscopic residuals vs incomplete debulking with residuals), or of tumor response (CR +**
497 **PR vs SD + PD); 2) Identification of the optimal cutoff for predictions of the likelihood of**
498 **complete cytoreductive surgery, or of tumor response using Youden criterion.**

499

500 **Table 4. C-index values regarding the predictive values of miRNA and CA125**
501 **percentage decreases, categorized by the 5 different cutoffs for PFS and OS.**

502

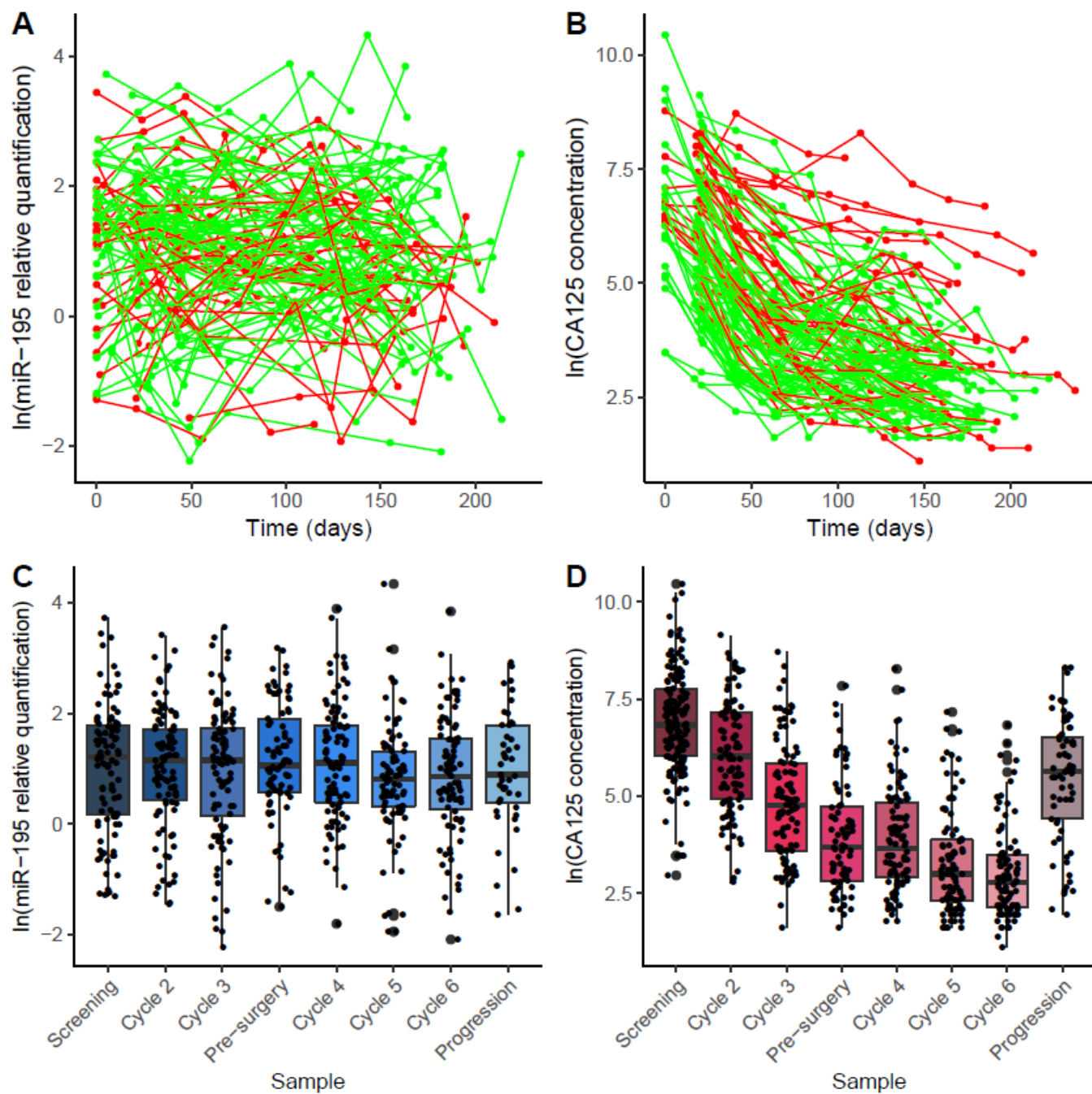


Figure 1.

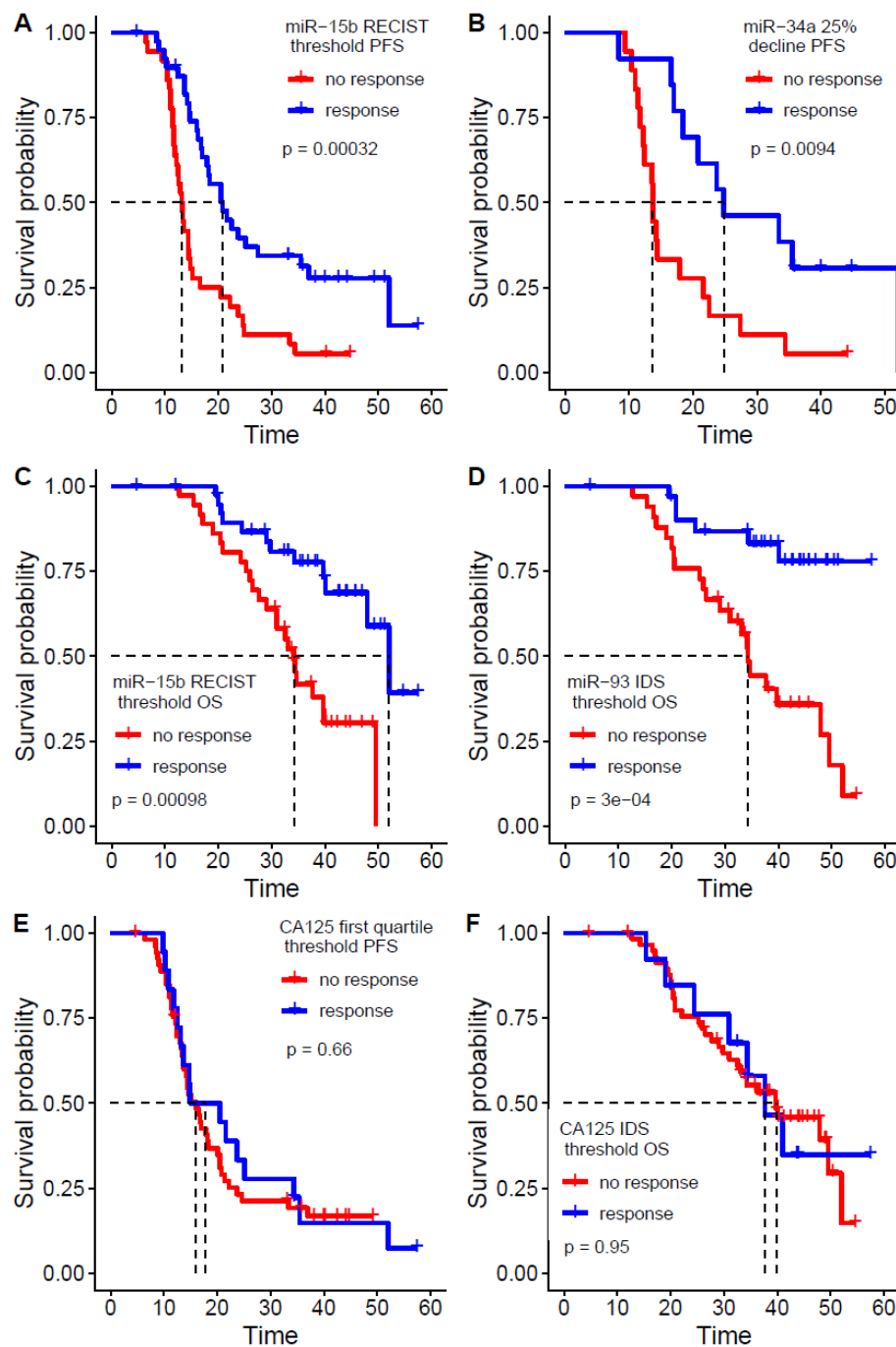


Figure 2.

Table 1. Patient characteristics at inclusion

Characteristics	MiRNA selection patients	Test patients
Patients number, <i>n</i>	8	111
Age, years, median (range)	65 (31-71)	64 (31-79)
ECOG PS, <i>n</i> (%)		
0-1	7 (88%)	98 (88%)
2	1 (12%)	12 (11%)
NA	0 (0%)	1 (1%)
FIGO stage, <i>n</i> (%)		
IIIc	7 (88%)	85 (77%)
IV	1 (12%)	26 (23%)
Histological type, <i>n</i> (%)		
Serous/papillary	8 (100%)	98 (88%)
Endometrioid	0 (0%)	1 (1%)
Mucinous	0 (0%)	1 (1%)
Clear cells	0 (0%)	1 (1%)
Undifferentiated	0 (0%)	3 (3%)
NA	0 (0%)	7 (6%)
Histological grade, <i>n</i> (%)		
Grade 1	0 (0%)	3 (3%)
Grade 2	1 (12%)	10 (9%)
Grade 3	5 (63%)	79 (71%)
NA	2 (25%)	19 (17%)
CA125 at inclusion (xULN), median (range)	24.4 (2.6-250.4)	26.9 (0.5-784.3)
IDS performed, <i>n</i> (%)	8 (100%)	86 (77%)
Completeness of cytoreduction, <i>n</i> (%)		
No macroscopic residuals	5 (63%)	70 (81%)
Tumoral residuals < 0,25 cm	0 (0%)	6 (7%)
Tumoral residuals 0,25 < R < 2.5 cm	3 (37%)	7 (8%)
Tumoral residuals > 2.5 cm	0 (0%)	2 (2%)
NA	0 (0%)	1 (1%)
Treatment with nintedanib, <i>n</i> (%)	5 (63%)	68 (61%)
Response to neo-adjuvant chemotherapy, <i>n</i> (%)		
CR	1 (12%)	2 (2%)
PR	3 (37%)	45 (41%)
SD	4 (50%)	57 (51%)
PD	0 (0%)	2 (2%)
NA	0 (0%)	5 (5%)
Progression free survival in months, median (95% CI)	15.6 (11.8-NR)	16.2 (14.4-18.4)
Overall survival in months, median (95% CI)	NR (38.6-NR)	40.1 (36.2-NR)
Death, <i>n</i> (%)	3 (37%)	55 (50%)

ECOG PS: ECOG Performance Status; IDS: Interval debulking surgery; NA: Non-available;

ULN: Upper limit of normal; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease CI: Confident interval; NR: Not reached.

Table 2. Expressions of the 11 miRNA and of CA125. Statistical significances of the comparisons of expressions on 3 different time windows using Wilcoxon signed-rank tests: 1) from screening (baseline) to IDS; 2) from IDS to cycle 4; 3) from cycle 6 to disease progression.

Serum biomarkers	% of samples with RQ greater than LoQ	Significances of expression differences on 3 time windows		
		1) Screening to IDS <i>p</i> value	2) IDS to Cycle 4 <i>p</i> value	3) Cycle 6 to Progression <i>p</i> value
hsa-miR-15b-5p	97%	0.986	0.184	0.001
hsa-miR-16-5p	98%	0.397	0.454	0.001
hsa-miR-20a-5p	92%	0.886	0.441	0.013
hsa-miR-21-5p	98%	0.405	0.920	0.005
hsa-miR-93-5p	90%	0.974	0.441	0.026
hsa-miR-122-5p	96%	0.296	0.309	0.437
hsa-miR-150-5p	90%	0.182	0.012	0.081
hsa-miR-195-5p	96%	0.660	0.186	0.007
hsa-miR-34a-5p	57%	0.915	0.080	0.117
hsa-miR-148b-5p	54%	0.379	0.624	0.181
hsa-miR-200b-3p	23%	0.375	0.461	0.500
CA125	100%	<0.001	0.109	<0.001

IDS: Interval debulking surgery; RQ: Relative quantification; LoQ: limit of quantification;

Table 3. Outcomes of the ROC curve AUC analyses on 1) Predictive ability of miRNA and CA125 percentage decreases during neoadjuvant chemotherapy regarding the likelihood of complete cytoreductive surgery (complete cytoreductive surgery with no macroscopic residuals vs incomplete debulking with residuals), or of tumor response (CR + PR vs SD + PD); 2) Identification of the optimal cutoff for predictions of the likelihood of complete cytoreductive surgery, or of tumor response using Youden criterion.

Serum marker	Predictive value of miRNA and CA125 kinetics using ROC curve AUCs		Optimal threshold of the percentage decline maximizing the prediction ability of	
	Prediction of complete cytoreductive surgery (95% CI)	Prediction of tumor response (95% CI)	Complete cytoreductive surgery	Tumor response
hsa-miR-15b-5p	0.55 (0.41-0.70)	0.50 (0.36-0.63)	-6%	+27%
hsa-miR-16-5p	0.55 (0.40-0.69)	0.64 (0.50-0.76)	-23%	-11%
hsa-miR-20a-5p	0.53 (0.38-0.68)	0.57 (0.43-0.72)	+11%	+29%
hsa-miR-21-5p	0.52 (0.37-0.66)	0.53 (0.40-0.66)	-32%	+9%
hsa-miR-93-5p	0.52 (0.37-0.67)	0.67 (0.54-0.80)	+15%	+111%
hsa-miR-122-5p	0.58 (0.43-0.73)	0.58 (0.45-0.72)	+8%	+18%
hsa-miR-150-5p	0.56 (0.41-0.72)	0.51 (0.37-0.65)	-32%	+5%
hsa-miR-195-5p	0.52 (0.37-0.67)	0.60 (0.46-0.73)	-13%	-33%
hsa-miR-34a-5p	0.54 (0.27-0.80)	0.53 (0.32-0.74)	-41%	+124%
hsa-miR-148b-5p	0.63 (0.40-0.86)	0.58 (0.37-0.79)	-30%	+168%
hsa-miR-200b-3p	0.88 (0.65-1.00)	0.86 (0.60-1.00)	-10%	-3%
CA125	0.57 (0.43-0.70)	0.63 (0.49-0.76)	-99%	-97%

ROC: Receiver operating characteristic; AUC: Area under the curve; IDS: Interval debulking surgery; CI: Confident interval.

Table 4. C-index values regarding the predictive values of miRNA and CA125 percentage decreases, categorized by the 5 different cutoffs for PFS and OS.

Serum marker	Optimal threshold for predicting complete cytoreductive surgery (SD)	Optimal threshold for predicting tumor response (SD)	1 st Quartile of percentage decrease distribution (SD)	Percentage decrease of 25% (SD)	Percentage decrease of 50% (SD)
Analyses for PFS					
hsa-miR-15b-5p	0.61 (0.04)	0.63 (0.03)	0.60 (0.03)	0.60 (0.03)	0.58 (0.03)
hsa-miR-16-5p	0.55 (0.04)	0.57 (0.04)	0.55 (0.03)	0.53 (0.03)	0.53 (0.03)
hsa-miR-20a-5p	0.57 (0.04)	0.51 (0.04)	0.50 (0.03)	0.52 (0.04)	0.51 (0.04)
hsa-miR-21-5p	0.59 (0.03)	0.60 (0.03)	0.58 (0.03)	0.61 (0.04)	0.60 (0.03)
hsa-miR-93-5p	0.60 (0.04)	0.57 (0.03)	0.58 (0.04)	0.58 (0.04)	0.57 (0.03)
hsa-miR-122-5p	0.54 (0.04)	0.56 (0.03)	0.55 (0.03)	0.57 (0.04)	0.56 (0.03)
hsa-miR-150-5p	0.59 (0.04)	0.57 (0.04)	0.59 (0.04)	0.58 (0.04)	0.56 (0.03)
hsa-miR-195-5p	0.60 (0.04)	0.56 (0.03)	0.57 (0.03)	0.58 (0.03)	0.53 (0.03)
hsa-miR-34a-5p	0.60 (0.05)	0.56 (0.04)	0.57 (0.05)	0.64 (0.06)	0.55 (0.05)
hsa-miR-148b-5p	0.49 (0.06)	0.54 (0.04)	0.47 (0.05)	0.55 (0.05)	0.51 (0.05)
hsa-miR-200b-3p	0.58 (0.11)	0.67 (0.11)	0.64 (0.11)	0.64 (0.11)	0.59 (0.08)
CA125	0.51 (0.03)	0.51 (0.04)	0.52 (0.03)	0.50 (0)	0.50 (0.02)
Analyses for OS					
hsa-miR-15b-5p	0.60 (0.05)	0.63 (0.05)	0.61 (0.04)	0.61 (0.04)	0.62 (0.04)
hsa-miR-16-5p	0.57 (0.05)	0.58 (0.05)	0.56 (0.04)	0.55 (0.04)	0.55 (0.04)
hsa-miR-20a-5p	0.57 (0.05)	0.53 (0.05)	0.55 (0.04)	0.55 (0.05)	0.48 (0.05)
hsa-miR-21-5p	0.59 (0.04)	0.61 (0.04)	0.59 (0.04)	0.60 (0.05)	0.60 (0.04)
hsa-miR-93-5p	0.66 (0.05)	0.60 (0.05)	0.59 (0.05)	0.64 (0.05)	0.57 (0.04)
hsa-miR-122-5p	0.54 (0.05)	0.56 (0.04)	0.54 (0.04)	0.59 (0.05)	0.55 (0.04)
hsa-miR-150-5p	0.58 (0.04)	0.55 (0.05)	0.58 (0.04)	0.58 (0.04)	0.59 (0.04)
hsa-miR-195-5p	0.63 (0.05)	0.58 (0.04)	0.59 (0.04)	0.60 (0.04)	0.55 (0.04)
hsa-miR-34a-5p	0.53 (0.07)	0.52 (0.06)	0.49 (0.07)	0.51 (0.07)	0.51 (0.06)
hsa-miR-148b-5p	0.53 (0.07)	0.52 (0.05)	0.54 (0.06)	0.55 (0.07)	0.50 (0.06)
hsa-miR-200b-3p	0.81 (0.18)	0.75 (0.19)	0.44 (0.18)	0.44 (0.18)	0.58 (0.12)
CA125	0.50 (0.03)	0.54 (0.04)	0.51 (0.04)	0.50 (0)	0.52 (0.02)

Abbreviations: SD: Standard deviation; IDS: Interval debulking surgery; PFS: Progression

free survival, OS: Overall survival, CI: Confident interval; NR: Not Reached.