Clinical Trial Protocol

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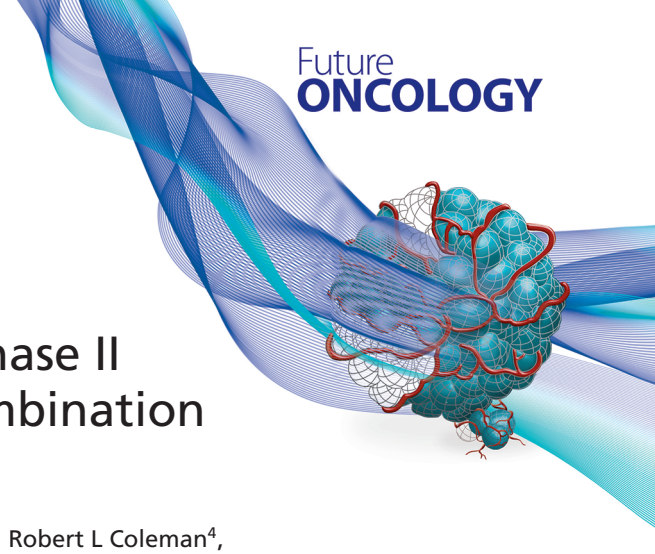

RaPiDS (GOG-3028): randomized Phase II study of balstilimab alone or in combination with zalifrelimab in cervical cancer

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Balstilimab (anti-programmed death 1) and zalifrelimab (anti-CTLA-4) are two new checkpoint inhibitors that have emerged as promising investigational agents for the treatment of cervical cancer, particularly in the setting of previously-treated, recurrent/metastatic disease. Here we describe the rationale and design of RaPiDS (NCT03894215), a two-arm Phase II study evaluating the safety, tolerability and efficacy of balstilimab administered alone or in combination with zalifrelimab in patients with advanced cervical cancer who progressed after first-line, platinum-based chemotherapy. Patients will be randomized in a 1:1 ratio. The primary end point is objective response rate, and key secondary objectives include safety, duration of response, progression-free survival, overall survival and quality of life outcomes.

Lay abstract: Current treatment options for women with recurrent/metastatic cervical cancer are limited. Immunotherapy is altering the therapeutic landscape in this setting yet opportunities remain to improve on current outcomes. Dual blockade of different immune checkpoints is an approach shown to be highly effective in other cancers. Balstilimab (anti-programmed death 1) and zalifrelimab (anti-CTLA-4) are two new checkpoint inhibitors showing promise in patients with advanced cervical cancer. The RaPiDS trial is designed to characterize the safety and activity of balstilimab, alone and in combination with zalifrelimab, in patients with recurrent/metastatic cervical cancer who progressed after prior platinum-based chemotherapy.

Clinical trial registration: NCT03894215 (ClinicalTrials.gov)

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Keywords: balstilimab • cervical cancer • CTLA-4 • immuno-oncology • PD-1 • zalifrelimab

Cervical cancer is the most common gynecologic malignancy and fourth leading cause of cancer mortality in women worldwide, responsible for an estimated 570,000 new cases and 311,000 deaths in 2018 alone [1]. Approximately 90% of cases occur in lower-resource countries, where incidence and mortality rates continue to increase [2]. This is in stark contrast to higher resource countries where dramatic reductions in these measures following the

implementation of screening have been observed. It is anticipated that widespread adoption of human papillomavirus vaccination programs will also have considerable impact [3]. However, the number of patients who still succumb to their disease has largely remained stagnant over the last two decades, primarily due to a lack of progress in the treatment of advanced and/or recurrent disease [4].

The outlook for women diagnosed with early-stage tumors (i.e., FIGO IB1–2) is good, with the 5-year survival rate for localized disease being >90% following radical hysterectomy with lymphadenectomy and adjuvant therapy according to established clinicopathologic criteria [5]. Similarly, many women with local advanced disease (i.e., FIGO stage IB3-IVA) can be rendered disease free with cisplatin-based chemoradiation and high-dose-rate intracavitary brachytherapy. However, the prognosis for those with recurrent cervical cancer who are not candidates for pelvic exenteration with urinary diversion as well as those who present with metastatic disease (i.e., FIGO stage ICB) remains particularly poor, as evidenced by median 5-year overall survival (OS) at just 17% [5]. For such patients, the foundation of standard-of-care is chemotherapy using a platinum-based combination regimen, most commonly the cisplatin-paclitaxel doublet [6]. Unfortunately, treatment is typically administered with palliative intent and has reached a plateau of effectiveness with respect to survival. In 2014, bevacizumab became the first targeted agent to be approved for use alongside platinum-based chemotherapy for the treatment of persistent, recurrent or metastatic cervical cancer [7]. This was based on the findings of the pivotal GOG 240 study, where addition of bevacizumab improved median OS by 3.7 months compared with chemotherapy alone [8]. However, its availability and cost are prohibitive for many low- and middle-income countries despite the availability today of biosimilars [9]. Moreover, patients treated with doublet chemotherapy, with or without bevacizumab, ultimately progress and optimal second-line and later options in this setting are limited [10].

Immunotherapy has revolutionized cancer treatment for multiple tumor types and agents targeting the programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) immune checkpoint pathway have now emerged as promising candidates for altering the cervical cancer therapeutic landscape [11–13]. Cervical cancer has a number of immunogenic characteristics that support it being amenable to immunotherapeutic interventions [13]. These include a virally-induced pathogenesis (human papillomavirus antigens), high tumor mutational burden (TMB) and frequency of neoantigen formation, high grade tumor infiltration (particularly $CD8^+$ cytotoxic T lymphocytes and macrophages), and amplifications in multiple checkpoint-controlling targets including PD-L1 [14–17]. Accordingly, multiple clinical trials evaluating the potential utility of targeted checkpoint antibodies (Abs) for cervical cancer treatment have been conducted since 2015, and numerous others are ongoing [13]. A significant advance was made with accelerated approval of the anti-PD-1 Ab pembrolizumab by the US FDA in 2018 for patients with PD-L1-positive, recurrent/metastatic cervical cancer following disease progression on or after chemotherapy. Approval was based on the KEYNOTE-158 study, where the objective response rate (ORR) was 14.3% and median duration of response (DOR) not reached in a cohort of PD-L1-positive patients with previously treated disease [18]. Along with a differentiated safety profile, the ORRs observed with pembrolizumab were similar or better than those achieved with currently used second-line therapies, which range between 4 and 14% [10].

Despite this progress, only a minority of patients respond to pembrolizumab monotherapy, and responses are limited to individuals with PD-L1-positive tumors [18]; thus, considerable opportunity exists to improve on these outcomes. In this regard, dual-targeted immunotherapy is a validated and effective strategy to increase the proportion of patients who achieve durable responses over anti-PD-1 monotherapy alone [19], typically involving the addition of Abs directed to cytotoxic T lymphocyte-associated protein 4 (CTLA-4) [20]. Mechanistically, PD-1/PD-L1 blockade restores the responsiveness of reactive T cells that become inactivated following chronic stimulation within the tumor microenvironment [21]. Alternatively, inhibition of CTLA-4 signaling promotes effector T-cell activation as well as reducing the suppressive activity of Treg, resulting in enhanced antitumor immunity [22]. The best characterized and clinically successful anti-PD-1/CTLA-4 combination is nivolumab plus ipilimumab, indicated for use in an increasing number of tumor types including melanoma, non-small-cell lung cancer, renal cell carcinoma, hepatocellular carcinoma, mesothelioma and colorectal cancer (reviewed in [20,23]). In multiple trials, combination treatment was shown to have synergistic effects on activation of antitumor immunity that resulted in higher response rates, greater durability and extended survival times as compared with monotherapy [23]. However, the addition of ipilimumab also led to an increased incidence of immune-mediated toxicities relative to those seen with nivolumab alone [24]. These safety concerns have now largely been mitigated by dose and schedule modifications, in particular lower and less frequent dosing of ipilimumab. Evaluation of other immunomodulatory combinations remains a highly active area of clinical endeavor [20] designed to optimize antitumor immunity as

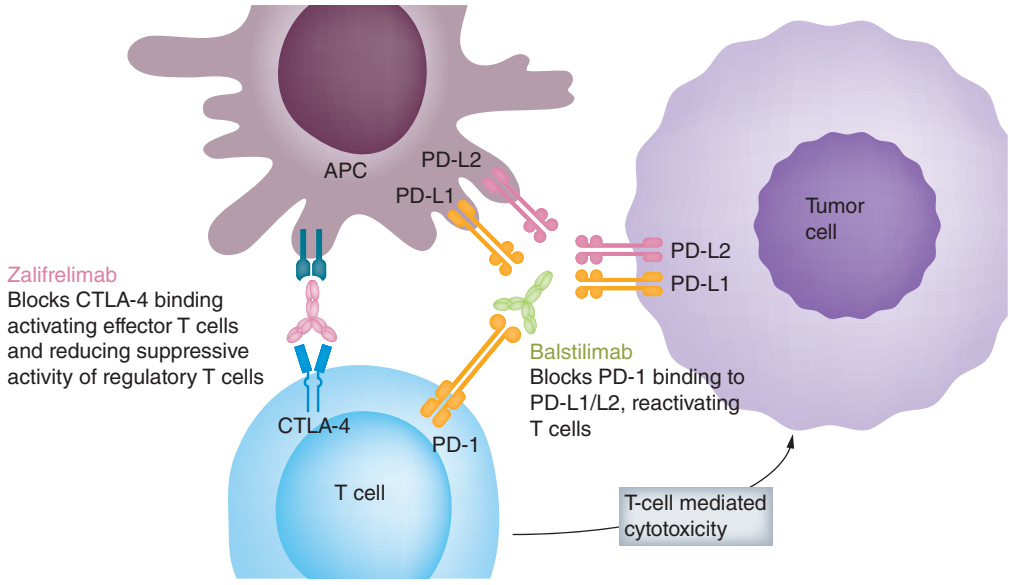

Figure 1. Balstilimab and zalifrelimab mechanisms of action.
APC: Antigen-presenting cell.

well as identify newer agents that preserve the superior efficacy of dual PD-1/CTLA-4 inhibition with favorable tolerability.

Balstilimab & zalifrelimab

Balstilimab (AGEN2034) is a human IgG4 anti-PD-1 monoclonal Ab (mAb) that binds with high affinity to human PD-1, designed to prevent the interaction between the receptor and its ligands PD-L1/PD-L2 [25]. By functioning as an PD-1 antagonist, balstilimab enhances T-cell receptor signaling and T-cell responsiveness to tumor-associated antigens (including neoantigen-specific responses) under conditions of T-cell receptor stimulation (Figure 1).

Zalifrelimab (AGEN1884) is a CTLA-4-targeting human IgG1 mAb that antagonizes the inhibitory checkpoints of immune cell activation regulated by CTLA-4 signaling (Figure 1) [26]. Preclinically, zalifrelimab has been shown to potentiate the activity of other immunomodulatory Abs (including balstilimab) *in vitro* and *in vivo*, and to effectively combine with PD-1 inhibition to elicit T cell-associated proliferative responses in nonhuman primate models [26]. In addition, zalifrelimab has exhibited encouraging signals of activity and favorable tolerability when administered as monotherapy to patients with PD-1 refractory solid tumors [27], further underscoring its potential as a suitable partnering agent for combination-based immunotherapy.

The RaPiDS study

Here we describe the design of the RaPiDS trial (NCT03894215), a randomized, blinded, two-arm Phase II study assessing the efficacy and safety of balstilimab alone (monotherapy) or with zalifrelimab (combination therapy) in patients with recurrent/metastatic cervical cancer who had relapsed or progressed following first-line, platinum-based chemotherapy. The trial is funded by Agenus, Inc., and is being conducted in collaboration with GOG-Partners (USA).

Background & rationale

The first-in-human, Phase I evaluation of single-agent balstilimab in patients with locally advanced or metastatic solid tumors established the recommended Phase II dose as 3 mg/kg, administered once every 2 weeks [28]. The safety profile of balstilimab was manageable and consistent with that reported for other PD-1 inhibitors, with the most frequently observed immune-related adverse events (irAEs; involving the gastrointestinal, endocrine and pulmonary systems) as anticipated for this drug class [29]. No dose-limiting toxicities were reported during escalation. Balstilimab showed early signals of efficacy across the 50-patient study population, including an overall ORR of 6% (three partial responses [PRs], in patients with cervical, breast and ovarian cancer) [25].

Planned Phase II expansion of balstilimab monotherapy was conducted as a single-arm trial assessing safety and efficacy in patients with recurrent/metastatic cervical cancer who had relapsed after a prior platinum-based treatment regimen (NCT03104699). In this study, the largest reported dataset for patients with advanced cervical cancer treated with a PD-1 inhibitor to date, balstilimab elicited meaningful clinical activity with favorable tolerability [30]. In an efficacy-evaluable cohort of 140 patients, the primary end point of confirmed ORR was 15%, including five complete responses (CRs; 3.6%) and 16 PRs (11.4%). Responses were durable, as evidenced by a median DOR of 15.4 months. In contrast to other PD-1 inhibitors evaluated in this disease setting [18,31,32], tumor responses to balstilimab occurred irrespective of tumor PD-L1 status or histology. Importantly, these observations suggest possible functional differentiation for balstilimab from other approved agents and a potential opportunity to extend the therapeutic reach of immune checkpoint blockade to a greater proportion of cervical cancer patients. Consistent with the Phase I experience, balstilimab had a manageable safety profile, characterized by low rates of grade 3/4 treatment-related toxicities (11.8%), infusion-related reactions and irAEs (primarily endocrine and gastrointestinal) that were again typical of checkpoint inhibitor therapies [29]. These efficacy and safety outcomes additionally identified balstilimab as an attractive candidate for use as a backbone in combination-based therapeutic approaches.

An independent Phase II trial evaluating the combination of balstilimab with zalifrelimab in a study population with the same enrollment criteria was initiated (NCT03495882), designed to assess the feasibility of dual immune checkpoint blockade for further improving clinical outcomes in these patients. Balstilimab was intravenously (iv.) dosed at 3 mg/kg once every 2 weeks, and zalifrelimab at 1 mg/kg once every 6 weeks (Q6W). Despite the caveat of an indirect cross-trial comparison, interim results reported for the two parallel studies performed in subjects with previously treated, recurrent/metastatic disease suggested that the addition of zalifrelimab to balstilimab could induce numerically higher efficacy measures over balstilimab alone – including superior ORRs, CR and PR rates, and durations of response [33]. These data support the hypothesis that combined anti-PD-1/CTLA-4 inhibition enhances antitumor activity compared with PD-1 blockade alone in advanced cervical cancer. In terms of safety, the overall rate of treatment-related adverse events were similar to that seen with balstilimab monotherapy, although a higher incidence of endocrine-related irAEs (hypo and hyperthyroidism; primarily grades 1/2) were observed with the combination. Collectively, the findings indicate that balstilimab has promising activity and tolerability as second-line treatment for patients with recurrent/metastatic cervical cancer and provide a rationale for further evaluation of this novel agent, both alone and in combination with zalifrelimab, in a randomized controlled trial in this setting.

Design

Study design

RaPiDS is a randomized, noncomparative, two-arm Phase II trial (Figure 2). During the screening phase, determination of patient eligibility, baseline characteristics, disease evaluation and clinical assessments are performed. Approximately 210 patients (target enrollment) will be randomized 1:1 into one of two arms as follows:

- Arm 1: balstilimab monotherapy plus placebo
- Arm 2: balstilimab plus zalifrelimab

Treatment is permitted for up to 24 months, or until disease progression (per Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1 as assessed by a blinded Independent Radiology Review Committee [IRRC]), development of unacceptable toxicity or any other protocol-defined criterion for withdrawal occurs. All patients who discontinue treatment will be followed for up to an additional 24 months from last dose or until death, withdrawal of consent, or becoming lost to follow-up. A safety follow-up visit will occur approximately 4 weeks after the last dose of trial treatment or before the start of any subsequent anticancer therapy, whichever comes first. Patients who discontinue study treatment for reasons other than progressive disease will continue follow-up visits (with associated evaluations) every 3 months until progression/start of a new therapy for up to 24 months. For survival follow-up, patients will be contacted every 2 months to assess survival, poststudy treatments and response. The end of the trial is defined as 24 months after the last patient has received the final planned treatment dose.

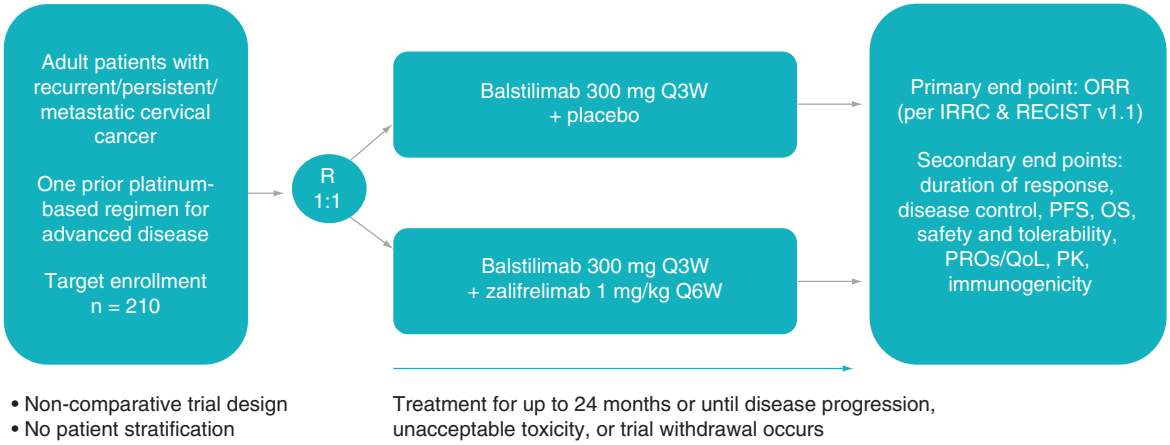

Figure 2. RaPiDS study design schema. The trial opened in June 2019 with an anticipated end date (including last patient follow-up) in 2024.
IRRC: Independent Radiology Review Committee; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; PK: Pharmacokinetics; PRO: Patient-reported outcome; Q3W: Once every 3 weeks; Q6W: Once every 6 weeks; QoL: Quality of life; R: Randomization; RECIST: Response Evaluation Criteria in Solid Tumors.

Key eligibility criteria

Eligible patients (≥18 years of age) are required to have a histologically or cytologically confirmed diagnosis of squamous-cell carcinoma, adenosquamous carcinoma or adenocarcinoma of the cervix, with metastatic, persistent and/or unresectable disease at the time of enrollment. Patients must have relapsed after a platinum-based treatment (first line) regimen for advanced (recurrent, unresectable or metastatic) disease. Patients are also required to have at least one lesion that meets the definition of measurable disease by RECIST v1.1, life expectancy of at least 3 months, an Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate hematologic, hepatic and renal function.

Patients meeting any of the following criteria are excluded: cervical cancer diagnosis of clear cell carcinoma, minimal deviation adenocarcinoma, gastric type adenocarcinoma or mesonephric carcinoma; prior therapy with an immune checkpoint inhibitor (e.g., anti–PD-1, anti–PD-L1 or anti–CTLA-4 Abs); more than one systemic treatment regimen for advanced cervical cancer; known severe hypersensitivity reactions to fully human mAbs, history of anaphylaxis or uncontrolled asthma; persisting toxicity related to prior therapy grade >1 severity (sensory neuropathy or alopecia of grade ≤2 is acceptable); active, or history of, autoimmune disease that required immunosuppressive systemic treatment within 2 years of the start of trial treatment; and received systemic corticosteroid therapy ≤7 days prior to the first dose of study drug or receiving any other form of systemic immunosuppressive medication.

Dose & schedule of therapy

Patients enrolled in arm 1 (balstilimab monotherapy) will receive iv. balstilimab 300 mg (flat dosing) once every 3 weeks (Q3W) and patients in arm 2 (combination therapy) will receive balstilimab 300 mg Q3W plus iv. zalifrelimab 1 mg/kg once every 6 weeks (Q6W). Pharmacokinetics (PK) modeling showed that the 300-mg Q3W balstilimab regimen being used in this trial has equivalent exposure to the recommended Phase II dose (3-mg/kg Q2W), and with a more convenient schedule for patients. For those in arm 1, placebo will be administered with balstilimab at time points that correspond to zalifrelimab dosing in arm 2. The blinded portion of the study applies to whether zalifrelimab or placebo is administered; balstilimab dosing is not blinded. Dosing and treatment schedules across both regimens are presented in Figure 3. The duration of each treatment cycle is 6 weeks and includes two dosing events, one on day 1 and another on day 22. On day 1 of the cycle, patients assigned to arm 1 will be dosed with balstilimab followed by placebo. Patients assigned to arm 2 will be dosed with the combination of balstilimab and zalifrelimab. Balstilimab will be administered first followed by either zalifrelimab or placebo. On day 22 of each cycle, all patients in both treatment arms will receive balstilimab only.

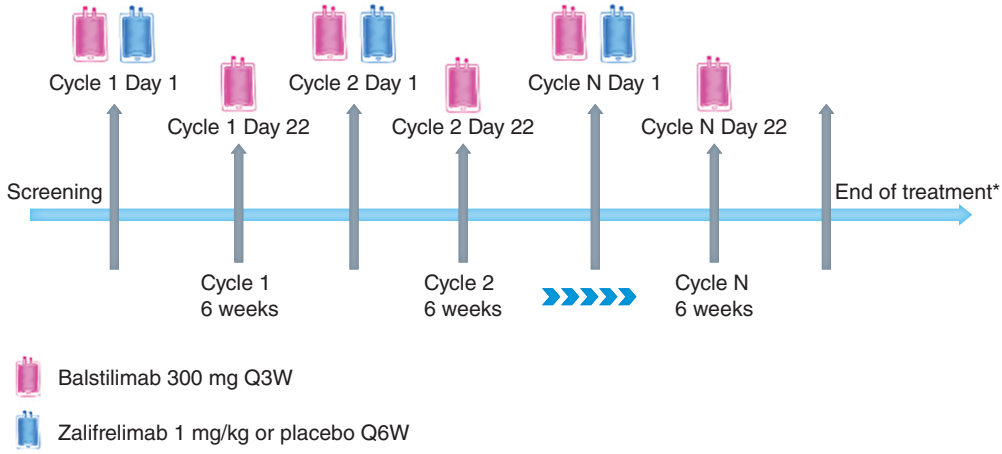

Figure 3. Treatment cycle dosing schema.
*Treatment up to 24 months, disease progression, unacceptable toxicity or trial withdrawal.
Q3W: Once every 3 weeks; Q6W: Once every 6 weeks.

Box 1. RaPiDS study end points.

Primary end points
- ORR, per RECIST v1.1 and determined by IRRC, for each treatment arm.

Secondary end points
- Efficacy: duration of response, stable disease, duration of stable disease and disease control rate – as determined by IRRC and investigators per RECIST v1.1.
- PFS, determined by IRRC and investigators per RECIST v1.1.
- Overall survival.
- Safety and tolerability.
- Time to confirmed progression per iRECIST, determined by investigator.
- PK parameters for balstilimab and zalifrelimab.
- Immunogenicity of balstilimab administered with placebo or zalifrelimab.
- Quality of life/patient-reported outcomes (FACT-Cx and BPI).

Exploratory end points
- Association of tumor PD-L1 expression with response.
- Association of TMB with response.
- Change in TCR repertoire from baseline and from trough.

BPI: Brief pain inventory; FACT-Cx: Functional assessment of cancer therapy – cervix; iRECIST: Immune RECIST; IRRC: Independent Radiology Review Committee; ORR: Objective response rate; PD-L1: Programmed death ligand 1; PFS: Progression-free survival; PK: Pharmacokinetics; RECIST: Response Evaluation Criteria in Solid Tumors; TCR: T-cell receptor; TMB: Tumor mutational burden.

Primary & secondary objectives

The primary objective of the study is to assess the ORR, determined by the IRRC and according to RECIST v1.1, in patients randomized to balstilimab monotherapy or combination treatment (Box 1). The ORR for each treatment arm will be quantified as the binomial proportion of intent-to-treat (ITT) patients with a best overall response of CR or PR. The study is not intended to formally compare the efficacy of the two experimental arms; findings for each arm will be evaluated against relevant historical controls (outcomes seen with chemotherapeutic regimens used in the second-line management of metastatic cervical cancer per clinical practice guidelines [34]) as appropriate. Key secondary objectives include DOR, disease control rate, progression-free survival, OS, safety and tolerability, PK, immunogenicity, and patient-reported outcomes (Box 1). Association of clinical responses with PD-L1 ligand expression or TMB will be assessed as exploratory end points.

Evaluations

Tumor response per RECIST v1.1 and based on blinded independent review will be used for the primary end point (ORR) analysis. Radiographic tumor evaluation by computed tomography or MRI of the chest, abdomen and pelvis

is performed within 21 days prior to the first dose of study treatment, and Q6W from the first dose until disease progression. The same imaging technique used at screening is required for all subsequent radiographic evaluations. In addition to the Investigator, radiographic scans are reviewed centrally by an IRRC, which determines whether criteria for tumor response or progression have been met. Patients may continue treatment beyond progressive disease per investigator's discretion and sponsor agreement.

Safety is continuously assessed by evaluating adverse events, including serious adverse events and deaths, as well as toxicities determined through changes in vital sign and clinical laboratory parameters. The adverse event reporting period begins from the time of patient consent through the end-of-treatment safety visit (4 weeks after last study drug dose and 90 days for a related adverse event). Grading is based on National Cancer Institute Common Terminology Criteria for Adverse Events v5.0. Adverse events of special interest for safety monitoring include infusion-related reactions, elevations in hepatic enzymes and any considered potentially immune related.

Blood samples are collected at various time points for PK and immunogenicity analyses. PK parameters being estimated for balstilimab and zalifrelimab include maximum and trough serum concentrations, clearance, half-life, volume of distribution, and area under the concentration-time curve. Quality of life patient-reported outcomes are assessed using Functional Assessment of Cancer Therapy - Cervix and Brief Pain Inventory questionnaires. Candidate predictive biomarkers being investigated in tumor tissue (archival tumor samples or fresh biopsy from previously nonirradiated lesions) include PD-L1 expression and TMB.

Statistical analyses

Planned enrollment into the ITT population is approximately 210 patients, allowing for attrition to provide at least 100 evaluable patients in each arm. All patients who receive any experimental treatment will be included in the safety and efficacy analyses. The primary end point of ORR, quantified as the binomial proportion of ITT patients with a best overall response of confirmed CR or PR according to RECIST 1.1, will be estimated for each arm along with a two-sided, 95% Wilson Score CI. With 100 patients randomized to each treatment modality, this approach has 90% power to detect a true ORR of $\geq$22.1 and $\geq$28.2% in the monotherapy and combination arms, respectively. The two treatment arms will be not be compared. The secondary end points of DOR, progression-free survival and OS will be summarized using the Kaplan–Meier method, with corresponding 95% CIs. Both noncompartmental and compartmental modeling techniques will be used to analyze PK. For other continuous end point data, descriptive statistics (including sample size, mean, median, standard deviation, minimum and maximum values) will be determined. For categorical variables, the number and percentage of patients in each category will be provided.

Conclusion

The RaPiDS trial described here is investigating the clinical activity and tolerability of balstilimab both as monotherapy and in combination with zalifrelimab in previously-treated patients with advanced cervical cancer. The results of this study will help define a role for these novel immunomodulatory agents in the second-line management of relapsed/metastatic disease, with potential to improve outcomes in this difficult-to-treat patient population.

Executive summary

Background

- Cervical cancer is the most common female genital tract malignancy and fourth leading cause of cancer mortality in women worldwide, responsible for more than 311,000 deaths annually.
- For patients diagnosed with recurrent/metastatic disease, treatment options beyond palliative platinum-based chemotherapy are limited and typically administered without expectation of cure.
- Targeting the programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) immune checkpoint pathway has provided an important advance in the treatment of patients with advanced cervical cancer; however opportunities remain to improve on current outcomes.
- Among these, dual blockade of the PD-1/PD-L1 and CTLA-4 immune checkpoints represents a rational, combination-based therapeutic strategy, as this approach has been shown to be highly effective in multiple tumor types.

Balstilimab

- Balstilimab (AGEN2034) is a human IgG4 anti-PD-1 monoclonal antibody (Ab) with meaningful and durable clinical activity in patients with metastatic, persistent or recurrent cervical cancer.

- In contrast to other inhibitors of the same class, tumor responses occurred irrespective of tumor PD-L1 status or histology; indicating a potential opportunity to extend the therapeutic reach of immune checkpoint blockade to a greater proportion of patients.

Zalifrelimab

- Zalifrelimab (AGEN1884) is a human IgG1 anti-CTLA-4 monoclonal Ab that has been shown to potentiate the activity of other immunomodulatory Abs, including balstilimab, in preclinical models.
- Zalifrelimab has shown encouraging efficacy and tolerability in early phase clinical evaluations, including in PD-1/PD-L1-refactory patients, further underscoring its potential as a suitable partnering agent for combination-based immunotherapeutic approaches.

RaPiDS study

- A randomized, two-arm Phase II trial to assess the safety and efficacy of balstilimab alone and in combination with zalifrelimab in women with recurrent/metastatic cervical cancer who relapsed or progressed following first-line, platinum-based chemotherapy.
- Patients are randomized 1:1 to receive balstilimab monotherapy or balstilimab in combination with zalifrelimab.
- The primary end point is overall response rate for each treatment arm.

Conclusion

- The results of this trial will help define the role of these novel immunomodulatory agents as potential new treatment options for a patient population with significant unmet clinical need.

Supplementary data

An infographic accompanies this paper and is included at the end of the references section in the PDF version. To view or download this infographic in your browser please click here: www.futuremedicine.com/doi/suppl/10.2217/fon-2021-0529

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Financial & competing interests disclosure

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Papers of special note have been highlighted as: • of interest; •• of considerable interest

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RaPiDS (GOG-3028): Randomized Phase II study of balstilimab alone or in combination with zalifrelimab in cervical cancer

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Trial registration no:
NCT03894215

Article URL
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Primary objective

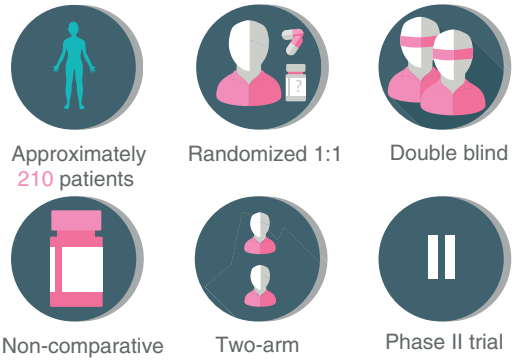
Primary objective

To evaluate ORR, per RECIST v1.1 and assessed by IRRC, for balstilimab plus placebo (monotherapy) and in combination with zalifrelimab

Secondary key objectives

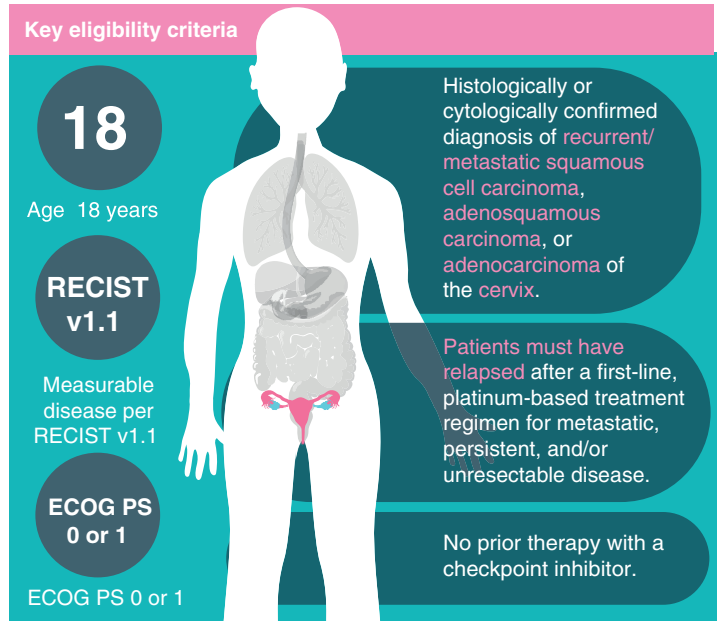
- To confirm the safety and tolerability of balstilimab as monotherapy and in combination with zalifrelimab
- To determine PFS, assessed by IRRC and investigators, for balstilimab monotherapy and in combination with zalifrelimab
- To assess DOR, per RECIST v1.1 and assessed by IRRC, for balstilimab monotherapy and in combination with zalifrelimab
- To evaluate OS for balstilimab monotherapy and in combination with zalifrelimab

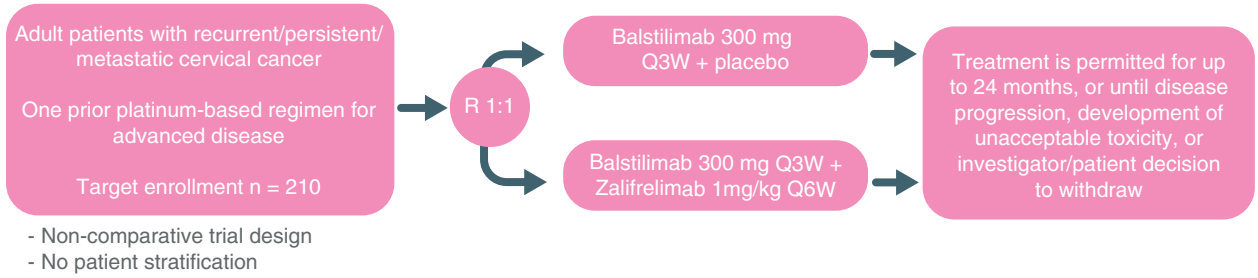
Study design and treatment



- In Arm 1, placebo will be administered with balstilimab at corresponding time points to zalifrelimab dosing in Arm 2.
- The blinded portion of the study applies to whether zalifrelimab or placebo is administered; balstilimab dosing is not blinded.
- Each treatment cycle is 6 weeks.

Key eligibility criteria





- Non-comparative trial design
- No patient stratification

Outcome measures/end points

Primary end point:
ORR for each treatment arm

Key secondary end points:
DOR, DCR, PFS, OS, safety and tolerability for each treatment arm

Exploratory end points:
Association of tumor PD-L1 expression with response; Association of TMB with response

Glossary

DCR: Disease control rate; DOR: Duration of response; IRRC: Independent Radiology Review Committee; IV: Intravenously; ECOG PS: Eastern Cooperative Oncology Group performance status; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; PD-L1: Programmed death ligand 1; Q3W: Once every three weeks; Q6W: Once every 6 weeks; RECIST: Response Evaluation Criteria in Solid Tumors; TMB: Tumor mutational burden