KEYNOTE-991: PHASE 3 STUDY OF PEMBROLIZUMAB PLUS ENZALUTAMIDE AND ANDROGEN DEPRIVATION THERAPY (ADT) FOR PATIENTS WITH METASTATIC HORMONE-SENSITIVE PROSTATE CANCER (MHSPC)

Background Combination of pembrolizumab, an anti–PD-1 antibody, added to enzalutamide, a nonsteroidal antiandrogen agent, has shown antitumor activity in abiraterone-resistant mCRPC (KEYNOTE-365, NCT02861573) and in patients with mCRPC for whom enzalutamide was ineffective (KEYNOTE-199, NCT02787005). These data indicate that the combination of pembrolizumab + enzalutamide with ADT warrants phase 3 evaluation. Also, efficacy in enzalutamide may be proimmunogenic, suggesting that it may be additive or synergistic in antitumor activity when combined with pembrolizumab.

Methods The KEYNOTE-991 (NCT04191096) phase 3 trial will evaluate the efficacy and safety of enzalutamide + ADT (LHRH agonist/antagonist during study treatment or bilateral orchiectomy) + pembrolizumab or placebo in patients with mHSPC. Eligibility criteria include age ≥18 years, mHSPC, ≥2 bone lesions or visceral disease, no prior treatment with next-generation hormone agents, adequate organ function, and ECOG PS 0 or 1. Patients must provide tissue for biomarker analysis. Approximately 1232 patients will be randomized in a 1:1 ratio to receive enzalutamide 160 mg orally once daily + ADT + pembrolizumab 200 mg IV every 3 weeks (Q3W) or enzalutamide 160 mg orally once daily + ADT + placebo IV Q3W. Treatment will continue with pembrolizumab up to 35 cycles and treatment with enzalutamide will proceed continuously from day 1 of cycle 1 until disease progression, unacceptable toxicity, or withdrawal of consent. The stratification factors are prior docetaxel therapy (yes or no) and presence of high-volume disease (yes or no). CT or MRI and radionuclide bone imaging will be used to assess response according to Prostate Cancer Working Group 3 (PCWG3)–modified RECIST v1.1 by blinded independent central review (BICR) Q12W from the date of randomization. Imaging will continue until the end of treatment and will resume Q12W during the posttreatment period. The co-primary end points are BICR-assessed radiographic PFS (according to PCWG3-modified RECIST v1.1) and OS. Key secondary end points are time to first subsequent antancerca therapy and time to symptomatic skeletal-related event. Other end points are PFS2 (progression after next line of therapy or death), PSA response rate, time to PSA progression, PSA undetectable rate, ORR, duration of response, time to soft tissue and radiographic bone progression per PCWG3-modified RECIST v1.1, safety, and patient-reported outcomes (eg, time to pain progression). Safety and tolerability will be evaluated using a tiered approach. KEYNOTE-991 is enrolling at 40 sites in Australia, Chile, Colombia, Israel, Japan, Poland, South Korea, Spain, Switzerland, Taiwan, and the United States.

Results N/A

Conclusions N/A

Trial Registration ClinicalTrials.gov, NCT03834519

Ethics Approval The study and the protocol were approved by the Institutional Review Board or ethics committee at each site.

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CLINICAL OUTCOMES OF OVARIAN CANCER PATIENTS TREATED WITH ALKS 4230, A NOVEL ENGINEERED CYTOKINE, IN COMBINATION WITH PEMBROLIZUMAB: ARTISTRY-1 TRIAL

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Background ALKS 4230 is a novel engineered cytokine that selectively targets the intermediate-affinity interleukin-2 receptor complex to activate CD8+ T cells and natural killer cells.1 The ARTISTRY-1 trial (NCT02799095) has shown encouraging efficacy and acceptable tolerability of ALKS 4230 among patients with advanced solid tumors.2 We report a detailed analysis of ovarian cancer (OC) patients who received combination therapy in ARTISTRY-1.

Methods ARTISTRY-1 is an ongoing multicohort phase 1/2 trial exploring intravenous ALKS 4230 as monotherapy and combined with pembrolizumab. OC patients were enrolled into a cohort with mixed anti PD 1/L1 unapproved tumor types who had progressed on prior chemotherapy. OC patients received ALKS 4230 (3 μg/kg) on days 1–5 and pembrolizumab (200 mg) on day 1 of a 21 day cycle. Outcomes
have generally been transient and manageable, with the majority being grade 1 and 2 in severity. Overall, based on preliminary data, the combination with ALKS 4230 did not demonstrate any additive toxicity to that already established with pembrolizumab alone. Additional safety and efficacy data are being collected in ongoing cohorts. In the monotherapy dose escalation portion of the study, ALKS 4230 alone increased markers of lymphocyte infiltration in 1 paired melanoma biopsy (1 of 1; on treatment at cycle 2); CD8+ T cell density and PD-L1 tumor proportion score increased 5.2- and 11 fold, respectively, supporting evidence that ALKS 4230 has immunostimulatory impact on the TME and providing rationale for combining ALKS 4230 with pembrolizumab (figure 1).

Conclusions The combination of ALKS 4230, an investigational agent, and pembrolizumab demonstrates an acceptable safety profile and provides some evidence of tumor shrinkage and disease stabilization in some patients with heavily pretreated OC. This regimen could represent a new therapeutic option for these patients.

Acknowledgements The authors would like to thank all of the patients who are participating in this trial and their families. The trial is sponsored by Alkermes, Inc. Medical writing and editorial support was provided by Parexel and funded by Alkermes, Inc.

Trial Registration ClinicalTrials.gov NCT02799095

Ethics Approval This trial was approved by Ethics and Institutional Review Boards (IRBs) at all trial sites; IRB reference numbers 16-229 (Dana-Farber Cancer Institute), MOD00003422/PH285316 (Roswell Park Comprehensive Cancer Center), 20160175 (Western IRB), i15-01394_MOD23 (New York University School of Medicine), TRIAL20190090 (Cleveland Clinic), and 000097 (ADVARRA).

REFERENCES
2. Vaidyanathan UN, Muzaffar J, Velcheti V, Winer I, Hoimes CJ, Rosen SD, et al. ALKS 4230 monotherapy and in combination with pembrolizumab (pembro) in patients (pts) with refractory solid tumors (ARTISTRY-1). Oral presentation at: European Society for Medical Oncology Annual Meeting; September 2020; virtual.

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Abstract 347 Table 1 Summary of response observations among patients with ovarian cancer

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Prior Therapies</th>
<th>Max. Reduction of Target Lesions (%)</th>
<th>CR*</th>
<th>CA125 (U/mL) Response From Baseline</th>
<th>Time on ALKS 4230 (Weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48</td>
<td>CBP/PAC/BEV, CBP/PGM/CBP, CBP/PLD, CBP/DOCC</td>
<td>70.6</td>
<td>CR</td>
<td>Normalised from 262 to 34.9 at cycle 4</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>83</td>
<td>CBP/PAC/DOCC, CBP/DOCC/NRT/AM</td>
<td>76.3</td>
<td>PR</td>
<td>Normalised from 125 to 16 at cycle 4</td>
<td>23</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>CBP/PAC, CBP/PLD, CBP/BEV, CBP/BEV, CBP/PLD</td>
<td>44.7</td>
<td>uPR</td>
<td>Reduced from 1400 to 260 at cycle 1</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td>75</td>
<td>CBP/PAC, PL/BEV, CBP/DOCC, TOP, N/R</td>
<td>21.6</td>
<td>SD</td>
<td>Reduced from 493 to 345 at cycle 3</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td>83</td>
<td>CBP/PAC, CBP/PAC/CBP, CBP/PLD, CBP/DOCC</td>
<td>18.3</td>
<td>SD</td>
<td>Normal at baseline at 10.6</td>
<td>21</td>
</tr>
</tbody>
</table>

*As assessed by the investigator. **CR due to node shrinkage to <10 mm short axis, which is considered normal.

Results Fourteen heavily pretreated patients with OC were enrolled. Patients received a median of 5 (range, 2–11) prior regimens and all were previously treated with platinum based therapy. Among 13 evaluable patients with ≥1 assessment, 9 experienced disease control and 4 experienced disease progression; median treatment duration was approximately 7 weeks. Three patients experienced an objective response, including 1 complete response, 1 partial response (PR), and 1 unconfirmed PR; all were platinum resistant and negative for BRCA mutations. Five patients experienced tumor burden reductions (table 1). Treatment-related adverse events at the doses tested presented include antitumor activity (RECIST v1.1) and safety as of 7/24/2020. To evaluate changes in tumor microenvironment (TME), baseline and on-treatment biopsies were collected.

Abstract 347 Figure 1 Increased markers of lymphocyte tumor infiltration

An increase in CD3+CD8+ T cells (A, red = CD3; blue = CD8; purple = CD3+CD8+; teal = tumor marker), GranzymeB (B, red = CD8; green = granzymeB; yellow = granzymeB+CD8+; teal = tumor marker), and PD-L1 (C, red = PD-L1; blue = tumor marker) in the tumor microenvironment of a single patient was observed after the patient received monotherapy ALKS 4230

Background Management of advanced endometrial cancer after failure with platinum therapy remains a challenge. Tumors characterized by DNA repair abnormalities; immunotherapy is promising in this setting as demonstrated in studies with checkpoint inhibitors (CPI). Overcoming emerging resistance to CPI through novel combinations is a focus of research. Retifanlimab is an investigational humanized immunoglobulin G4 monoclonal antibody that is being developed as a potential combination agent, and pembrolizumab demonstrates an acceptable safety profile and provides some evidence of tumor shrinkage and disease stabilization in some patients with heavily pretreated OC. This regimen could represent a new therapeutic option for these patients.

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