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# TEDOVA: vaccine OSE2101 +/- pembrolizumab as maintenance in platinum-sensitive recurrent ovarian cancer

Rayan Kabirian[a] [ID], Olivier Tredan[b], Frederik Marmé[c], Xavier Paoletti[d], Lauriane Eberst[e], Coriolan Lebreton[f], Thibault De La Motte Rouge[g], Renaud Sabatier[h], Antoine Angelergues[i], Michel Fabbro[j], Toon Van Gorp[k], Laura Mansi[l], Laurence Gladieff[m], Emilie Kaczmarek[n], Jérôme Alexandre[o], Thomas Grellety[p], Laure Favier[q], Julia Welz[r], Jean-Sébastien Frenel[s] and Alexandra Leary[*,a]

[a]Department of Medical Oncology, Gustave Roussy, Villejuif, & GINECO, France; [b]Centre Léon Bérard, Lyon, & GINECO, France; [c]Medical Faculty Mannheim, Heidelberg University & AGO Study Group, Germany; [d]Biostatistic Unit, Institut Curie, Paris, France; [e]Institut de Cancérologie de Strasbourg Europe, ICANS, Strasbourg, & GINECO, France; [f]Institut Bergonié, Bordeaux, & GINECO, France; [g]Centre Eugène Marquis, Rennes, & GINECO, France; [h]Aix-Marseille Univ, CRCM, Inserm, CNRS, Institut Paoli-Calmettes, Department of Medical Oncology, Marseille, & GINECO, France; [i]Groupe Hospitalier Diaconesses-Croix Saint-Simon, Paris, & GINECO, France; [j]Institut du Cancer de Montpellier (ICM), Montpellier, & GINECO, France; [k]Leuven Cancer Institute, Division of Gynaecological Oncology, University Hospital Leuven, BGOG, Belgium; [l]CHU Besançon – Hôpital jean Minjoz, Besançon, & GINECO, France; [m]Oncopole Claudius Regaud, IUCT-Oncopole, Toulouse, & GINECO, France; [n]Centre Oscar Lambret, Lille, & GINECO, France; [o]Université de Paris Cité, AP-HP, Hôpital Cochin, Paris, & GINECO, France; [p]Centre Hospitalier de la Côte Basque, Bayonne, & GINECO, France; [q]Centre Georges François Leclerc, Dijon, & GINECO, France; [r]Evang. Kliniken Essen-Mitte - ESSEN & AGO Study Group, Germany; [s]Institut de Cancérologie de l'Ouest, Centre René Gauducheau, 44800, Saint Herblain, & GINECO, France

## ABSTRACT

Ovarian cancer is a leading cause of death from gynecological cancers worldwide. Platinum-based chemotherapy provides the cornerstone of the medical management. In first line and subsequent relapses, maintenance strategies are offered to prolong intervals between lines of chemotherapy. Current maintenance options involve bevacizumab and poly ADP-ribose polymerase inhibitors, but these lines of therapy can only be used once in the disease course. Patients in first or second platinum sensitive relapse after poly ADP-ribose polymerase inhibitors and bevacizumab represent an area of unmet medical need. This academic sponsored, international Phase II randomized trial is evaluating the combination of a therapeutic cancer vaccine (OSE2101) with anti-PD1 (pembrolizumab) as maintenance therapy, in patients with platinum-sensitive recurrence regardless of number of prior lines and no progression after platinum-based chemotherapy.

**Clinical Trial Registration:** NCT04713514 (ClinicalTrials.gov)

## TWEETABLE ABSTRACT

Ongoing Phase II study randomizing vaccine OSE2101 +/- Pembrolizumab vs supportive care as maintenance in platinum-sensitive recurrent ovarian cancer.

## PLAIN LANGUAGE SUMMARY

Phase II study evaluating vaccine OSE2101 +/- Pembrolizumab vs supportive care as maintenance in patients with recurrent platinum-sensitive ovarian cancer.

Ovarian cancer often becomes a long-term condition that needs ongoing treatment. After chemotherapy, women usually receive additional treatments to keep the cancer under control. There are only two approved treatments for this: bevacizumab administered every 3 weeks, and poly ADP-ribose polymerase inhibitors (PARP) inhibitors, which are pills that women can take if their cancer responds to platinum-based chemotherapy. However, if women have already been treated with both bevacizumab and a PARP inhibitor, there are no approved options left to maintain control of the cancer after chemotherapy.

A new potential treatment, called OSE2101, is being studied: it is a vaccine designed to activate the body's immune cells to fight against cancer. The TEDOVA study is looking at how well this vaccine works in women with ovarian cancer who have already been treated with both bevacizumab and a PARP inhibitor and whose cancer is responding to platinum-based chemotherapy again.

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**CONTACT** Alexandra Leary Tel.: +33 01 42 11 66 99; ✉ Alexandra.leary@gustaveroussy.fr

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Participants are randomly assigned to one of three groups after their chemotherapy: standard supportive care, OSE2101 vaccine alone and the combination of OSE2101 vaccine with pembrolizumab.

The goal of the TEDOVA study is to see if the combination of the OSE2101 vaccine and pembrolizumab can better control the cancer and to make sure the treatments are safe. The study is being run by ARCAGY-GINECO and is currently recruiting patients in France, Germany and Belgium. The study will continue to accept new patients until the end of 2024, and it is registered on ClinicalTrial.gov under the number NCT04713514.

## 1. Introduction

### 1.1. Background & rationale

The prognosis of ovarian cancer (OC) varies by stage. Type I epithelial OCs are considered to be relatively indolent and genetically stable, while Type II epithelial OCs are thought to be biologically aggressive from the beginning, with a tendency to metastasize early [1]. High-grade serous – accounting for approximately 75% of epithelial OCs – develop according to the type II pathway and present *p53* and *BRCA* mutations. These advanced stage has a poor prognosis [2] with most patients unfortunately relapsing after primary management. Initial treatment of advanced OC includes surgery and platinum-based chemotherapy (CT). These treatments can be followed by a maintenance strategy consisting of poly ADP-ribose polymerase inhibitors (PARPi) alone, anti-angiogenic bevacizumab alone or the combination of bevacizumab and PARPi [3]. In case of relapse, OC is managed as a chronic disease with iterative lines of chemotherapy.

*BRCA1/2* germline mutations are the strongest known genetic risk factors for epithelial OCs and are found in 6–15% of women diagnosed with that disease. *BRCA1/2* mutated carriers respond better than noncarriers to platinum-based chemotherapies. This yields greater survival, even though the disease is generally diagnosed at a later stage and higher grade [4]. One other major prognostic factor is the platinum-free interval (PFI) defined as the time between the last platinum CT and recurrence, which is important to interpret in combination with other specific clinical and molecular factors [5]. Current options for platinum-sensitive patients include bevacizumab and/or PARPi FDA-approved Olaparib as maintenance after platinum-based chemotherapy regardless of *BRCA*/HRD status, if they have not been previously administered [6–10]. Thus, women with OC presenting with platinum sensitive relapse after prior bevacizumab and PARP inhibition represent a crucial unmet medical need.

Immune therapies (mainly, checkpoint inhibitors) have opened new opportunities in cancer therapy [11]. Unfortunately, in the case of OC, previous studies targeting checkpoints inhibitors Programmed Death Ligand-1 (PD-L1) or Programmed Death-1 (PD-1) have been disappointing [12–14], partly explained by the low levels of endogenous tumor specific cytotoxic T cells or low mutation load [15]. In particular, ovarian tumors are frequently described as immunogenically 'cold', characterized by a highly immune-tolerant microenvironment. Pembrolizumab is a humanized monoclonal antibody therapy that targets the cell surface receptor PD-1, thus inhibiting its interaction with PD-L1 and PD-L2 [16,17]. The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control [11,18,19]. Pembrolizumab is currently under investigation in several studies of patients with platinum-sensitive recurrent OC (see Supplementary Table S1). Previous Phase II KEYNOTE-100 study in recurrent OC [14] included 285 women with one to three prior lines of treatment and a PFI between 3 and 12 months and 86 women with four to six prior lines and a PFI ≥3 months. Pembrolizumab was administered as a single-agent, and showed modest activity with 7.4 and 9.9% objective response rates respectively.

A recent therapeutic cancer vaccine OSE2101 is under clinical investigation in several localizations. OSE2101 is designed to activate cytotoxic T-lymphocytes (CTL) against five tumor-associated antigens highly expressed in non-small-cell lung cancer but also OC: carcinoembryonic antigen; p53; HER-2/neu and melanoma antigens 2 and 3 (Figure 1) [20,21]. OSE2101 is composed of 10 synthetic peptides of which 9 derive from these tumor-associated antigens, that have been modified to increase HLA and/or T cell receptor binding affinity and one pan-DR epitope. The pan-DR epitope is a rationally designed helper T-lymphocyte epitope included to augment the magnitude and duration of CTL responses.

Each CTL epitope is restricted by HLA-A2. which is expressed by approximately 45% of the general population as well as cancer patients [22].

The innovation is to associate epitopes designed and modified chemically of different tumor associated antigens in the same vaccine.

Immunogenicity of OSE2101 is under investigation in maintenance among patients with locally
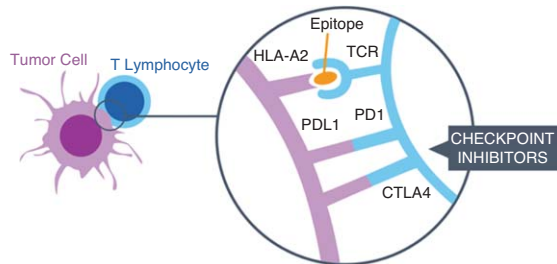
| OSE2101 (TEDOPI®): Combination of epitopes (synthetic peptides) | |
| --- | --- |
| Epitopes derived from tumour associated antigens (TAAs) modified to increase the binding to the T Cell Receptor and/or class I HLA-A2 | P53<br>CEA<br>HER2<br>MAGE-A2<br>MAGE-A3 |
| Epitope stimulating the helper function of CD4 T cells | Pan DR T helper cell epitope (PADRE) |



**Figure 1.** Description of OSE2101 (Tedopi®) combination of epitopes. Adjuvant (Montanide ISA 51™) is entrapping all epitopes in ISE2101 in a form amenable for efficient uptake and processing/presentation by antigen presenting cells through subcutaneous route.
CEA: Carcinoembryonic Antigen; CTLA4: Cytotoxic T-lymphocyte-associated protein 4; HER2: Human Epidermal Growth Factor Receptor 2; HLA-A2: Human Leucocyte Antigen A2; P53: Protein Tumor 53; PD1:Programmed Death 1; PDL1:Programmed Death Ligand 1; MAGE-A2: Melanoma A2 Antigen; MAGE-A3: Melanoma A3 Antigen; TCR: T Cell Receptor.

advanced/metastatic pancreatic ductal adenocarcinoma (NCT03806309). It has also been previously published in a NSLCL Phase II study [23]. In the ATALANTE-1 study [24] including 118 randomized patients with HLA-A2 positive advanced non-small-cell lung cancer with secondary resistance to immunotherapy, OSE2101 monotherapy was associated with an improved overall survival in the secondary resistance to immunotherapy subgroup (11.1 vs 7.5 months) and better quality of life (vs standard of care chemotherapy). Safety data in ATALANTE-1 are also reassuring with 11.4% of treatment-related severe (not higher than grade 3) adverse event (TRAEs) (vs 35.1% in standard of care group). No grade 4 or 5 TRAE were observed.

Combination of vaccines containing multi-epitopes with immunotherapy is a recent era of personalized immunotherapy with tumor-specific neoantigens. The general mechanism of action is the recruitment and activation (interferon $\gamma$ production) of tumor specific CD8$^+$ T cells [25,26]. Immunoinformatics and bioinformatics approaches are promising strategies under investigation [27,28] including in OC [29] to find potential epitopes for a multi-epitope vaccine [30].

Associating a multi-epitope vaccine to an immune checkpoint inhibitor has the potential to change immunogenically 'cold' ovarian tumors into 'hot' tumors and more effectively harness a T cell-mediated immune response against tumor-associated antigens or tumor-specific neoantigens [31].

Within this landscape, the randomized, Phase II TEDOVA/GINECO-ov244b/ENGOT-ov58 will evaluate the association of the therapeutic cancer vaccine OSE2101 with or without the anti-PD1 antibody pembrolizumab as maintenance therapy, in patients with platinum-sensitive recurrence, with prior PARPi and bevacizumab exposure, who had no disease progression after platinum-based chemotherapy. The TEDOVA trial is sponsored by ARCAGY-GINECO, and is currently recruiting in France, Germany and Belgium. The first patient was randomized in August 2021. As of November 2023, 105 patients have been randomized. The duration of the inclusion period is estimated of around 36 months.

## 2. Objectives

### 2.1. Primary objective

The primary objective is to evaluate the progression-free survival (PFS) benefit according to RECIST 1.1 of maintenance OSE2101 alone or in combination with PD1 inhibitor after platinum-based CT in relapsed OC.

### 2.2. Secondary objectives

- To compare the best overall response rate for patients with measurable disease at randomization.
- Safety and tolerability, in terms of AEs (with a particular focus on immune related), deaths, laboratory data, vital signs and electrocardiogram.
- Time to subsequent first and second treatments (TTST-1 and TTST-2).
- Overall survival

### 2.3. Trial design (*Figure 2*)

This international multicenter study is a randomized Phase II open-label three arms trial, comparing best supportive care vs OSE2101 vs OSE2101 in combination with Pembrolizumab as maintenance treatment for patients with platinum sensitive relapsed OC, regardless of the number of prior lines. Patients must have been previously treated with bevacizumab and a PARPi, or have a contraindication, or not be eligible to these treatments (i.e., no approval for PARPi treatment in low grade OC). After positive prescreening for HLA A2 and at least four cycles of platinum-based chemotherapy, patients with complete response (CR), partial response (PR) or stable disease (SD) will be randomized (1:1:2) in one of three arms: best supportive care, OSE2101 monotherapy or OSE2101 in combination with pembrolizumab.Treatment

**SCREENING**
*Within 28 days before randomization*

- Epithelial non-mucinous OC
- Platinum senstive relapse
- CR, PR or SD after platinum based CT
- Prior or not eligible to PARPi
- Prior or not eligible to bevacizumab
- Prior ICI allowed if relapse after at least 6 months of ICI

HLA-A2⁻

★ HLA Testing

HLA-A2⁺

Treatment with at least 4 cycles of platinum based CT before randomization

Randomization 1:1:2
Stratification according to best response to platinum : SD vs PR/CR

**Observational Cohort**
Followed in a separate cohort to record treatment and outcomes

**Arm A : Best Supportive Care**
N = 45

**Arm B : OSE2101**
q3w till W18, then q6w up to W48, then q12w until intolerance, PD, or up to 2 years*
N = 45

**Arm C : OSE2101 + Pembrolizumab**
OSE2101 as above + Pembro q6w untill intolerance, PD, or up to 2 years *
N = 90

\* Even after objective radiological disease progression, study treatmemts may be continued up to 2 years as long as patients are experiencing clinical benefit as assessed by the investigator. After 24 months of treatment, and in case the investigator thinks that he patient may get a clinical benefit by prolonging the experimental treatment OSE2101, the investigator and the sponsor will discuss the best option of how to pursue this treatment.

**Figure 2.** Study design.
CR: Complete response; CT: Chemotherapy; OC: Ovarian cancer; PARPi: Poly ADP-ribose polymerase inhibitors; PD: Progression disease; PR: Partial response; q3w: Every 3 weeks; SD: Stable disease; W18: Week 18.

will be administrated until progression, intolerance or up to 2 years from the first dose of study treatment.

## 3. Materials & methods

A total of 180 patients with HLA-A2 positive phenotype will be randomized using an Interactive Web Response System according to the best response to platinum therapy stratification factor (SD vs PR/CR)

The three study arms in 1:1:2 ratio are described in Figure 2:

- Arm A (n = 45): Observation/best supportive care
- Arm B (n = 45): OSE2101: every 3 weeks until week 18, then every 6 weeks up to week 48, then every 12 weeks until disease progression, intolerance, patient withdrawal of consent or up to 2 years
- Arm C (n = 90): OSE2101 + Pembrolizumab: OSE2101 same schedule as arm B plus pembrolizumab IV every 6 weeks until disease progression, intolerance, patient withdrawal of consent or up to 2 years

HLA-A2 negative patients will be followed, as study participants, in a separate observational cohort to record treatment and outcomes.

### 3.1. Participant timeline

Inclusion began in Q2 2021 for 3 years with an estimated date of last patient included in Q3 2024. The estimated date of end of treatment and study is Q4 2025, which corresponds to the date of disease progression according to RECIST1.1 of last patient.

### 3.2. Eligibility criteria

Eligibility criteria are developed in Table 1.

### 3.3. Recruitment

After documented signed informed consent, patients undergo blood sampling for HLA-A2 genotyping before inclusion, determined by PCR performed centrally by a certified lab. The informed consent includes the possibility to collect clinical data in patient with HLA-A2 phenotype negative. Only patients with HLA-A2 positive phenotype who have completed at least four cycles of platinum chemotherapy and are free of progression will be randomized.

### 3.4. Randomization

Patients are included in the three arms of the study with several assessments performed at each study visit (Figure 3) and tumor imaging assessment every 12 weeks.

**Table 1.** Key inclusion and exclusion criteria in TEDOVA protocol.

| Key inclusion criteria | Key exclusion criteria |
|---|---|
| 1. Written informed consent | 1. Contra-indications or severe hypersensitivity (Grade 3 or higher) to immune therapies |
| 2. Histologically proven non-mucinous epithelial ovarian cancer | 2. Ongoing immunotherapy |
| 3. Positive HLA-A2 phenotype | 3. Use of systemic corticosteroids (>10 mg/day equivalent prednisone), not stopped at least 7 days before study treatment start |
| 4. Age ≥18 years | 4. Use of interferons, interleukins or live vaccine within 30 days prior to the first dose of study drug |
| 5. ECOG Performance Status 0–1 | 5. Prior cancer vaccine therapy |
| 6. Platinum sensitive ovarian cancer regardless of the number of prior lines of platinum-based chemotherapy. Patient must have received at least four infusions of platinum during the last line of platinum-based chemotherapy | 6. Eligible for cytoreductive surgery at the time of inclusion |
| 7. Previously treated with a PARP inhibitor or not eligible to PARPi | 7. Clinical, radiological or biological progression (according Gynaecologic Cancer Intergroup criteria) at the end of last chemotherapy |
| 8. Previously treated with bevacizumab or contra-indication to bevacizumab | 8. Prior radiotherapy within 2 weeks of start of study intervention |
| 9. Patient may have received prior immune checkpoint inhibitor (ICI), and had a relapse after receiving the ICI without concomitant chemotherapy for at least 6 months | 9. Active autoimmune disease that has required systemic treatment in the past 2 years (corticosteroids or immunosuppressive drugs) |
| 10. Randomization must be within 8 weeks of the last dose of chemotherapy | 10. History of serious adverse reactions to any vaccine |
| 11. Adequate organ function: white blood cell ≥3000/mm³; neutrophils ≥1500/mm³; platelets ≥100 × 10³/mm³; hemoglobin ≥9 g/dl; ALT and AST ≤2.5 × ULN; total bilirubin ≤1.5 × ULN; serum creatinine ≤1.5 × ULN or creatinine clearance ≥40 mL/min (using Cockcroft–Gault formula) | 13. History of other malignancies (except for basal cell or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix or other *in situ* cancer considered as cured) unless the patient has been free of the disease for at least 5 years. |
| 12. Archival or fresh tumor tissue must be available for evaluating relevant biomarkers | 11. Immune-deficient status |
| | 12. History of any chronic hepatitis |
| | 13. Uncontrolled or significant cardiovascular disease |
| | 14. Uncontrolled brain metastases |
| | 15. Life expectancy of less than 12 weeks |
| | 16. Pregnant or breastfeeding women |



**Figure 3.** Study follow-up.

* Even after objective radiological disease progression, study treatmemts may be continued as long as patients are experiencing clinical benefit as assessed by the investigator.
After 24 months of treatment, and in case the investigator thinks that he patient may get a clinical benefit by prolonging the experimental treatment OSE2101, the investigator and the sponsor will discuss the best option of how to pursue this treatment.

*Legend:*
*PR : Presential – face to face Visit - on site visit*
*TC : teleconsultation – phone contact*

### 3.5. OSE2101 vaccine administration

OSE2101 vaccine is a 1 ml emulsion injected by subcutaneous administration. It is advisable to inject the vaccine preferably in the same area or in a site drained by the same lymph nodes (e.g., at anterior side of the thigh or in shoulder of the nondominant arm). Avoid injection into the thighs in patients who have had pelvic and aortic lymph node dissection. Patients have to be monitored for at least 5 h after each injection for reaction after injection including cytokine release syndrome (CRS) using CRS Severity (CTC-AE v5.0) grading scheme. OSE2101 vaccine is administered every 3 weeks for seven doses, then every 6 weeks for the remainder of year one, then every 12 weeks until progression, limiting toxicity, patient withdrawal or up to 2 years.

In Arm C, OSE2101 vaccine will be administered before the perfusion of pembrolizumab.

Dose reductions are not allowed. In case of NCI-CTCAE Grade 3 severe adverse effect, the definitive cessation of treatment has to be considered.

Antipyretics have to be administered prior to study drug administration (1 h before injection and every 6 h for the first 2–3 days), ketoprofen 100 mg twice a day and an antihistamine day 1. In addition, topical steroid cream is proposed at the site of injection.

### 3.6. Pembrolizumab administration

Pembrolizumab 400 mg is administered at the same time as OSE2101, as an intravenous infusion over 30 min, every 6 weeks until progression, limiting toxicity, patient withdrawal or up to 2 years. Immune-related adverse events (AEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab/combination treatment, including pneumonitis, colitis, liver toxicity, diabetes, hypothyroidism or myocarditis. Participants may not have any dose modifications (no change in dose or schedule) of pembrolizumab in this study. Most immune-related AEs were reversible and could be managed with interruptions of pembrolizumab/combination treatment, administration of corticosteroids and/or other supportive care.

### 3.7. Statistical methods & sample size determination

This proof-of-concept trial aims to assess the efficacy of two investigational treatments (Arms B and C) compared with best supportive care (Arm A) as the control group. The primary end point is PFS, measured from randomization to disease progression. Sample size calculations were conducted using SAS 9.4 power analysis software.

The trial is designed with a type I error rate ($\alpha$) of 5% and a type II error rate ($\beta$) of 10%, with one-sided tests. Previous trials have shown short median PFS in patients with platinum-sensitive relapse who responded to re-challenge with platinum doublet: 5.5 months for *BRCA*-mutated patients and less than 4 months for non-*BRCA*-mutated patients. We anticipate a slightly shorter PFS (<4 months) in our population, as most patients will have received a PARP inhibitor and are required to have non-progression on platinum chemotherapy rather than an objective response per RECIST criteria. The combination of OSE2101 and pembrolizumab is hypothesized to outperform both OSE2101 alone and best supportive care (BSC). If the combination does not outperform BSC, no difference is expected between OSE2101 alone and BSC.

Hierarchical testing (fixed sequence procedure) will be employed to compare the treatment arms, using three one-sided log-rank tests in a predefined order:

1. **H1**: Arm C (OSE2101 + pembrolizumab) vs Arm A (BSC)
   - If H1 is statistically significant, proceed to:
2. **H2**: Arm C (OSE2101 + pembrolizumab) vs Arm B (OSE2101)
   - If both H1 and H2 are statistically significant, proceed to:
3. **H3**: Arm B (OSE2101) vs Arm A (BSC)

All one-sided tests in this sequence will use a nominal $\alpha$ value of 0.05. If H1 is not rejected, further tests will be exploratory.

The sample size is calculated to ensure 90% power to detect an improvement in PFS for the combination therapy compared with BSC, with a hazard ratio (HR) of 0.57 (assuming median PFS increases from 4 to 7 months under the exponential distribution of PFS), and an imbalanced randomization of 2:1. This design requires 121 events (progression or deaths) to test H1. Assuming a 2-year accrual period and a minimum 1-year follow-up per patient, 180 patients need to be randomized across Arm A (n = 45), Arm B (n = 45) and Arm C (n = 90) to observe the required events.

With 45 patients in the OSE2101 monotherapy arm, the trial will have 78% power to detect an HR of 0.57 compared with the BSC arm.

### 3.8. Statistical methods

#### 3.8.1. Primary end point analysis
PFS will be defined from the date of randomization to the date of first documented disease progression (according to RECIST v1.1) as reported by the investigator, or death from any cause. PFS will be estimated using the Kaplan–Meier method. Patients who are alive and free of progression at the cut-off dates will be censored at the date of their last tumor assessment.

For each treatment group, the median PFS and the probability of PFS at 4, 6 and 12 months will be reported along with two-sided 95% confidence intervals (CIs). The comparison of PFS between Arm C (combination therapy) and Arm A (BSC) will be conducted using a one-sided log-rank test, stratified by the randomization stratification factor. HRs and their CIs will be estimated using a Cox model, also stratified by the randomization stratification factor. If any stratum has no events, it will be combined with another stratum. The proportional hazards assumption will be visually checked with Schoenfeld residuals and tested for a linear time trend using the Therneau test at a 5% significance level. Potential interactions

between treatment effect and the stratification factor will be explored, although the small sample sizes may limit the power of these analyses.

### 3.8.2. Secondary end points analyses

*3.8.2.1. Best Overall Response Rate (ORR).* Response in OC will be assessed according to RECIST 1.1 in the Objective Response analysis set. ORR is defined as the proportion of subjects achieving a CR or PR among patients with measurable disease. Patients without radiological assessments will be considered treatment failures (included in the denominator). Patients who receive no treatment after randomization will be excluded from the analysis (not included in the denominator).

The ORR for each treatment arm, along with the exact two-sided 95% CIs, will be estimated. Additionally, the difference in response rates and the stratified odds ratio, with corresponding 95% CIs, will be calculated. The Cochran–Mantel–Haenszel test will be used to compare the overall treatment arms, controlling for stratification factors. If significant, pairwise comparisons between arms will be conducted without adjustments for multiple testing.

A sensitivity analysis excluding non-evaluable patients will also be performed.

*3.8.2.2. Safety analysis.* In the Safety analysis set, safety and tolerability will be assessed in terms of AEs, serious AE, AE of special interest, immune related AE, toxic deaths, laboratory data; AE will be described according to Medical Dictionary for Regulatory Activities (MedDRA) terms (version 23.0) and graded according to NCI Common Terminology Criteria for Adverse Events (CTC-AE) version 5.0 [32].

*3.8.2.3. Time to subsequent treatment (TTST-1 & TTST-2), overall survival.* Time to start of subsequent therapy or death (TTST) is measured from the date of randomization to the date of anti-cancer therapy following the discontinuation of the study treatment (TTST-1) or the second treatment (TTST-2), or until death. Patients without such events will be censored at the date of their last tumor assessment.

Both TTST end points will be estimated using the Kaplan–Meier method and compared with log-rank tests, stratified by the best response to chemotherapy in the full analysis set population. If the initial comparison is rejected, pairwise comparisons between treatment arms will be performed. Stratified HRs and their CIs will be estimated using a stratified Cox semi-parametric model. The proportional hazards assumption will be visually checked with Schoenfeld residuals and tested for a linear time trend with the Therneau test at a 5% significance level.

Details of subsequent therapies aimed at controlling OC will be reported, as well as the cause of death by treatment arms.

### 3.9. Safety monitoring

The Data Safety Monitoring Board will be constituted by the sponsor and will be composed of statisticians and clinical experts. Severe toxicity (Grade 3 or 4 non hematological or Grade 4 hematological) at least possibly related to the study treatments, will be closely monitored. An interim safety analyses has been performed after 40 patients being treated at least during 3 weeks (30 in the combined investigational arms). This analysis performed in June 2023 was reassuring and led to the implantation of a mitigation plan for CRS with adjunction of ketoprofen and an antihistamine as premedication before OSE2101 injection.

### 3.10. Ethical conduct

An Institutional Review Board/Ethics Committee from each study site approved the final study protocol, including the final version of the Informed Consent Form. Each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study, with signed written and dated informed consent. Investigators of each center are in charge of enrolment of each participant.

Appropriate coded identification (i.e., patient number) will be used to protect confidentiality. The investigator will make a separate confidential record of these details (patient identification code list) to permit identification of all patients enrolled in a clinical trial in case follow-up is required.

### 3.11. Current status

To date 316 patients have been screened: 152 HLA-A2+ and 155 HLA-A2- (5 with results pending). Overall, 107 patients have been randomized, eight due for randomization and 37 screen-failed. Among 155 HLA-A2- patients, 22 are screen failed and 110 have been included in the observational cohort. Four patients have withdrawn consent before being tested. Screen-failures are largely attributable to progressive disease after HLA-A2 testing.

## 4. Conclusion

Patients with OC presenting with platinum sensitive relapse post-PARP inhibition and bevacizumab represent a crucial unmet medical need. They have no available

maintenance strategies and recent data suggest that progression after prior PARP inhibitor exposure is associated with particularly poor outcomes [33,34]. Novel effective maintenance therapies are thus needed like proteomics technologies (mass spectrometry and protein array analysis) which have advanced the dissection of the underlying molecular signaling events. Proteomics analysis of OC, as well as their adaptive responses to therapy, can uncover new therapeutic choices, which can reduce the emergence of drug resistance and potentially improve patient outcomes [35].

Anti-PD1/PDL1 alone is clearly not sufficient to stimulate an effective antitumor immune response in OC. Whether the combination with a therapeutic cancer vaccine targeting several tumor-associated antigens is worthy of investigation.

This multicentre international Phase II proof of concept study will determine whether maintenance with vaccine OSE2101 and pembrolizumab can improve PFS in women with no progression after platinum-based CT and previous exposure to PARP inhibition and bevacizumab.

### Article highlights

**Advanced epithelial ovarian cancer**
- Most patients diagnosed with ovarian cancer (OC) have no evidence of disease after standard treatment with debulking surgery and platinum-based chemotherapy. Long-term survival depends on the recurrence of the disease, the delay between the last platinum-based chemotherapy defining the platinum-sensibility which is a major prognostic factor.

**Study rationale**
- Women with platinum-sensible relapse (more than 6 months after the last platinum received) will be managed as patients with a chronic disease requiring iterative lines of platinum-based chemotherapy. After several cycles of treatment, chemotherapy is usually stopped and one of the major priorities is to extend platinum-free interval proposing maintenance strategies, as targeted therapy bevacizumab or poly ADP-ribose polymerase inhibitors (PARPi). When those lines of therapy have been received during previously, they cannot be reuse. That is the reason of developing new therapies and associations as maintenance therapy.

**TEDOVA study**
- TEDOVA is a Phase II, randomized, open-label, multicenter study assessing the efficacy of vaccine OSE2101 + anti PD-1 pembrolizumab as maintenance therapy in women with platinum-sensible relapse of OC. We included women with HLA-A2 phenotype (~45% of the general population) with platinum sensitive OC regardless of the number of prior lines of platinum-based chemotherapy. Patients must have been previously treated with bevacizumab and a PARPi, or have a contra-indication.

**End points**
- The primary end point is to evaluate the progression free survival of maintenance OSE2101 alone or in combination with PD1 inhibitor.
- The secondary end points are to compare the best overall response rate for patients with measurable disease at randomization, the safety and tolerability, the time to subsequent first and second treatments and the overall survival.

**Key eligibility**
- Eligible patients were aged ≥18 years of age with histologically proven non-mucinous epithelial OC, positive HLA-A2 phenotype, and platinum sensitive OC regardless of the number of prior lines of platinum-based chemotherapy. Patients must have been previously treated with bevacizumab and a PARPi, or have a contraindication.

**Study procedures**
- A total of 180 patients with an HLA-A2 positive phenotype will be randomized into three study arms in a 1:1:2 ratio: Arm A (n = 45) will receive observation/best supportive care, Arm B (n = 45) will receive OSE2101 and Arm C (n = 90) will receive OSE2101 plus pembrolizumab. Patients will be followed until disease progression, intolerance, withdrawal of consent, or for up to 2 years.

**Statistics**
- One-sided log-rank tests will be conducted in a predefined sequence:
  ○ **H1**: Compare Arm C (OSE2101 + pembrolizumab) with Arm A (best supportive care).
  ○ If H1 shows a statistically significant difference, then proceed to:
  ○ **H2**: Compare Arm C (OSE2101 + pembrolizumab) with Arm B (OSE2101).
  ○ If both H1 and H2 show statistically significant differences, then proceed to:
  ○ **H3**: Compare Arm B (OSE2101) with Arm A (best supportive care).
  ○ A total of 121 events (progressions or deaths) is required to perform the first test of H1.

## Financial disclosure

## Competing interests disclosure

Pfizer, Novartis-Sandoz, Lilly, MSD, Astra-Zeneca, Pierre Fabre, Seagen, Daiichi-Sankyo, Gilead, Eisai. F Marmé: Participation on an Advisory Board from AstraZeneca, EISAI, GenomicHealth, Gilead/Immunomedics, Immunicom, MSD, Myriad, Novartis, PharmaMar, Roche, Seagen; invited speaker by AstraZeneca, Clovis, Daiichi Sankyo, GSK, GSK/Tesaro, Lilly, Pfizer, Seagen. X Paoletti: Consulting or advisory role for MSD, Ipsen (personal). C Lebreton: Honoraria from Eisai, Clovis Oncology, MSD Oncology, GlaxoSmithKline; travel and accommodations from GlaxoSmithKline and MSD Oncology. Thibault De La Motte Rouge: Consulting fees for AstraZeneca, GSK, Clovis Oncology, Pfizer, Gilead, Seagen, Sanofi; honoraria for lectures, presentations, speakers from GSK, MSD; support for attending meetings and/or travel from Pfizer, Gilead, Eisai; participation on a data safety board or advisory board from MSD. R Sabatier: Consulting fees from GSK and EISAI. TV Gorp: Consulting fees (via institution) from AstraZeneca, BioNTech, Eisai, GSK, ImmunoGen, Incyte, Karyopharm, MSD, OncXerna, Seagen, Tubulis, Zentalis. Sponsored research (via institution): Amgen, AstraZeneca, Roche. Honoraria for lectures (via institution): GSK, ImmunoGen, MSD. L Gladieff: Institutional honoraria for symposium participation and support for attending meetings from MSD. J Alexandre: Honoraria from GSK, Astra Zeneca, Eisai, MSD. J-S Frenel: Consulting fees from Pfizer, Lilly, Novartis, Astra Zeneca, Clovis Oncology, GSK, Gilead, Daiichi Sankyo, Seagen, Exact Science, MSD; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Lilly, Novartis, Astra Zeneca, Gilead, Daiichi Sankyo, Seagen, MSD. Al Leary: Honoraria/expenses from Astra Zeneca, Clovis, GDK; participation at a consulting/advisory board for Astra Zeneca, Clovis, GSK, MSD, Merck Serono, Ability, Zentalis, Agenus, Blueprint. R Kabirian: No disclosure. L Eberst: No disclosure. A Angelergues: No disclosure. M Fabbro: No disclosure. L Mansi: No disclosure. E Kaczmarek: No disclosure. T Grellety: No disclosure. L Favier: No disclosure. J Welz: No disclosure. The authors have no other competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript apart from those disclosed.

## Ethical conduct of research

An Institutional Review Board/Ethics Committee approved the final study protocol, including the final version of the Informed Consent Form. Each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study, with signed written and dated informed consent. The study will be conducted in accordance with the principles outlined in the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice.

## Data availability statement

The datasets generated and/or analyzed during the current study will be available from the corresponding author upon reasonable request. Data will be shared in accordance with institutional guidelines and will require a data use agreement to ensure the confidentiality of participants.

## Previous presentation

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## ORCID

Rayan Kabirian https://orcid.org/0000-0001-5165-9743

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