ATOMICC trial: a randomized, open-label, phase II trial of anti-PD1, dostarlimab, as maintenance therapy for patients with high-risk locally advanced cervical cancer after chemoradiation

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ABSTRACT

Background Currently, women diagnosed with high-risk locally advanced cervical cancer are at high risk of recurrence after treatment with concurrent chemoradiation and represent a population with high unmet need.

Primary Objective The primary objective is to evaluate the progression-free survival of high-risk locally advanced cervical cancer patients who have achieved a partial or complete response after chemoradiation after receiving dostarlimab as maintenance therapy.

Study Hypothesis The study aims to demonstrate that the use of dostarlimab, as maintenance therapy, would significantly increase progression-free survival in these patients.

Trial Design ATOMICC trial is a phase II, randomized, open-label, multicenter study to assess the efficacy and safety of anti-PD1, dostarlimab, as maintenance therapy in patients with high-risk locally advanced cervical cancer who have achieved a partial or complete response after chemoradiation. The control arm entails a clinical and radiological follow-up, with no further treatment (current standard of care). ATOMICC trial is an investigator-driven trial sponsored by GEICO (Grupo Español de Investigación en Cáncer de Ovario) and supported by GlaxoSmithKline (GSK).

Major Inclusion/Exclusion Criteria Women aged over 18 years with a biopsy-confirmed squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the cervix meeting the following staging criteria: International Federation of Gynecology and Obstetrics (FIGO) 2009 stages IB2, IIA2, IIB with pelvic lymph node involvement, FIGO stages IIIA, IIIB, IVA, and any FIGO 2009 stage with para-aortic lymph node involvement are eligible for the trial. All patients must have achieved a partial or complete response after definitive concurrent chemoradiation. Women diagnosed with FIGO stage IVB, having undergone a previous hysterectomy, or having a history of active autoimmune disease will not be considered eligible.

Primary Endpoint Progression-free survival defined as the time from the date of randomization to the date of first disease progression or death due to any cause, whichever occurs first.

Sample Size A total of 132 patients are expected to be recruited in the study, using a 1:2 (control:experimental arm) randomization allocation ratio.

Estimated Dates for Completing Accrual and Presenting Results The trial was launched in Q2-2019 and the trial is estimated to be closed for recruitment in Q3-2022. Results are expected to be released in Q3-2024.

Trial Registration The trial is registered at ClinicalTrials.gov (NCT03833479).

INTRODUCTION

Cervical cancer is the fourth most common cancer in women worldwide. In 2020, its global incidence was 604 127 and the number of annual deaths 341 831.[1] Approximately 84% of new cervical cancer cases are diagnosed in developing countries due to the lack of effective cervical cancer screening programs and human papillomavirus (HPV) vaccination. HPV can be detected in 99.7% of cervical cancer, particularly the HPV 16 and 18 subtypes. The most common cervical cancer histologic types are squamous cell (70%–80%) and adenocarcinoma, including adenosquamous (20%–25%).[2]

The treatment of newly diagnosed cervical cancer mainly relies on the International Federation of Gynecology and Obstetrics (FIGO) stage. Patients with early-stage disease (FIGO 2018, stage I-IIA (<4 cm)) could be treated with surgery and/or radiotherapy with high cure rates (80%–90% at 5 years). However, those diagnosed with locally advanced cervical cancer (FIGO 2018, stage IB3-IVA) are only candidates for concomitant chemoradiation with the worst prognosis. Concomitant chemoradiation was established as the standard of care in 1999 following the results from five clinical trials which showed an improvement in 5-year overall survival in the concomitant chemoradiation arm compared with radiation alone.[3] According to a Cochrane meta-analysis published in 2010, the concomitant chemoradiation approach showed a global improvement of 6% in 5-year overall survival compared with radiation therapy alone

(hazard ratio (HR) 0.81).[4] It must be stressed that lymph node involvement was not accurately evaluated across most of the trials. This is a remarkable limitation of the meta-analysis since lymph node status is one of the most relevant prognostic factors alongside FIGO stage. Indeed, patients with nodal disease regardless of FIGO stage and patients with FIGO stage III and IV comprise the subgroup of locally advanced cervical cancer who are at greatest risk for recurrence and death from the disease (high-risk locally advanced cervical cancer) and represent the population with the highest unmet need.[5]

Several strategies have been explored to overcome these poor survival outcomes, without great success. Small retrospective cohort studies have shown that performing hysterectomy after concomitant chemoradiation has no significant impact on both overall and disease-free survival.[6] In addition, the role of adjuvant chemotherapy after concomitant chemoradiation in the locally advanced cervical cancer population was evaluated in the OUTBACK trial. Unfortunately, this trial showed no evidence that adding adjuvant chemotherapy after concomitant chemoradiation significantly improved overall survival.[7]

There is fast-growing clinical evidence for the use of immunotherapy in cervical cancer patients, supported by a robust biological rationale. Immune-editing allows HPV-infected cells to overcome immune surveillance, permitting selection of cancer clones with increased resistance to immune detection and elimination resulting in tumor growth. The activation of the PD-1/PD-L1 pathway seems to play an important role in this process. Many authors have demonstrated the overexpression of PD-1/PD-L1 in about 54%–67% and 12% of squamous and adenocarcinoma cervical cancer, respectively.[8]

Several studies have explored the efficacy of immune checkpoint inhibitors monotherapy and as a combination in pre-treated advanced cervical cancer. The KEYNOTE-158 trial included a cohort of 98 patients with advanced cervical cancer, regardless of PD-L1 status, and received treatment with pembrolizumab 200 mg every 3 weeks. The overall response rate was 12.2% in the study population. However, responses were only seen in the PD-L1-positive subgroup, and the duration of response was not reached.[9] As a result, in June 2018, pembrolizumab was approved by the US Food and Drug Administration (FDA) in pre-treated PD-L1-positive cervical cancer. The activity of nivolumab was evaluated in the phase I/II CheckMate-358 study. Nineteen patients with recurrent or metastatic squamous cervical cancer, which had been treated with up to two lines of previous therapies, received nivolumab 240 mg every 2 weeks. The overall response rate was 26.3% with a disease control rate of 68.4%. Responses were observed regardless of PD-L1.[10] Moreover, the efficacy and safety of balstilimab have been investigated in the phase II C-700–01 trial. A total of 161 pre-treated recurrent, persistent, or metastatic cervical cancer patients, regardless of PD-L1 status, were treated with balstilimab 3 mg/kg every 2 weeks, for up to 2 years. The overall response rate was 15%, with an observed median duration of response of 15.4 months. Responses were demonstrated regardless of PD-L1 status.[11] Moreover, the EMPOWER-Cervical-1/GOG-3016/ENGOT-cx9, a phase III study compared cemiplimab (anti-PD1 agent) versus physician choice's chemotherapy in patients with recurrent or metastatic cervical cancer, regardless of PD-L1 status. All patients must have progressed after one prior line of platinum-based treatment. The trial met its primary endpoint and showed cemiplimab improved overall survival compared with chemotherapy (median overall survival: 12.0 vs 8.5 months; HR 0.69).[12]

Beyond showing its superiority after platinum failure, immunotherapy has been moved to the frontline setting. The phase III MK-3475–826/KEYNOTE-826 study evaluated the efficacy and safety of adding pembrolizumab to the platinum-based chemotherapy plus/minus bevacizumab, in the frontline setting. The dual primary endpoints were progression-free survival and overall survival, each tested sequentially in patients with a PD-L1 combined positive score (CPS)≥1%, in the intention-to-treat population, and finally in patients with a PD-L1 CPS≥10%. In patients with a PD-L1 CPS≥1%, median progression-free survival was 10.4 months in the pembrolizumab group and 8.2 months in the placebo group. In the intention-to-treat population, the median progression-free survival was 10.4 and 8.2 months, respectively. Overall survival at 24 months was 53.0% in the pembrolizumab group and 41.7% in the placebo group, and 50.4% and 40.4% in the PD-L1 CPS≥1% and intention-to-treat populations, respectively.[13]

Bearing in mind the proven clinical activity of anti-PD1/PD-L1 agents in pre-treated advanced cervical cancer and the poor prognosis of high-risk locally advanced cervical cancer despite definitive concomitant chemoradiation, the ATOMICC trial was primarily designed to evaluate the role of the anti-PD1 agent, dostarlimab (former TSR- 042), as maintenance therapy after concomitant chemoradiation, aiming at increasing the progression-free survival and subsequently the overall survival of this population.

METHODS

Trial Design

The ATOMICC trial is a phase II, randomized, open-label, multicenter study to assess the efficacy and safety of anti-PD1, dostarlimab, as maintenance therapy in patients with high-risk locally advanced cervical cancer who achieved a partial or complete response after concomitant chemoradiation (Figure 1).

A total of 132 patients will be randomized in a 1:2 ratio (control:-experimental arm) to the treatment as specified below:

- Arm A: no further therapy (clinical and radiological follow-up exclusively).
- Arm B: intravenous dostarlimab. Patients will receive dostarlimab at a fixed dose of 500 mg every 3 weeks for the first four doses followed by dostarlimab at a fixed dose of 1000 mg every 6 weeks for up to 24 months.

Dostarlimab will be administered until documented disease progression, unacceptable toxicity, death, withdrawal of consent, study termination by sponsor or procedure requirements, or completion of 2 years of treatment, whichever occurs first.

Randomization will be stratified on three factors:

- Histology (squamous vs adenosquamous/adenocarcinoma)
- FIGO 2009 stage (IB2, IIA2, and IIB with pelvic positive lymph nodes vs III/ IVA vs any FIGO stage with para-aortic positive lymph nodes)
- Response to chemoradiation (complete response vs partial response).

It is noteworthy that the FIGO staging system 2009 was still valid at the time of ATOMICC trial's design conception. The high-risk

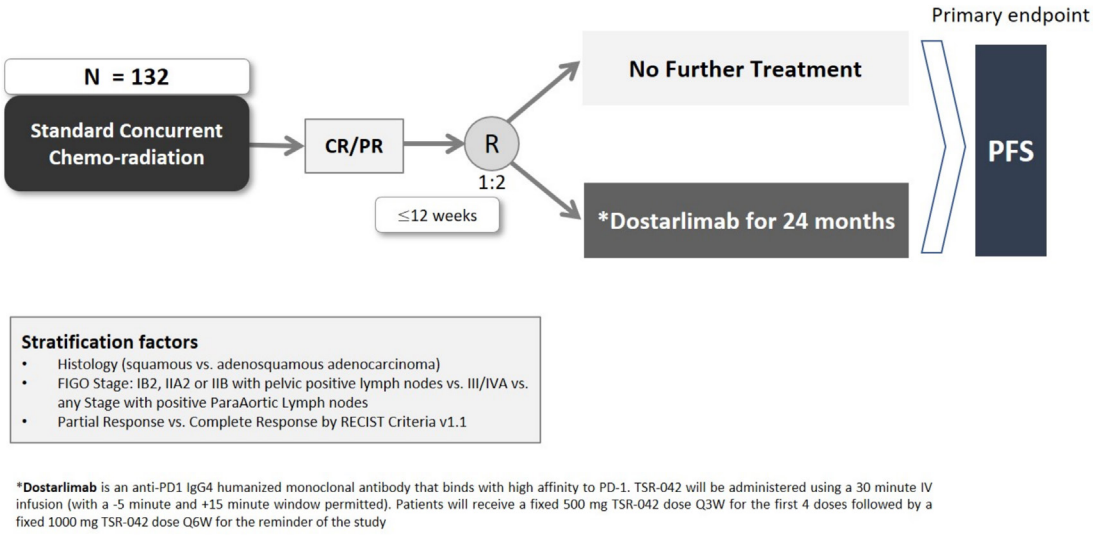

Figure 1 Study design. CR, complete response; PFS, progression-free survival; PR, partial response;

locally advanced cervical cancer patients enrolled in this trial would correspond to the stages IIIA, IIIB, IIIC1, IIIC2, and IVA of the current FIGO staging system 2018.

Participants

Key inclusion and exclusion criteria are shown in Table 1.

Outcomes

The primary endpoint of the study is to evaluate the progression-free survival of patients with high-risk locally advanced cervical cancer who have achieved a partial or complete response after concomitant chemoradiation and received dostarlimab as maintenance therapy. Progression-free survival will be based on tumor assessment performed by the investigators according to the RECIST v1.1. The secondary objectives include overall survival, toxicity assessment, and health-related quality of life. Quality of life will be measured using the Functional Assessment of Cancer Therapy-Cervix, EQ-5D-5L, the PROMIS-Cancer-Fatigue Short Form 4a, and the Brief Pain Inventory. As key exploratory endpoints, we will assess the expression of PD-L1 in tumor-infiltrating lymphocytes and cervical cancer cells and explore the correlation between its expression and clinical outcomes, as well as the relationship between the phenotype of tumor-infiltrating lymphocytes, oncogenic HPV, histological subtypes with stromal immune markers, and clinical outcomes.

Sample Size

The sample size calculation is based on the estimated progression-free survival rate at 2 years, assuming a progression-free survival rate of 45% at 2 years in the control arm and expecting an increase to 59% with the experimental treatment, which corresponds to a HR of 0.66. Using a 1:2 randomization, a total of 132 evaluable patients are required (approximately 44 in the control arm and 88

Table 1 Key inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the cervix	FIGO 2009 stage IVB
At diagnosis: ► FIGO 2009 stages IB2, IIA2, IIB with pelvic lymph node involvement by biopsy-proven, positive nodes by MRI, CT, or PET ► FIGO 2009 stages IIIA, IIIB, IVA ► Any FIGO 2009 stage with para-aortic lymph node involvement by biopsy-proven, more positive nodes by MRI, CT, or PET	Patients who have undergone a previous hysterectomy or will have a hysterectomy as part of their initial cervical cancer therapy
Concomitant chemoradiation with curative intent is mandatory (at least four doses of weekly cisplatin). Brachytherapy permitted	Prior treatment with any anti-VEGF drug, CD137 agonists, or immune checkpoint inhibitors
Patients must have achieved a PR or CR after concomitant chemoradiation	History of autoimmune disease especially when uncontrolled and/or requiring active treatment, or those having recently received therapeutic antibiotics, systemic immunostimulatory agents, or systemic immunosuppressive medications

CR, complete response; CT, computed tomography; FIGO, International Federation of Gynecology and Obstetrics; MRI, magnetic resonance imaging; PET, positron emission tomography; PR, partial response; VEGF, vascular endothelial growth factor.

in the experimental arm). A total 10% dropout rate is assumed. The study will be considered sufficiently mature for final analysis after the observation of 74 progression-free survival events. This number of events provides 80% power, with one-sided type I error of 0.2, for detecting significant superiority of the experimental arm using a stratified log-rank test.

Randomization and Blinding

Patients meeting the eligibility criteria will be randomized using an Interactive Web Response System (IWRS) in a 1:2 ratio to Arm A (control arm) or Arm B (dostarlimab). Subjects will be identified by a unique subject number that will remain consistent for the duration of the study. Once the eligibility of a patient has been confirmed, the investigator should contact the IWRS Centralized Randomization Center for allocation.

Concerning blinding, this trial will be run in an open-label design due to the following considerations:

- The control arm is the current standard of care for women diagnosed with high-risk locally advanced cervical cancer after chemoradiation.
- Progression-free survival is the appropriate primary endpoint for this study based on the eligible study population as it is a reliable surrogate endpoint for overall survival.
- The schedule of study procedures is the same in the control and experimental arms, so equivalent patient assessment and monitoring between arms are ensured.
- Patient-reported outcomes assessment will consist of an exploratory and descriptive analysis

Statistical Methods

Time-to-event endpoints (progression-free survival and overall survival) will be analyzed according to the Kaplan–Meier method. For statistical comparison, the stratified log-rank test on the intention-to-treat population will be primarily used to compare treatment arms using the stratification factors used in randomization. Cox proportional hazards model will be used to calculate the risk reduction. The HR and the associated one-sided 80% confidence interval (CI) and two-sided 95% CI will be reported to evaluate the impact of treatment, stratification variables, and other potential prognostic factors on the time-to-event efficacy endpoints.

To evaluate patient-reported outcomes, the longitudinal analysis will be performed using linear mixed models adjusting for baseline scores.

DISCUSSION

There is still room to improve survival outcomes of women diagnosed with high-risk locally advanced cervical cancer, since approximately half of them will experience a recurrence within 2 years after the standard concomitant chemoradiation. In an effort to improve survival in patients with high-risk locally advanced cervical cancer after concomitant chemoradiation, we have undertaken the ATOMICC/GEICO 78 C trial (NCT03833479), a randomized, open-label, phase II study to assess the efficacy and safety of dostarlimab as maintenance therapy . The study aims to demonstrate that the use of dostarlimab as maintenance therapy would significantly increase progression-free survival in these patients with a target reduction of the hazard of progression or death by 34%, with an acceptable safety profile.

The use of immune checkpoint inhibitors in cervical cancer patients is supported by a strong biological rationale and extensive clinical evidence. All these data have encouraged researchers to explore immunotherapy earlier in the course of the disease, when the host immune system is more robust.The incorporation of immunotherapy after concomitant chemoradiation seems to be one of the best scenarios since takes advantage of an "ideal tumor microenvironment" induced by radiation and cytotoxic agents.[14]

Supporting the ATOMICC trial's approach, the PACIFIC trial reported positive results of durvalumab maintenance treatment in patients with unresectable, stage III non-small cell lung cancer without disease progression after concomitant chemoradiation.[15] Consolidative durvalumab was associated with significant improvements in the primary endpoints of overall survival (HR 0.68) and progression-free survival (HR 0.52). An exploratory 4-year survival analysis demonstrated that consolidative durvalumab provided durable progression-free surviva and sustained overall survival benefit. Although cervical cancer is a different entity, these results support the use of immune checkpoint inhibitors as maintenance therapy following concomitant chemoradiation.

Beyond the ATOMICC trial strategy, two randomized phase III trials are currently assessing the use of concurrent and adjuvant immune checkpoint inhibitors with concomitant chemoradiation, with a comparable study design: CALLA trial (NCT03830866) and KEYNOTE-A18/ENGOT-cx11/GOG-3047 (NCT04221945), with durvalumab and pembrolizumab, respectively. These three trials are directly competing with each other in the same setting of the disease since they are enrolling an identical population of high-risk locally advanced cervical cancer women, namely those with squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma FIGO 2009 stages IB2-IIB node-positive and stage IIIA-IVA with any node stage. However, these studies differ essentially concerning their endpoints. Thus, progression-free survival is the primary endpoint in both the CALLA and ATOMICC trials, and a dual co-primary endpoint – progression-free survival and overall survival – was set in the KEYNOTE-A18 study.

Assuming all these trials will meet their primary endpoints, deciding which is the optimal approach – immune checkpoint inhibitor-throughout treatment or maintenance therapy exclusively – will be a matter of discussion, and evaluating the balance between the efficacy and tolerability of these two approaches will be a crucial factor for this clinical decision.

Either way, immunotherapy will be certainly positioned as a standard of care in the locally advanced cervical cancer setting in the very near future. In this context, our objective is that the therapeutic strategy employed in the ATOMICC trial, using an anti-PD1 as maintenance therapy concomitant chemoradiation, will lead to a significant improvement in the prognosis of patients with high-risk locally advanced cervical cancer with an acceptable toxicity profile, resulting in a new standard of treatment.

Contributors Study design: AO, GV. Assisted in the preparation of the article: all authors. Reviewed the article and provided approval for submission: all authors. Agree to be accountable for all aspects of the work presented: all authors. AO is responsible for the overall content as guarantor.

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Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants and was approved by the Ethics Committee from Vall d'Hebron Hospital, Barcelona, Spainnº de EudraCT 2018-002155-15 Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Commissioned; internally peer reviewed.

Data availability statement No data are available.

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