TPS5600

GOG 3016/ENGOT-cx9 (EMPOWER Cervical-1): An Open-Label, Multi-National, Randomized, Phase 3 Trial of Cemiplimab, an Anti-PD-1, versus Investigator's Choice (IC) Chemotherapy in ≥2 Line Recurrent or Metastatic Cervical Cancer

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Background

Cervical cancer

- The global annual incidence of cervical cancer is approximately 527,000 cases per year, and there were approximately 265,700 deaths in 2012.[1]
- Recurrent and/or metastatic disease occurs in approximately one third of cervical cancer patients in the US and Europe and prognosis remains poor.[2]
- Platinum-based chemotherapy, with or without bevacizumab, is the standard first-line treatment for recurrent and/or metastatic cervical cancer, but offers modest survival benefit.[3]
- Following platinum-based chemotherapy, with or without bevacizumab, median survival is only 7 months.[4]
- There remains an urgent need for effective second-line options.

Cemiplimab

- Cemiplimab (REGN2810) is a high affinity, highly potent, human, hinge-stabilized IgG4 monoclonal antibody, generated using VelocImmune® technology,[5,6] directed against programmed death-1 (PD-1) receptor blocking the interactions of PD-1 with PD ligand-1 (PD-L1) and PD-L2.[7]
- Clinical antibodies that block the interaction between PD-1 and PD-L1 restore the cytotoxic function of tumor antigen-specific T-cells, yielding durable objective responses in multiple cancers.[8]

Preliminary evidence of clinical benefit of PD-1 antibodies in cervical cancer

- Cemiplimab has demonstrated encouraging efficacy and favorable tolerability profile in the phase 1 dose escalation and expansion cohorts for a variety of solid tumors including cervical cancer, cutaneous squamous cell carcinoma, non-small-cell lung cancer, and hepatocellular cancer.[9,10]
- Almost all cervical squamous cell carcinomas are associated with high-risk strains of human papillomavirus, and tumor responses have been observed in cervical cancer patients treated with PD-1 inhibitors.[11]
- Cervical squamous carcinomas may evade immune response by expression of PD-L1, detectable by immunohistochemistry (>5% staining) in 54% (83/154) of squamous tumors, and 14% (7/49) of adenocarcinomas.[12]
- Here, we describe the ongoing Phase 3 study assessing the overall survival (OS) for patients with recurrent or metastatic platinum-refractory cervical cancer treated with either cemiplimab or investigator's choice (IC) of chemotherapy.

Methods

Study design

- This is an open-label, randomized, Phase 3 clinical trial of cemiplimab versus IC chemotherapy in recurrent or metastatic platinum-refractory cervical carcinoma (**NCT03257267**) (**Figure 1**).

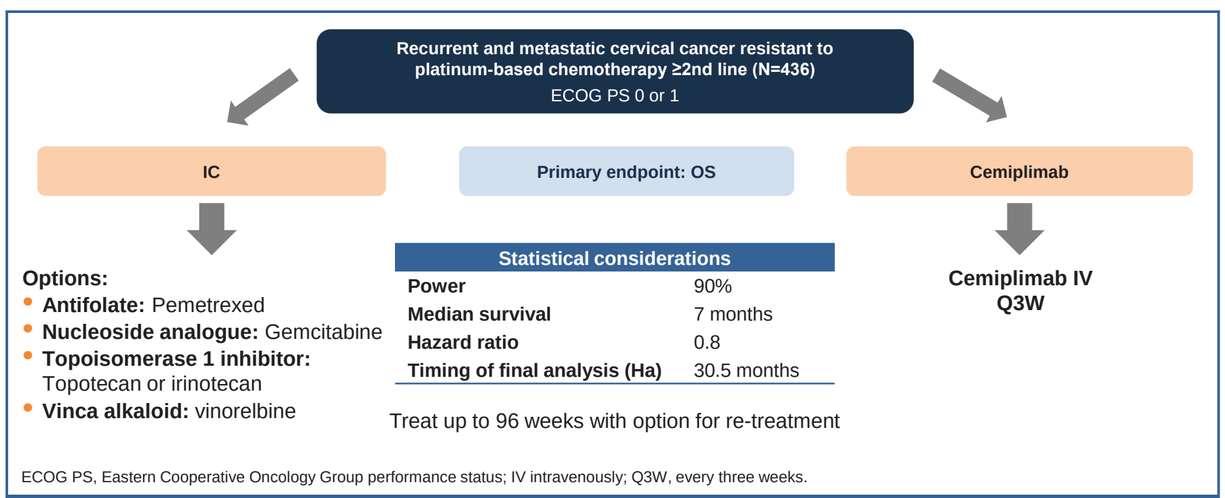

Figure 1. Study design

- Patients will be randomized (1:1) to:
  - Cemiplimab Q3W IV, or
  - IC chemotherapy including one of the following:
    - Pemetrexed 500 mg/m^2 Q3W
    - Gemcitabine 1000 mg/m^2 days 1 and 8, every 21 days
    - Topotecan 1 mg/m^2 daily x 5 days, every 21 days
    - Irinotecan 100 mg/m^2 days 1, 8, 15, and 22, followed by 2 weeks rest, for a 42-day (6-week) cycle
    - Vinorelbine 30 mg/m^2 days 1 and 8, every 21 days.
- Treatments will be given IV for up to 96 weeks
- Tumor imaging is to be conducted on day 42 (±7 days) of cycles 1–4, 6, 8, 10, 12, 14, and 16.
  - To account for differences in drug administration schedules, one cycle is defined as 6 weeks
- Follow-up will continue until death or withdrawal of consent.

Outcome measures

- The primary endpoint is OS (**Table 1**).

Patient eligibility

- Patients must have previously been treated with platinum-based chemotherapy with or without bevacizumab for treatment of recurrent and/or metastatic cervical cancer and subsequently progressed.
- Other key inclusion and exclusion criteria are provided in **Table 2**.

Table 1. Primary, secondary, and exploratory objectives

Primary objective
• To compare **OS** for patients with recurrent or metastatic platinum-refractory cervical cancer treated with either cemiplimab or IC chemotherapy
Secondary objectives
• To compare **PFS** of cemiplimab versus IC chemotherapy
• To compare **ORR** (partial response + complete response) of cemiplimab versus IC chemotherapy per RECIST v1.1[13]
• To compare the **duration of response** of cemiplimab versus IC chemotherapy
• To compare the **safety profiles** of cemiplimab versus IC chemotherapy by describing AEs
• To compare **quality of life** for patients treated with cemiplimab versus IC chemotherapy using the EORTC QLQ-C30
Exploratory objectives
• To measure concentrations of cemiplimab in serum and characterize the **pharmacokinetics** of cemiplimab
• To assess the **immunogenicity** of cemiplimab
• To explore **associations between the clinical efficacy of cemiplimab and molecular features** in tumor samples collected prior to study treatment initiation
• To explore the **pharmacodynamic activity** of cemiplimab on the immune system in peripheral blood samples

AE, adverse event; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; ORR, overall response rate; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

Table 2. Key inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Recurrent, persistent, and/or metastatic cervical cancer, for which there is not a curative-intent option (surgery or radiation therapy with or without chemotherapy). Acceptable histologies are squamous carcinoma, adenocarcinoma, and adenosquamous carcinoma. Sarcomas and neuro-endocrine carcinomas are not eligible histologies	• Ongoing or recent (within 5 years) evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments
• Tumor progression or recurrence within 6 months of last dose of platinum therapy that was used to treat metastatic, persistent, or recurrent cervical cancer†	• Prior treatment with an agent that blocks the PD-1/PD-L1 pathway
• Measurable disease as defined by RECIST 1.1	• Prior treatment with systemic immune modulating agents (other than anti-PD-1/PD-L1 agents) that was within 28 days prior to enrollment, or within 90 days prior to enrollment if there was an immune-related AE, or associated with toxicity that resulted in discontinuation of the immune-modulating agent
• ECOG PS ≤1	• Active or untreated brain metastases
• ≥18 years old	• Immunosuppressive corticosteroid doses (>10 mg prednisone daily or equivalent) within 4 weeks prior to the first dose of cemiplimab
• Life expectancy >12 weeks	• Active infection requiring therapy
• Adequate organ or bone marrow function	• History of pneumonitis within the last 5 years
• Received prior bevacizumab therapy or had clinically documented reason why not administered	• Documented allergic or acute hypersensitivity reaction attributed to antibody treatments
• Received prior paclitaxel therapy or had clinically documented reason why not administered	• Known allergy to doxycycline or other tetracycline antibiotics
	• Concurrent history of malignancy other than cervical cancer within 3 years of first planned dose of cemiplimab, except for tumors with negligible risk of metastasis

†Under review and outcome will be subject to formal trial modification.

Statistical assumptions and analysis

- Key factors relating to study analysis are summarized in **Table 3**.

Table 3. Study analysis: Key factors

Sample size	436
Randomization	Parallel 1:1 assignment (cemiplimab versus IC chemotherapy)
Primary endpoint	OS, defined as the time from randomization to the date of death.
Power	90%
Alpha	1-sided type 1 error rate limited to 0.025
Hazard ratio assumption	0.8 hazard ratio (7 months versus 8.75 months)
Assumed dropout rate	10%
Events needed	330 deaths
Duration	32 months (20 months enrollment; 12 months follow-up after enrollment)

- Patients will be stratified for the primary efficacy analysis by histology and geographic region.
  - Stratification factors will include prior bevacizumab use, histology, and ECOG performance status.
- An independent data monitoring committee will monitor safety data during the study conduct.

Summary

- There is an unmet need for systemic therapy options for patients with platinum-resistant, recurrent, and metastatic cervical cancer.
- Cemiplimab is a hinge-stabilized IgG4 PD-1 monoclonal antibody with suggested activity in cervical cancer, cutaneous squamous cell carcinoma, non-small-cell lung cancer, and hepatocellular cancer.
- Preliminary clinical data demonstrate efficacy of PD-1 blockade against cervical cancer.
- This prospective, randomized, Phase 3 clinical trial of PD-1 inhibition with cemiplimab is warranted for patients with recurrent/metastatic cervical cancer to potentially improve OS.
- This study is ongoing and is actively enrolling patients.

References

1. Ferlay J, Soerjomataram I, Ervik M, et al. http://globocan.iarc.fr, accessed on May 10, 2018.
2. American Cancer Society. https://www.cancer.org/cancer/cervical-cancer/detection-diagnosis-staging/survival.html, accessed May 10, 2018.
3. Boussios S, Seraj E, Zarkavelis G, et al. *Crit Rev Oncol Hematol*. 2016;108:164–174.
4. Lorusso D, Ferrandina G, Pignata S, et al. *Ann Oncol*. 2010;21:61–66.
5. Macdonald LE et al. *Proc Natl Acad Sci*. 2014;111:5147–5152.
6. Murphy AJ et al. *Proc Natl Acad Sci*. 2014;111:5153–5158.
7. Burova E et al. *Mol Cancer Ther*. 2017;16:861–870.
8. Caldwell Jr C, et al. *Sci Rep*. 2017;7:13682.
9. Papadopoulos KP, Crittenden M, Johnson, M, et al. *J Clin Oncol*. 2016;34:3024.
10. Papadopoulos KP et al. *J Clin Oncol*. 2017;35(suppl;abstr 9503).
11. Gillison ML, Blumenschein G, Fayette J, et al. *J Clin Oncol*. 2017;35:6019–6019.
12. Heeren AM, Punt S, Bleeker MCG, et al. *Mod Pathol*. 2016;29:753–763.
13. Eisenhauer EA, Therasse P, Bogaerts J, et al. *Eur J Cancer*. 2009;45:228–247.

Acknowledgments

We thank the patients, their families, all investigators involved in this trial in progress, and all personnel involved with the study at the study sites. The study is funded by Regeneron Pharmaceuticals, Inc., and Sanofi. Medical writing support and typesetting was provided by Emmanuel Ogunnowo of Prime, Knutsford, UK, funded by Regeneron Pharmaceuticals, Inc., and Sanofi.

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Poster presented at the 2018 American Society of Clinical Oncology Annual Meeting, June 1–5, Chicago, Illinois.