B A R M C C A P F

A Nonrandomized Controlled Trial

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IMPORTANCE

Globally, cervical cancer is one of the most common and lethal gynecologic cancers.[1] Most cervical cancers are driven by the human papillomavirus (HPV),[2] which has been linked to the upregulation of transforming growth factor β (TGF-β) signaling.[3]

The preferred first-line treatment for patients with persistent, recurrent, or metastatic cervical cancer whose tumors express programmed cell death 1 ligand 1 (PD-L1) is pembrolizumab plus platinum-based chemotherapy, with or without bevacizumab, based on the results of the KEYNOTE-826 trial.[4] However, as pembrolizumab is restricted to those whose tumors express PD-L1, most patients with recurrent or metastatic disease are typically treated with chemotherapy, often with poor response rates and a short duration of response (DOR).[5]

For patients with recurrent or metastatic cervical cancer with disease progression during or after platinum-based chemotherapy, second-line treatment options include cytostatic agents, such as vinorelbine, topotecan, gemcitabine, pemetrexed, or nanoparticle albumin-bound paclitaxel; however, response rates are low (5% to 29%), with short DORs ranging from 2.1 to 5 months.[5] As a result, there is no established consensus for second-line treatment, and better treatment options are needed.[5]

While there is no globally accepted standard-of-care treatment for recurrent or metastatic cervical cancer after first-line systemic therapy, the therapeutic landscape is rapidly evolving. Immunotherapy agents, such as pembrolizumab[6] and cemiplimab,[7] have shown clinical activity in patients with recurrent or metastatic cervical cancer. Despite the promise of immunotherapies, the limited response rates (particularly in monotherapy) as well as first-line treatment eligibility being restricted to PD-L1 expression leave significant room for improvement.

Recent studies have investigated the potential of dual-inhibition approaches and bispecific immunotherapies for recurrent or metastatic cervical cancer. Ipilimumab plus nivolumab has shown promising clinical activity compared with nivolumab monotherapy,[8] while cadonilimab—a bispe-

reporting guideline. All patients provided written informed consent before enrolling in the study.

P E C

Key inclusion criteria were recurrent or metastatic cervical cancer (irrespective of PD-L1 tumor expression) with disease progression during or after the prior platinum-containing chemotherapy, measurable disease, an Eastern Cooperative Oncology Group performance status of 0 or 1, and a life expectancy of 12 weeks or more. Key exclusion criteria were active central nervous system metastases causing clinical symptoms or requiring therapeutic intervention, interstitial lung disease, or a history of pneumonitis that required oral or intravenous steroids. There was no limit on the number of previous courses of therapy allowed, but prior PD-1 inhibitor therapy was not permitted.

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The primary study end point was the confirmed objective re-

PD-L1–positive tumors vs PD-L1–negative tumors (17.5 months [95% CI, 12.5 months to not reached] vs ot P4 0 TD9.01-240.1-240.1(not)-2409.9 L18-20(m)75mo 6,47.9-16.3ot 01.

or more) for metastatic disease were 25.0% (95% CI, 5.5-57.2), 20.0%; (95% CI, 10.4-33.0), 27.1% (95% CI, 15.3-41.8), 18.8% (95% CI, 4.0-45.6), and 13.3% (95% CI, 1.7-40.5), respectively (eFigure 4 in Supplement 3).

Subgroup analyses revealed that responses were observed regardless of PD-L1 expression and histology (eFigure 4 in Supplement 3). Of 86 patients with PD-L1–positive tumors and 55 with PD-L1–negative tumors, the confirmed ORRs were 25.6% (95% CI, 16.8-36.1) and 18.2% (95% CI, 9.1-30.9), respectively. Patients with SCC (n = 92) and adenocarcinoma (n = 49) had confirmed ORRs of 28.3% (95% CI, 19.4-38.6) and 12.2% (95% CI, 4.6-24.8), respectively. Patients with high-risk HPV–positive disease (n = 102) had a confirmed ORR of 25.5% (95% CI, 17.4-35.1), while patients with HPV-negative disease (n = 22) had an ORR of 9.1% (95% CI, 1.1-29.2). Of the 4 patients with low-risk HPV–positive disease, none had a confirmed response.

The median PFS was 1.9 months (95% CI, 1.8-2.2; Figure 2A), and the PFS rates at 6 and 12 months were 30.6% (95% CI, 23.1-38.5) and 20.1% (95% CI, 13.3-28.0), respectively. The median PFS was similar between patients with PD-L1–positive tumors (1.9 months; 95% CI, 1.8-4.3) and PD-L1–negative tumors (1.9 months; 95% CI, 1.7-2.0) and between those with SCC (2.0 months; 95% CI, 1.8-5.4) and adenocarcinoma (1.9 months; 95% CI, 1.8-1.9) (eFigure 5 in Supplement 3). However, more patients with PD-L1–negative tumors or adenocarcinoma histology experienced progression at the first assessment.

The median OS was 13.7 months (95% CI, 10.6-17.1), and the OS rate at 12 months was 53.0% (95% CI, 44.2-61.1) (Figure 2B). Longer median OS was observed in patients with

heavily pretreated population. The higher incidence of bleeding events observed with bintrafusp alfa has been seen in other clinical studies of bintrafusp alfa, in which a higher frequency of low-grade bleeding events has been observed than with immune checkpoint inhibitors or targeted agents.[20-22] Notably, the incidence of bleeding AEs, anemia, and immune-related AEs in this study was higher than previously reported with bintrafusp alfa in other indications, while the incidence of TGF-β inhibition–mediated skin AEs was lower.[22] Exposure safety for bleeding AEs was established in previous studies and indicated that the cervical cancer tumor type was associated with a higher probability of AEs in addition to exposure.[22] Mechanistically, the association of TGF-β inhibition with bleeding events may be related to the inhibition of the TGF-β2 isoform, a hematopoietic regulator.[22] As bintrafusp alfa has a higher affinity for the TGF-β1 and TGF-β3 isoforms,[23] dose reduction may be a feasible management approa2cB usp

nocarcinoma/adenosquamous carcinoma (median, 13.3 months) vs SCC (median, 11.1 months).[7] The prolonged OS in SCC vs adenocarcinoma observed here with bintrafusp alfa may reflect the underlying role of TGF-β in the physiology of cervical cancer.[29] The oncogenic effect of TGF-β in cervical cancer may warrant further investigation of therapies targeting TGF-β.

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This study has limitations. The single-arm, open-label design may restrict the interpretation of the study data. Additionally, the relatively small sample size precludes any meaningful comparisons between patient subgroups.

Conclusions

In conclusion, this phase 2 nonrandomized controlled trial of bintrafusp alfa met its primary end point, which may support the further exploration of bifunctional molecules, particularly those targeting TGF-β and PD-L1, in patients with cervical cancer. While this study focused on patients with recurrent or metastatic cervical cancer with disease progression during or after platinum-containing chemotherapy, the effects of bintrafusp alfa on patients who received checkpoint inhibitors as first-line treatment remains unexplored.

ARTICLE INFORMATION

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