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Impact of adding the immune checkpoint inhibitor atezolizumab to first-line chemotherapy on progression-free survival in poor-prognosis ovarian cancer: A retrospective analysis from the IMagyn050 trial

Benoit You [a,w,*], Charles Anderson [b], Sabrina Chiara Cecere [c], Aurore Carrot [d], Tashanna Myers [e], Florian Heitz [f,x], Sudarshan Sharma [g], Fatih Selçukbiricik [h], Carol Aghajanian [i], Josefin Fernebro [j], Stephanie Blank [k], Maria Elena Laudani [l], Premal H. Thaker [m], Mayu Yunokawa [n], Lyndsay Willmott [o], Alla Lisyanskaya [p], Roberto Hegg [q], Yvette He [r], Charles Landen [s], Yvonne G. Lin [t], Jesús Alarcón [u], Kathleen N. Moore [v]

[a] Lyon University Hospital, IC-HCL, CICLY, EPSILYON, CITOHL, Lyon University, Lyon, France
[b] Willamette valley cancer institute and research center, Eugene, OR, USA
[c] National Cancer Institute of Naples (IRCCS) Fondazione « G. Pascale », Naples, Italy
[d] Lyon University, Lyon, France
[e] Baystate Mary Lane Hospital, Ware, MA, United States
[f] AGO Study Group and Ev. Kliniken Essen-Mitte, Essen, Germany
[g] The University of Chicago, Chicago, IL, United States
[h] Koç University Hospital, Koç University School of Medicine Department of Medical Oncology, Istanbul, Turkey
[i] Memorial Sloan Kettering Cancer Center, New York, NY, United States
[j] Karolinska University Hospital, Stockholm, Sweden
[k] Icahn School of Medicine at Mount Sinai, New York, United States
[l] Department of Surgical Sciences, University of Turin, Torino, Italy
[m] Washington University School of Medicine and Siteman Cancer Center, Saint Louis, MO, United States
[n] Japanese Foundation for Cancer Research, Cancer Institute Hospital of JFCR, Tokyo, Japan
[o] Abrazo Central Campus, Phoenix, United States
[p] St. Petersburg Oncology & Gynecology, City Clinical Oncology Dispensary, St Petersburg, Russia
[q] Perola Centro de Pesquisa em Oncologia, São Paulo, Brazil
[r] Biometrics, Parexel International, Chengdu, China
[s] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Alabama at Birmingham, Birmingham, United States
[t] Genentech-Roche, San Francisco, United States
[u] Hospital Son Espases, Palma De Mallorca, Spain
[v] University of Oklahoma Health Sciences Center, Oklahoma City, United States
[w] GINECO, Paris, France
[x] Charité - Universitätsmedizin Berlin, Campus Virchow, Berlin, Germany

HIGHLIGHTS

- Exploratory analysis of the IMagyn050 placebo-controlled randomized phase III trial.
- Poor prognostic ovarian cancer patients: suboptimal surgery and KELIM score < 1.0.
- This subpopulation experienced a PFS benefit from atezolizumab addition in 1st line.
- The PFS gain was observed in both neoadjuvant and adjuvant settings.
- Further validation about the concept of treatment intensification is warranted.

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ABSTRACT

Purpose. Adding the anti-PD-L1 antibody atezolizumab to frontline chemotherapy-bevacizumab regimen did not improve progression-free survival (PFS) in ovarian cancer (OC) patients in IMagyn050 trial. This post-hoc analysis assessed the efficacy of atezolizumab in a subgroup of patients with particularly poor prognosis, as defined by the GCIG meta-analysis—characterized by a poor chemosensitivity and a suboptimal surgical resection.

* Corresponding author at: Lyon University Hospital, IC-HCL, CICLY, EPSILYON, CITOHL, Lyon University, Lyon, France.
E-mail address: benoit.you@chu-lyon.fr (B. You).

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Methodology. This analysis included 1199 evaluable participants with ≥3 available CA-125 concentrations, as required for KELIM score. The prognostic factors were identified through univariable and multivariable analyses. If both the KELIM score (unfavorable <1.0, vs favorable ≥1.0) and surgical outcome (suboptimal, vs optimal resection) demonstrated independent prognostic value, they were to be combined into prognostic subgroups. The PFS benefit of atezolizumab versus placebo was then evaluated within each of these defined subgroups.

Results. Both the KELIM score and surgical outcome were independent prognostic factors. Combining these two parameters generated three distinct prognostic subgroups. In the poor prognosis subgroup ($n = 269$), defined by both an unfavorable KELIM score (<1.0) and suboptimal cytoreduction, the addition of atezolizumab was associated with a significantly longer median PFS compared to placebo (14.3 vs 11.3 months; HR 0.75, 95 % CI 0.59–0.95). This benefit was observed in both neoadjuvant and adjuvant settings. No significant PFS benefit was observed in the other prognostic subgroups.

Conclusion. The poor prognostic OC patient subgroup, may have an extension of PFS from treatment intensification with atezolizumab added to frontline chemotherapy-bevacizumab regimen. This hypothesis-generating outcome warrants further understanding on the added role of ICI in the frontline setting.

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1. Introduction

In patients with advanced stage III-IV high-grade epithelial ovarian cancers, the standard first-line treatment involves a cytoreductive surgery, aiming to achieve no residual macroscopic disease, followed by a regimen of platinum-based chemotherapy. This is commonly followed with maintenance therapy using bevacizumab and/or a poly (ADP-ribose) polymerase (PARP) inhibitor to reduce the risk of recurrence and improve patient survival [1–3].

For cases where optimal primary cytoreduction (PDS) is not achievable, patients are frequently managed with neoadjuvant chemotherapy (NACT) to reduce the tumor burden. If there is a favorable response after 3 to 4 cycles of platinum-based chemotherapy, the patient may then undergo interval debulking surgery (IDS) [1–3].

The clinical benefit of incorporating immune checkpoint inhibitors (ICIs) into the first-line treatment regimen for advanced epithelial ovarian cancer has been evaluated in multiple phase III trials, including the JAVELIN OVARIAN 100 trial with avelumab (NCT02718417), the DUO-O trial with durvalumab (NCT03737643), IMagyn050 trial with atezolizumab (NCT03038100), ATHENA-COMBO with nivolumab (NCT03522246), and recently KEYLYNK-001 with pembrolizumab (NCT03740165) [4–9]. Although some studies showed trends toward improved progression-free survival (PFS), none of these trials unequivocally demonstrated a statistically significant survival benefit from adding ICIs to standard systemic therapy.

This lack of ICI benefit persisted even in subgroup analyses that accounted for the extent of cytoreductive surgery, histological subtypes, or BRCA/homologous recombination deficiency (HRD) status. The limited efficacy of immune checkpoint inhibitors (ICIs) in ovarian cancer remains poorly understood. One possible explanation is the immunologically "cold" nature of these tumors, characterized by a high infiltration of immunosuppressive cells, such as tumor-associated macrophages (TAMs), compared to other cancer types [10,11]. TAMs are known to impair T cell effector functions and promote angiogenesis [11].

Whether a subgroup of patients with particularly poor prognosis may derive meaningful clinical benefit from the addition of ICIs to the standard of care remains uncertain. Following a strategy that has proven successful in other solid tumors, most trials investigating ICIs in ovarian cancer were designed to assess whether tumors with high PD-L1 expression might derive greater benefit. However, this approach has not demonstrated efficacy in ovarian cancer. In the IMagyn050 trial, PFS was numerically longer with the addition of atezolizumab for patients with PD-L1 positive tumors (VENTANA SP142 immune cells ≥1 %), but this did not achieve statistical significance [6,7]. Similarly, in the KEYLYNK-001 study, the Combined Positive Score (CPS)—a metric commonly used in other solid tumors—was evaluated using a threshold of CPS ≥10. However, the modest benefit observed with ICI treatment was neither clinically nor statistically significant [9]. Although cross-trial comparisons are limited due to heterogeneity in patient populations, the complex immune microenvironment of ovarian cancer—particularly high-grade serous carcinoma—remains a critical area for further investigation. Some recent insights into this immune landscape were provided by an exploratory analysis of the randomized NeoPembrOv trial, which suggested that variations in CD8B/FOXP3 and CD8B/ENTPD1 ratios, as well as tumor-specific alterations in KDR and VEGFR2 expression, may modulate the efficacy of pembrolizumab in combination with carboplatin and paclitaxel [11]. However, these findings require further validation.

Another option is to investigate the benefit of adding ICI to chemotherapy as a treatment intensification in poor prognostic subgroups of patients, based on clinical data.

In the Gynecologic Cancer InterGroup (GCIG) meta-analysis involving 5884 patients treated in the first-line setting, those with disease characterized by both a poor chemosensitivity (unfavorable modeled CA-125 KELIM score < 1.0) and a suboptimal surgical outcome (post-operative residual lesions >1 cm) exhibited very unfavorable overall survival outcomes [12]. The modeled CA-125 KELIM is derived from the longitudinal kinetics of CA-125 and calculated using at least three CA-125 timepoints measured within the first 100 days of adjuvant or neoadjuvant chemotherapy. It has been reported as a reproducible and pragmatic indicator of chemotherapy efficacy, using data from over 18,000 patients enrolled in clinical trials or national registries [13,14], and cited as such in ESGO-ESMO and ASCO guidelines [1,13]. Consequently, patients who derived minimal benefit from both components of the first-line medical-and-surgical treatment sequence—namely, *(1)* disease that could not be optimally debulked surgically, and *(2)* disease with poor chemotherapy sensitivity—were left with bulky disease at the end of first-line sequential treatment, resulting in poor survival outcomes [12,14].

In this context, any strategy that could enhance the prognosis for this patient population would be of significant clinical interest. Among the therapeutic options, adding bevacizumab to adjuvant chemotherapy appears to be a rational approach, as two post-hoc analyses of the ICON-7 and GOG-0218 trials consistently suggested an association with improved overall survival in patients exhibiting both of these poor prognostic characteristics [15,16].

The combination of immune checkpoint inhibitors (ICIs) with anti-angiogenic agents is supported by extensive preclinical and clinical evidence, as both therapies are believed to work synergistically to enhance the immune response against cancer cells [11,17].

We hypothesized that the addition of an ICI to the platinum-based chemotherapy and bevacizumab regimen could enhance survival outcomes in advanced ovarian cancer patients who belong to the poor

prognostic subgroup characterized by both an unfavorable KELIM score of <1.0 and a suboptimal debulking surgery.

The objective of the present study, conducted on the IMagyn050 population, was to retrospectively confirm the poor prognosis of this specific patient subgroup, and to evaluate whether the addition of the ICI atezolizumab to standard therapy may have conferred clinical benefit in this high-risk group.

2. Methodology

2.1. Patients and treatments

This was a post-hoc retrospective analysis of the dataset of IMagyn050 placebo-controlled randomized phase III trial (NCT03038100) that investigated the efficacy of adding the anti-PD-L1 monoclonal antibody atezolizumab to carboplatin area under the curve 6 on day 1 + paclitaxel 175 mg/m2 on day 1 during cycles 1–6 + bevacizumab 15 mg/kg on day 1 during cycles 2–22. The patients randomly assigned to the experimental arm received atezolizumab 1200 mg on day 1 of cycles 1–22, combined with the same chemotherapy regimen + bevacizumab 15 mg/kg during cycles 1–6 as above.

The outcomes of the trial were previously reported, and no statistically significant PFS or OS benefit from atezolizumab addition was observed in the ITT and PD-L1 populations, or in key subgroups (e.g., disease stage, histology, and BRCA or homologous recmbination status) [6,7].

All patients provided written informed consent before any trial specific procedures or treatment. The protocol was approved by all institutional ethics committees.

2.2. Collected data

Serum CA-125 was measured at each cycle as per protocol. To be included in this analysis, patients were required to have at least 3 available CA-125 measurements within the first 100 days of adjuvant chemotherapy following primary debulking surgery, or during neoadjuvant chemotherapy prior to the date of interval debulking surgery (IDS). The following data were collected: ECOG performance status (0, or 1–2); disease stage (III, or IV); histological subtype (high-grade serous, or others); treatment approach (primary debulking surgery, or neoadjuvant chemotherapy); surgical outcome based on post-operative residual disease as assessed by the surgeon (optimal surgery with no gross residual lesion, or suboptimal surgery with residual lesions >1 cm); immune-cell PD-L1 expression (<1 %, or ≥ 1 %); and treatment arm (atezolizumab, or placebo); somatic or germline BRCA mutation status (BRCA mutation, or BRCA wild-type).

2.3. Estimation of KELIM of patients enrolled in the IMAGYN 050 trial

To normalize the distribution and eliminate right-skewness, the CA-125 levels were log-transformed. The details about the early longitudinal CA-125 kinetics mathematical modeling using a semi-mechanistic kinetic-pharmacodynamic (K-PD) model were previously described [14,18–21]. KELIM was standardized by the optimized cut-off to provide an easy reading of patient KELIM outcome, as follows: Standardized (std) KELIM = brut KELIM estimated by the model / median (0.06 $days^{-1}$). KELIM was dichotomized into a KELIM score: a std. KELIM <1.0 was considered unfavorable, and a std. KELIM ≥1.0 was considered favorable.

2.4. Benefit from atezolizumab in the poor prognostic group

Univariable and multivariable Cox proportional hazards models were used to find the significant and independent factors regarding PFS, among the collected factors described above (, in addition to patient KELIM score (unfavorable <1.0, or favorable ≥1.0). A backward selection procedure was applied for the multivariable analysis.

Since the KELIM score and surgical outcomes were confirmed to be significant, they were combined to create 3 prognostic groups: a favorable prognostic group consisting of patients with both a favorable KELIM score ≥ 1.0 and an optimal debulking surgery; an intermediate group comprising patients with either a favorable KELIM score or an optimal debulking surgery; and an unfavorable group composed of patients with both an unfavorable KELIM score < 1.0 and a suboptimal debulking surgery with residues >1 cm. This approach is consistent with the methodology previously applied in the ICON-7, GOG-0218, ICON-8 trials, and the GCIG meta-analysis [12,22–24].

The benefit from atezolizumab was explored in these 3 subgroups of patients using univariable Cox proportional hazards models.

All survival analyses were conducted using a landmark time point set at 100 days after the initiation of chemotherapy. Indeed, since CA-125 levels were modeled from day 0 to day 100, the patients who experienced disease progression within the first 100 days after the chemotherapy start were excluded from the analysis. This exclusion was necessary to avoid bias related to the prediction of an event that would have already happened [14,18–21].

The hazard-ratios were computed using the Cox proportional hazard model, and with the 95 % confidence intervals.

All analyses were performed using R Statistical Software (v4.1.2; R Core Team 2021) [25].

3. Results

3.1. Patient characteristics

1301 ptients were enrolled in the IMagyn050 trial. Among 1239 patients assessable for KELIM score, 943 (76.1 %) were treated with primary debulking surgery (PDS) followed by adjuvant chemotherapy, and 296 patients (23.9 %) received neoadjuvant chemotherapy (NACT) potentially followed by interval debulking surgery (Suppl Fig. 1). The median number of CA-125 measurements per patient was 5 in the PDS cohort, and 3 in the NACT cohort. Among them, 1199 patients were assessable for PFS using univariable and multivariable analyses. The key demographic and clinical characteristics of these patients are shown in Table 1. The distribution of patients treated with atezolizumab or placebo was well-balanced between patients with favorable or unfavorable KELIM.

3.2. Model adjustment and qualification

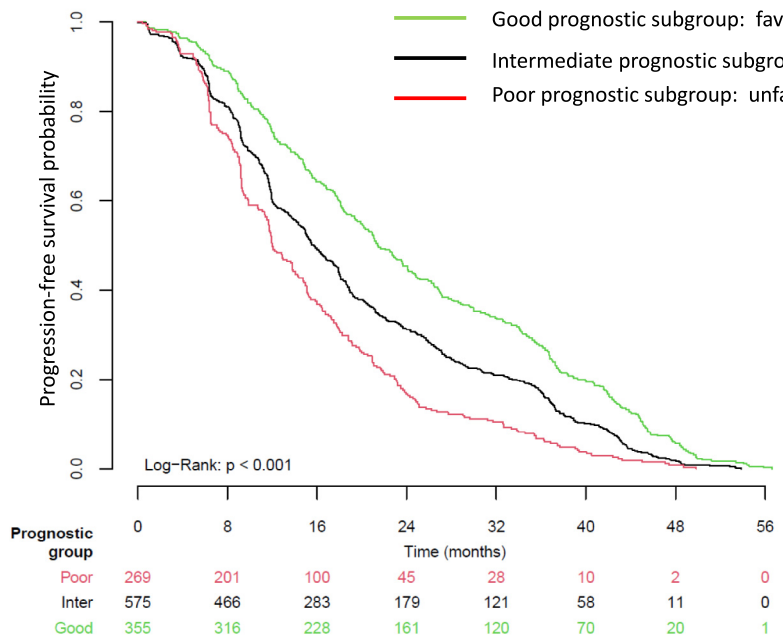
The qualification analyses from the final semi-mechanistic model, are presented in the Supplementary material (Suppl Figs. 2). According to the qualification tests, KELIM score could adequately be estimated in the assessed patients. The median KELIM was 0.057 $days^{-1}$ for all 1239 patients; 0.056 $days^{-1}$ for the -PDS cohort; and 0.057 $days^{-1}$ for the NACT cohort. Consistent with previous publications, KELIM did not differ significantly across treatment arms (Wilcoxon test, $P = 0.11$) (Table 1).

3.3. Prognostic factor regarding Progression- Free Survival (PFS)

3.3.1. Independent prognostic value of KELIM and surgery outcome

The median follow-up times were 19.9 months in the standard arm, and 19.8 months in the experimental arm.

Table 2 displays the outcomes of the univariable analyses meant to identify the significant prognostic covariates to be assessed in the multivariable models. Consistent with the initial hypotheses, a KELIM score < 1.0 and a suboptimal surgery were significantly associated with a shorter PFS. The other significant covariates included the BRCA mutational status, and the immune cell PD-L1 expression (Table 2).



	Median [CI 95%] (months)	HR [CI 95%]	P-Value
Poor	12.0 (11.7, 14.1)	2.07 (1.76, 2.44)	<0.001
Intermediate	15.7 (14.8, 17.5)	1.46 (1.24, 1.67)	<0.001
Good	21.4 (19.9, 24.1)	-	-

Fig. 1. Progression-Free Survival (PFS) in the Three Prognostic Subgroups Defined by KELIM Score and Surgical Outcome.
(*Good Prognostic Group*: "Two Green Flags," characterized by a favorable KELIM score (≥ 1.0) and an optimal debulking surgery; *Intermediate Prognostic Group*: "One Green Flag and One Red Flag," with either a favorable KELIM score (≥ 1.0) or an optimal debulking surgery; *Poor Prognostic Group*: "Two Red Flags," comprising patients with both an unfavorable KELIM score (< 1.0) and a suboptimal debulking surgery.)

A Cox multivariable analysis confirmed that KELIM score < 1.0 and a suboptimal surgery exhibited independent prognostic values (KELIM ≥1.0 vs < 1.0, HR, 0.61, 95 % 0.54–0.69; and suboptimal vs optimal surgery, HR, 1.27, 95 % 1.13–1.43)(data not shown).

As a consequence, KELIM score and surgery outcome were combined to build the pre-specified prognostic groups, with significantly different PFS profiles (Fig. 1).

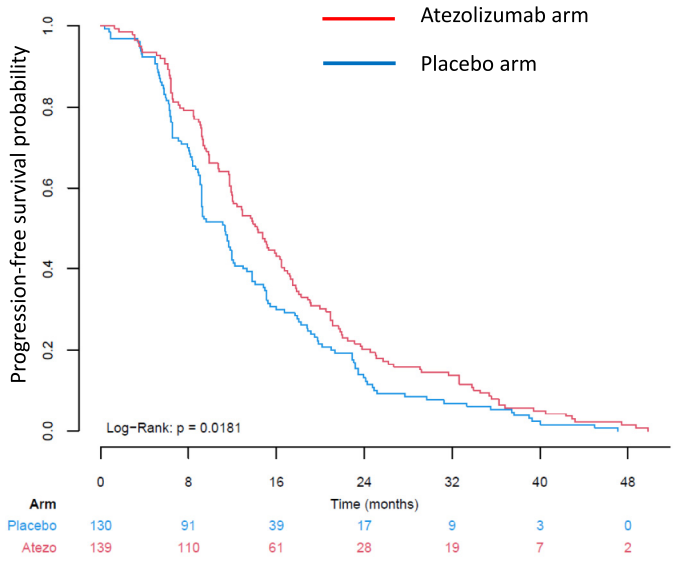
The multivariable proportional hazards model (including these 3 prognostic subgroups, BRCA mutational status, and the immune cell PD-L1 expression) confirmed that the patients belonging to the poor prognostic group (composed of patients with both an unfavorable KELIM score < 1.0, and a suboptimal surgery with residual lesion >1 cm) had a significant worse PFS (HR, 2.05, 95 % CI 1.74–2.41), as did those with a BRCA wild-type tumor (HR, 1.19, 95 % 1.03–1.38). On the other hand, a PD-L1-positive tumor was associated with a better PFS (HR, 0.79, 95 % 0.7–0.89) (Table 3).

3.3.2. Benefit from atezolizumab in the 3 prognostic groups

As shown in Fig. 2, the patients belonging to the poor prognostic group had a PFS benefit from atezolizumab addition (median, 14.3 vs 11.3 months; HR, 0.75, 95 % 0.59–0.95). The patients belonging to the favorable and intermediate prognostic groups did not derive any benefit from atezolizumab addition (favorable prognostic group, median, 21.7 vs 21 0.2 months; HR, 0.95, 95 % CI 0.77–1.17; intermediate prognostic group, median, 14.9 vs 16.7 months; HR, 1.04, 95 % CI, 0.98–1.22) (Fig. 3).

Table 1
Characteristics of the assessed patients.

	Level	Atezolizumab	Placebo	Overall
n		597	602	1199
Age	Mean (SD)	58.67 (10.50)	59.12 (10.70)	58.90 (10.60)
Disease Stage (%)	Stage III	424 (71.0)	426 (70.8)	850 (70.9)
	Stage IV	173 (29.0)	176 (29.2)	349 (29.1)
Baseline ECOG Performance Status (%)	0	324 (54.3)	329 (54.7)	653 (54.5)
	1 or 2	273 (45.7)	273 (45.3)	546 (45.5)
Treatment Setting (%)	Neoadjuvant chemotherapy	131 (21.9)	139 (23.1)	270 (22.5)
	Primary Debulking Surgery	466 (78.1)	463 (76.9)	929 (77.5)
Surgery Status (%)	Optimal Surgery (Residual Disease ≤1 cm)	382 (64.0)	382 (63.5)	764 (63.7)
	Suboptimal Surgery (Residual Disease >1 cm)	215 (36.0)	220 (36.5)	435 (36.3)
Histology Subtype (%)	High-grade Serous	459 (76.9)	457 (75.9)	916 (76.4)
	Non High-grade Serous	138 (23.1)	145 (24.1)	283 (23.6)
BRCA Mutational Status (%)	Mutation	124 (20.8)	116 (19.3)	240 (20.0)
	Not Evaluable	105 (17.6)	126 (20.9)	231 (19.3)
	Wild Type	368 (61.6)	360 (59.8)	728 (60.7)
Immune cell PD-L1 Expression (%)	Negative <1 %	237 (39.7)	234 (38.9)	471 (39.3)
	Positive ≥1 %	360 (60.3)	368 (61.1)	728 (60.7)
KELIM Score (%)	Unfavorable <1.0	354 (59.3)	324 (53.8)	678 (56.5)
	Favorable ≥1.0	243 (40.7)	278 (46.2)	521 (43.5)



	Median [CI 95%] (months)	HR [CI 95%]	P-Value
Placebo	11.3 (9.2, 13.0)	-	-
Atezolizumab	14.3 (11.2, 16.5)	0.75 (0.59, 0.95)	0.02

Fig. 2. Progression-free survivals according to the treatment arm (Atezolizumab vs Placebo) in the poor prognostic group. (Patients with both an unfavorable KELIM score < 1.0 and a suboptimal debulking surgery)

This benefit was observed in both the PDS (median PFS, 14.5 vs 11.7 months, HR, 0.75, 95 % CI 0.58–0.98) and the NACT (12.5 vs 8.3 months, HR, 0.88, 95 % CI 0.46–1.70) populations, with a lower of statistical significance due to the smaller numbers of patients.

4. Discussion

The present study confirms our assumption that the treatment intensification with an ICI given in combination with the chemotherapy and bevacizumab might have improved the PFS of patients belonging to the poor prognostic subgroup, characterized by a sub-optimal cutoreductive surgery and an unfavorable KELIM score < 1.0 in 1st line setting. However, it did not impact the PFS of patients from the other subgroups.

Advances in surgical management and the integration of PARP inhibitors, guided by a deeper understanding of tumor biology, have led to incremental improvements in clinical outcomes for ovarian cancer patients over the past decade [1–3].

Despite these therapeutic advances, a specific subgroup of ovarian cancer patients with two critical risk factors (2 red flags) — *1)* suboptimal surgical resectability and *2)* poor response to first-line platinum-based chemotherapy — continue to derive limited benefit from these developments. Indeed, PARP inhibitors have primarily demonstrated activity in patients whose disease exhibits high platinum-sensitivity and minimal residual disease burden at the initiation of maintenance therapy. In contrast, the subgroup of high-risk disease patients with bulky residual disease at the end of 1st line chemotherapy, potentially as a consequence of the limited chemosenstivity, have reduced long-term prognosis despite treatment with PARP inhibitors as shown in PRIMA and PAOLA-1 trials [26,27].

The poor survival of this subgroup of patients has been consistently observed across several independent datasets and corroborated by the GCIG meta-analysis [12]. Two therapeutic strategies may hold potential for improving the prognosis of these patients.

First, the post-hoc analysis of the ICON-8 trial suggested that a weekly dose-dense regimen, specifically with weekly 80 mg/m^2

Table 2
Outcomes of the univariable analyses testing the association between covariates and the relative risk of disease progression or death.

		Hazard-Ratio	95 % CI	*P*-value
Treatment Arm	Arm-Placebo	Reference	–	–
	Arm-Atezolizumab	0.97	(0.87, 1.09)	0.66
Treatment Setting	Setting - Interval Surgery	Reference	–	–
	Setting - Primary Surgery	1.08	(0.95, 1.24)	0.25
Histological Subtypes	Histology - HG Serous	Reference	–	–
	Histology - Non HG Serous	1.04	(0.91, 1.19)	0.57
Surgery Outcome	Optimal Surgery (with no gross residual lesions)	Reference	–	–
	Suboptimal Surgery (residual lesions >1 cm)	1.26	(1.12, 1.42)	<001
BRCA Mutational Status	BRCA mutation	Reference	–	–
	BRCA Wild-Type	1.25	(1.08, 1.45)	<0.01
	BRCA-Not Evaluable	1.12	(0.93, 1.34)	0.23
Immune cell PD-L1 expression	<1 %	Reference	–	–
	≥1 %	0.79	(0.7, 0.88)	<0.01
Baseline Performance Status	0	Reference	–	–
	1 or 2	1.08	(0.97, 1.21)	0.17
Disease Stage	III	Reference	–	–
	IV	1.10	(0.97, 1.25)	0.13
KELIM Score	Unfavorable <1.0	Reference	–	–
	Favorable ≥1.0	0.59	(0.53, 0.67)	<0.001

Table 3
Final multivariable model composed of the covariates independently associated with the relative risk of disease progression or death(Good prognostic group: favorable KELIM score ≥ 1.0 & optimal debulking surgery with no gross residual lesion; Intermediate prognostic group with either a favorable KELIM score ≥ 1.0 or an optimal debulking surgery; Poor prognostic group composed of patients with both an unfavorable KELIM score < 1.0 and a suboptimal debulking surgery with residual lesion ≥1 cm).

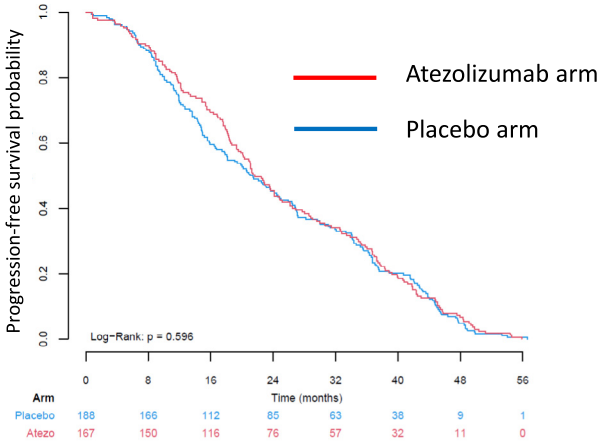
Variables left after backward selection	Variables left after backward selection	Hazard-Ratio	95 % CI	P-value
Prognostic subgroups	Good	Reference		
	Intermediate	1.45	(1.26, 1.65)	<0.01
	Poor	2.05	(1.74, 2.41)	<0.01
BRCA Mutational Status	BRCA mutation	Reference		
	BRCA-Wide Type	1.19	(1.03, 1.38)	0.02
	BRCA-Not Evaluable/Unknown	1.09	(0.90, 1.30)	0.38
Immune cell PD-L1 expression	<1 %	Reference		
	≥1 %	0.79	(0.70, 0.89)	<0.01

paclitaxel, might increase progression-free survival (PFS) and overall survival (OS) in this population [22]. This hypothesis underpins the ongoing phase III SALVOVAR trial (NCT06476184), which is testing the potential OS benefit associated with chemotherapy intensification in patients whose disease is characterized by an unfavorable KELIM score < 1.0 and who are not candidates for complete interval debulking surgery after 3–4 cycles of neoadjuvant chemotherapy.

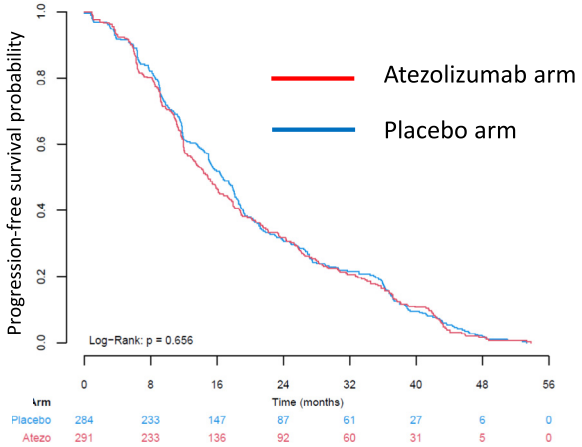
The second strategy involves the addition of bevacizumab to chemotherapy, which is thought to chemosensitize the disease and improve overall survival (OS) in patients with high-risk disease—characterized by suboptimal primary debulking surgery (PDS) for stage III disease or stage IV disease—and an unfavorable KELIM score < 1.0 [15,16]. This clinical activity has been consistently demonstrated in the datasets of both the ICON-7 and GOG-0218 trials [15,16]. However, despite the advantage provided by the combination of bevacizumab and chemotherapy, the survival benefit remains modest, highlighting the need for additional therapeutic strategies to further improve outcomes in this high-risk patient population.

Combining an immune checkpoint inhibitor (ICI) to bevacizumab and chemotherapy was supported by biological data, along with substantial body of clinical evidence showing the synergistic anticancer effects of combining anti-angiogenic drugs with immunotherapy, across solid tumors [17]. Although a PFS benefit was not observed in the overall population of ovarian cancer patients in the IMagyn050 trial, it was deemed essential to evaluate the potential benefit of adding atezolizumab to the bevacizumab and chemotherapy regimen specifically in the subgroup of patients presenting with the two red flags. This particular subpopulation has historically derived the most significant benefit from bevacizumab, making it a priority for further investigation.

The present analysis aligns with prior studies that underscore the independently poor prognosis of this subgroup. It suggests that this subpopulation may achieve a significant PFS benefit from ICI addition—a novel finding, as all previous trials investigating ICIs in the first-line setting for ovarian cancer have failed to demonstrate any survival advantage.



	Median [CI 95%] (months)	HR [CI 95%]	P-Value
Placebo	21.2 (17.9, 25.9)	-	-
Atezolizumab	21.7 (19.9, 26.2)	0.95 (0.77, 1.17)	0.60



	Median [CI 95%] (months)	HR [CI 95%]	P-Value
Placebo	16.7 (15.0, 18.3)	-	-
Atezolizumab	14.9 (13.1, 17.4)	1.04 (0.88, 1.22)	0.66

Fig. 3. Progression-Free Survival by Treatment Arm (Atezolizumab vs. Placebo) in the Good and Intermediate Prognostic Groups.
(Good Prognostic Group: Patients with a favorable KELIM score (≥ 1.0) and optimal debulking surgery; Intermediate Prognostic Group: Patients with either a favorable KELIM score (≥ 1.0) or optimal debulking surgery.)

Interestingly, recent findings from the KEYLYNK-001 trial suggest that patients with high-risk disease (stage III with post-operative R1 residual lesions) derived the greatest benefit from the addition of pembrolizumab to first-line chemotherapy (HR, 0.54; 95 % CI, 0.41–0.72). Similarly, patients with low loss-of-heterozygosity (LOH), presumed to be less platinum-sensitive, also showed a trend toward benefit (HR, 0.80; 95 % CI, 0.60–1.07), aligning with the findings presented here [9]. Consequently, we hypothesize that the addition of an ICI to first-line chemotherapy may enhance chemosensitivity in patients with bulky, poorly chemosensitive disease, thereby facilitating greater tumor debulking before the initiation of maintenance therapy.

Translational research studies are needed to understand the biological determinants of ICI activity in ovarian cancer. The ancillary dynamic analysis of NeoPembrOv trial showed that adding the ICI pembrolizumab to chemotherapy induces tumor microenvironment remodeling, and suggests that potentiating effector T cells by depleting or neutralizing regulatory T cells expressing CD39 and targeting VEGFR2 along with endothelial cells could be options for sensitizing high-grade serous carcinomas to ICI [11].These outcomes are hypothesis-generating, and warrant validation in other trials, such as DUO-O (NCT03737643), JAVELIN OVARIAN 100 NCT02718417), ATHENA-COMBO (NCT03522246), or KEYLYNK-001 (NCT03740165) trials. The results of ENGOT-OV44/FIRST (NCT03602859) were reported as positive in a press release (December 20, 2024), but the magnitude of benefit has not yet been disclosed.

Additional limitations of the present analysis include its post-hoc nature relying on non-prospectively validated predefined prognostic groups; the absence of homologous recombination deficiency (HRD) status assessment as it was not a validated stratification factor when the trial was designed; the high proportion of patients operated suboptimal surgery with residual lesion >1 cm after primary debulking surgery as per inclusion criteria; and the lack of radiological overall response rate (ORR) data.

Despite these limitations, this exploratory analysis suggests that the bleak prognosis of ovarian cancer patients characterized by the two critical prognostic factors—poor chemotherapy sensitivity (assessed by an unfavorable KELIM score < 1.0) and non-amenability to optimal cytoreduction—may be ameliorated by incorporating atezolizumab into the first-line regimen of chemotherapy and bevacizumab. This represents the first potential survival gain associated with immunotherapy in this context. This strategy could potentially offer a less toxic and more tolerable alternative—both in terms of treatment burden, dosing frequency, and overall tolerability—compared to the dose-dense chemotherapy approach evaluated in the SALVOVAR trial. Further validation through analyses of additional datasets is warranted, before considering a prospective trial where ICI could be used a chemosensitizing agent in patients with bulky and poorly chemosensitive disease.

Prior presentation

Presented at ESGO 2024 congress, Barcelona, Spain, March 2024 (oral abstract).

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AC: Employed by Lyon University Hospital (HCL) and Lyon University, Lyon, France.

CRediT authorship contribution statement

Benoit You: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Charles Anderson:** Writing – review & editing, Validation, Investigation. **Sabrina Chiara Cecere:** Writing – review & editing, Validation, Investigation, Conceptualization. **Aurore Carrot:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Formal analysis. **Tashanna Myers:** Writing – review & editing, Investigation. **Florian Heitz:** Writing – review & editing, Investigation. **Sudarshan Sharma:** Writing – review & editing, Investigation. **Fatih Selçukbiricik:** Writing – review & editing, Investigation. **Carol Aghajanian:** Writing – review & editing. **Josefin Fernebro:** Writing – review & editing, Investigation. **Stephanie Blank:** Writing – review & editing, Investigation. **Maria Elena Laudani:** Writing – review & editing, Investigation. **Premal H. Thaker:** Writing – review & editing, Investigation. **Mayu Yunokawa:** Writing – review & editing, Investigation. **Lyndsay Willmott:** Writing – review & editing, Investigation. **Alla Lisyanskaya:** Writing – review & editing, Investigation. **Roberto Hegg:** Writing – review & editing, Investigation. **Yvette He:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Data curation. **Charles Landen:** Writing – review & editing, Investigation. **Yvonne G. Lin:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Jesús Alarcón:** Writing – review & editing, Investigation. **Kathleen N. Moore:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

BY: Boards and consulting: MSD, Astra-Zeneca, GSK, BAYER, Roche-Genentech, BiodenaCare, Novartis, LEK, Amgen, Clovis Oncology, Merck Serono, BMS, SEAGEN, Myriad, EISAI, Pfizer, Pharma&, Abbvie; Invitations congress: Roche-Genentech, Astra Zeneca, BMS, MSD Oncology, Bayer, Boehringer Ingelheim, Pfizer, GSK; Symposium: MSD, Astra-Zeneca, GSK, BAYER, BiodenCare, Roche-Genentech, Novartis, LEK, Amgen, Clovis Oncology, Boehringer Ingelheim.

PHT: Grant or contracts: Merck, GSK, Imunon; Advisory board or DSMB: Iovance, Astra Zeneca, Glaxo Smith Kline, Zentalis, Novocure, Seagen, Immunogen/Abbvie, Caris, Merck, Imunon, Verastem, Mural Oncology; Stocks: Imunon; TRavel: GSK.

LW: Astra Zeneca (speaker bureau); Merck (speaker bureau); Genmab (speaker bureau); Seagen (speaker bureau).

YGL: Employee of Genentech-Roche. Stocks/shares in Roche.

YH: Employed by Roche-Genentech, San Francisco, USA.

KNM: Boards for: Abbvie, Aadi, Astra Zeneca, Blueprint pharma, Caris, Corcept, Duality, BioNTech, Eisai, GSK, Genentech/Roche, Immunogen, Janssen, Lilly, Merck, Mersana, Novartis, Regeneron, Schrodinger, VBL Therapeutics, Verastem, Zentalis and Zymeworks.

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All other coauthors disclose no links of interest

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2025.04.577.

Data availability

Qualified researchers may request access to individual patient-level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). For further details on Roche's Global Policy on the sharing of clinical information and how to requestaccess to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

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