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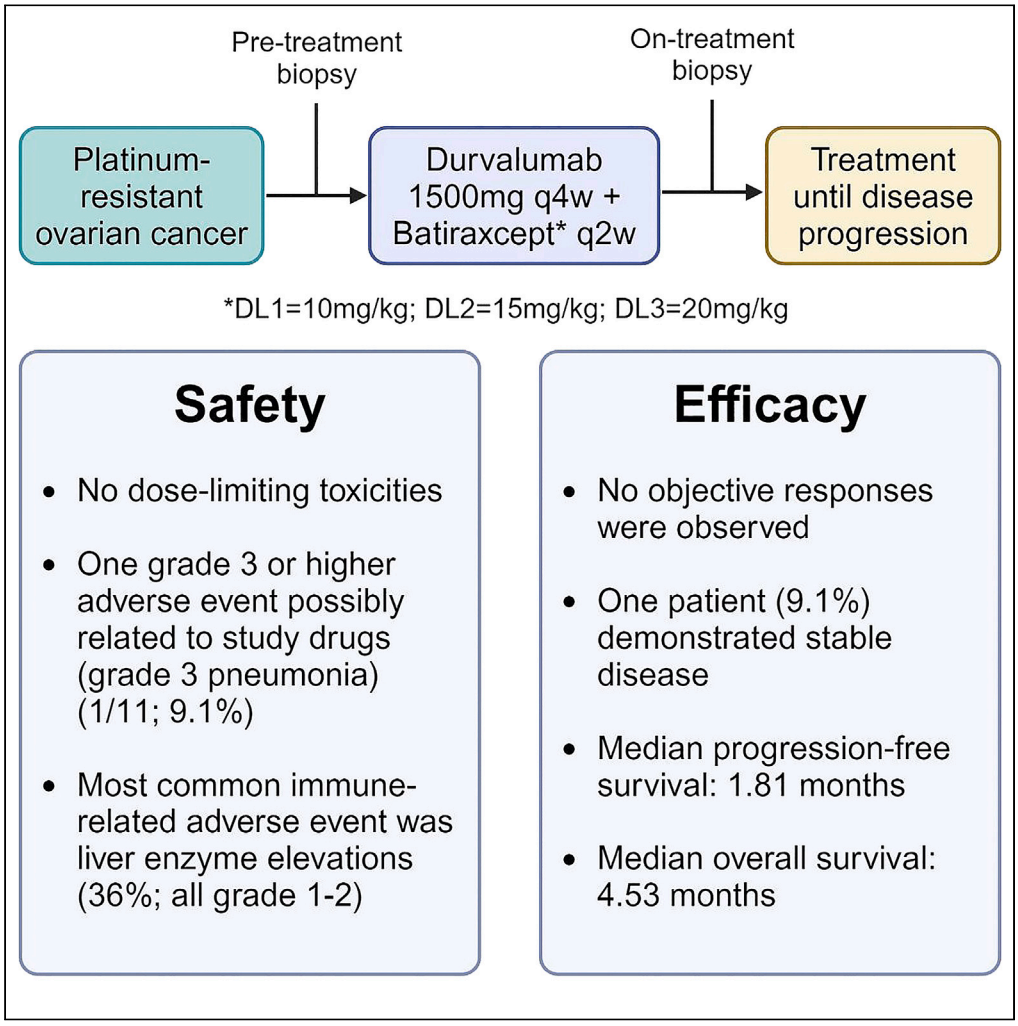


Anne Knisely, Emily M. Hinchcliff, Elisabeth Gardiner, ..., Shannon N. Westin, Karen H. Lu, Amir A. Jazaeri

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## Highlights

No dose-limiting toxicities occurred among all patients who received study drugs

Of 11 patients who received durvalumab and batiraxcept, no responses were noted

Median progression-free and overall survival were 1.8 and 4.5 months, respectively

Batiraxcept effectively reduced serum GAS6 levels at 1-h post-treatment

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# Phase 1b study of batiraxcept in combination with durvalumab in patients with platinum-resistant ovarian cancer

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## SUMMARY

**Combining an immune checkpoint inhibitor with batiraxcept (AVB-S6-500), an AXL inhibitor that acts via selective binding to growth arrest-specific protein 6 (GAS6), may improve anti-tumor immunity in platinum-resistant ovarian cancer (PROC). This phase 1b trial of durvalumab in combination with escalating doses of batiraxcept enrolled patients with recurrent PROC (NCT04019288). The primary objective was to determine the toxicity profile of the combination. Eleven patients were enrolled on the trial. No dose-limiting toxicities were observed, and no objective responses were noted. Median progression free survival (PFS) was 1.81 months (95% confidence interval (CI) 1.71–2.40), and median overall survival (OS) was 4.53 months (95% CI 2.10–24.74). Batiraxcept effectively reduced serum GAS6 levels at 1-h post-treatment, resulting in trough levels below the limit of detection in all cases but one. In conclusion, the combination of batiraxcept and durvalumab was safe and tolerable but did not demonstrate anti-tumor activity in a heterogenous population of patients with recurrent PROC.**

## INTRODUCTION

Ovarian cancer is an immunogenic malignancy, with tumor-infiltrating lymphocytes correlated with improved patient survival.[1] However, the activity of immune checkpoint inhibitors (ICIs), particularly programmed cell death 1 (PD-1) and programmed death ligand 1 (PD-L1) inhibitors, as monotherapy in recurrent ovarian cancer has been disappointingly low, with response rates typically only 5–15%.[2–4] The low response rates in ovarian cancer have largely been attributed to low mutational burden and multiple resistance mechanisms within the immunosuppressive tumor microenvironment (TME).[5]

AXL is a receptor tyrosine kinase that is overexpressed in many cancer types and is associated with resistance to therapy and poor clinical outcomes.[6–10] AXL and its high affinity ligand growth arrest-specific protein 6 (GAS6) are involved in key oncologic pathways related to cell proliferation, chemotaxis, angiogenesis, epithelial-mesenchymal transition, and immune regulation.[11] High pre-treatment GAS6 levels have also been shown to be associated with worse oncologic outcomes in platinum-resistant ovarian cancer.[12] However, GAS6 levels are positively correlated with markers of inflammation, such as C-reactive protein, in non-small cell lung cancer,[13] and a preclinical study in gastric cancer found that GAS6 mainly originates from cancer-associated fibroblasts,[14] demonstrating that this biomarker is not specific to cancer cells.

In the context of the immune system, AXL is present on the surface of various cells of the innate immune system and has been found to broadly inhibit toll-like receptors and related cytokine cascades.[15] AXL also suppresses T cell function via upregulation of immune-checkpoint ligands, further contributing to an immunosuppressive TME.[16] AXL knockout in a murine breast cancer model results in an increase in antigen-presenting cells and $CD8^+$ T cell infiltration with an associated decrease in secretion of myeloid supportive cytokines.[17] Therefore, AXL inhibition and ICI may synergize to create improved anti-tumor immune responses, and this has been demonstrated with anti-PD-1 therapy in pre-clinical tumor models.[18] Clinically, in patients with melanoma, AXL transcript levels were significantly correlated with resistance to anti-PD-1 checkpoint therapy,[19,20] highlighting the importance of investigating AXL inhibitors in the clinic with the goal of increasing ICI efficacy.

Batiraxcept is a highly sensitive and specific inhibitor of AXL that acts via selective binding to and sequestration of GAS6. When combined with chemotherapy, this compound has shown efficacy in treatment of ovarian cancer in pre-clinical models, where decrease in

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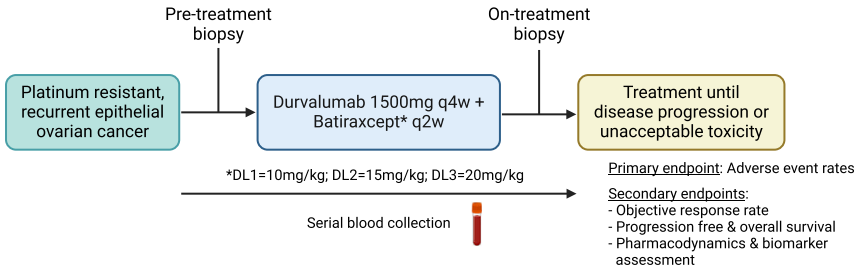


**Figure 1. Study schema**

Patients with recurrent, platinum resistant epithelial ovarian cancer were given durvalumab 1,500 mg every 4 weeks in combination with escalating doses of batiraxcept (AVB-S6-500) until disease progression. DL, dose level.

GAS6 levels was predictive of response and survival.[12] A phase 1b study that examined escalating doses of batiraxcept in combination with paclitaxel or pegylated liposomal doxorubicin in platinum-resistant ovarian cancer (PROC) demonstrated safety and reasonable efficacy and established a recommended phase 2 dose of 15 mg/kg.[21] A phase 3 trial evaluating the efficacy of weekly paclitaxel with or without batiraxcept in the same patient population (NCT04729608) has completed accrual but has not yet been published. Given the strong preclinical rationale for combining AXL inhibition and ICI, the objective of this phase 1b trial (NCT04019288) was to assess the recommended phase 2 dose and safety of batiraxcept in combination with durvalumab, a monoclonal PD-L1 inhibitor, in PROC (Figure 1).

## RESULTS

### Patient characteristics

The trial enrolled 11 patients with recurrent ovarian cancer from December 2019 to January 2021. Demographic and clinical factors for the study population are summarized in Table 1. The median age at the time of consent was 58 years old (range 45–73 years). The majority of patients were White (72.7%) and non-Hispanic (81.8%). Most patients had clear cell histology (54.5%); four patients (36.4%) had high grade serous carcinoma and one (9.1%) had endometrioid histology. Subjects had received a median of 4 prior lines of therapy (range 1–6). Most patients ($n$ = 8; 72.7%) received prior bevacizumab. A minority of patients ($n$ = 3; 27.3%) received prior immunotherapy. Eight patients for which tumor mismatch repair (MMR) status was known ($n$ = 9) had MMR proficient tumors; MMR status was indeterminant for one patient and unknown for the other two patients. Patients on trial received investigational therapy for a median of 2 cycles (range 1–6). Three patients received batiraxcept dosed at 10 mg/kg, 3 received 15 mg/kg dosing, and the remainder ($n$ = 5) received 20 mg/kg dosing.

**Table 1. Demographic and clinical characteristics of study population (*N* = 11)**

| Characteristic | |
|---|---|
| Median (Range) | |
| Age at consent | 58.0 (45.0–73.0) |
| Prior lines of therapy | 4.0 (1.0–6.0) |
| *N* (%) | |
| Race | |
| White/Caucasian | 8 (72.7) |
| Asian | 1 (9.1) |
| Other | 1 (9.1) |
| Unknown | 1 (9.1) |
| Ethnicity | |
| Hispanic or Latino | 2 (18.2) |
| Not Hispanic or Latino | 9 (81.8) |
| Histology | |
| High grade serous | 4 (36.4) |
| Clear cell | 6 (54.5) |
| Endometrioid | 1 (9.1) |

**Table 2. Summary of treatment-related adverse events by grade**

| Adverse event name | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Total |
|---|---|---|---|---|---|
| Alanine aminotransferase elevated | 1 | 0 | 0 | 0 | 1 |
| Alkaline phosphatase elevated | 1 | 0 | 0 | 0 | 1 |
| Anemia | 0 | 2 | 0 | 0 | 2 |
| Anorexia | 0 | 2 | 0 | 0 | 2 |
| Aspartate aminotransferase elevated | 3 | 0 | 0 | 0 | 3 |
| Bloating | 1 | 0 | 0 | 0 | 1 |
| Constipation | 2 | 2 | 0 | 0 | 4 |
| Cough | 1 | 0 | 0 | 0 | 1 |
| Creatinine increased | 3 | 0 | 0 | 0 | 3 |
| Diarrhea | 1 | 0 | 0 | 0 | 1 |
| Dyspnea | 0 | 1 | 0 | 0 | 1 |
| Fatigue | 0 | 3 | 0 | 0 | 3 |
| GGT increased | 1 | 0 | 0 | 0 | 1 |
| Headache | 1 | 0 | 0 | 0 | 1 |
| Hypercalcemia | 1 | 0 | 0 | 0 | 1 |
| Hyperparathyroidism | 1 | 0 | 0 | 0 | 1 |
| Hypertension | 1 | 0 | 0 | 0 | 1 |
| Hypokalemia | 1 | 0 | 0 | 0 | 1 |
| Hyponatremia | 2 | 1 | 0 | 0 | 3 |
| Infusion related reaction | 0 | 3 | 0 | 0 | 3 |
| Investigations – Other | 2 | 0 | 0 | 0 | 2 |
| Lipase increased | 0 | 1 | 0 | 0 | 1 |
| Lung infection | 0 | 0 | 1 | 0 | 1 |
| Lymphocyte count decreased | 1 | 0 | 0 | 0 | 1 |
| Nausea | 3 | 2 | 0 | 0 | 5 |
| Rash maculo-papular | 2 | 0 | 0 | 0 | 2 |
| Serum amylase increased | 1 | 1 | 0 | 0 | 2 |
| Vomiting | 1 | 2 | 0 | 0 | 3 |
| White blood cell count decreased | 1 | 0 | 0 | 0 | 1 |
| Total | 32 | 20 | 1 | 0 | 53 |

## Safety and dose delays

No dose-limiting toxicities were noted among all patients who received study drugs ($n$ = 11). Treatment-related adverse events (AEs) by grade are summarized in Table 2. There was one grade 3 or higher AE possibly related to study drugs (a case of pneumonia). Five patients experienced any immune-related AEs, most commonly liver enzyme elevations (36%, grade 1–2). Grade 2 infusion reactions with batiraxcept occurred with the first two subjects, prompting institution of a premedication regimen, after which only one of the nine remaining patients experienced an infusion reaction. Dose delays >1 week occurred in 6 (55%) patients; 3 patients experienced delays for cancer related or medical complications (small bowel obstruction, pneumonia, and severe fatigue), while 3 patients experienced delays for non-medical reasons (COVID/travel and weather).

## Efficacy and survival

No objective responses were noted across any of the dose levels. One patient with clear cell carcinoma demonstrated stable disease for three months; all other patients had progressive disease (Figure 2). Best percentage changes in target lesion size are baseline are illustrated in waterfall and spider plots (Figure 3). The median follow-up time for subjects was 4.53 months (range 1.94–26.18). Survival curves are shown in Figure 4. Median progression-free survival was 1.81 months (95% CI: 1.71–2.40), and median overall survival was 4.53 months (95% CI: 2.10–24.74).

## Pharmacokinetics (PK)/pharmacodynamics and biomarker assessments

Tumors exhibited PD-L1 expression with a mean combined positive score (CPS) of 26.8 (range 2–100), with most patients (8/11; 72.7%) with CPS scores of 10 or higher. Only four patients (36.4%) had positive AXL expression on pre-treatment biopsies, and only three patients (27.3%)

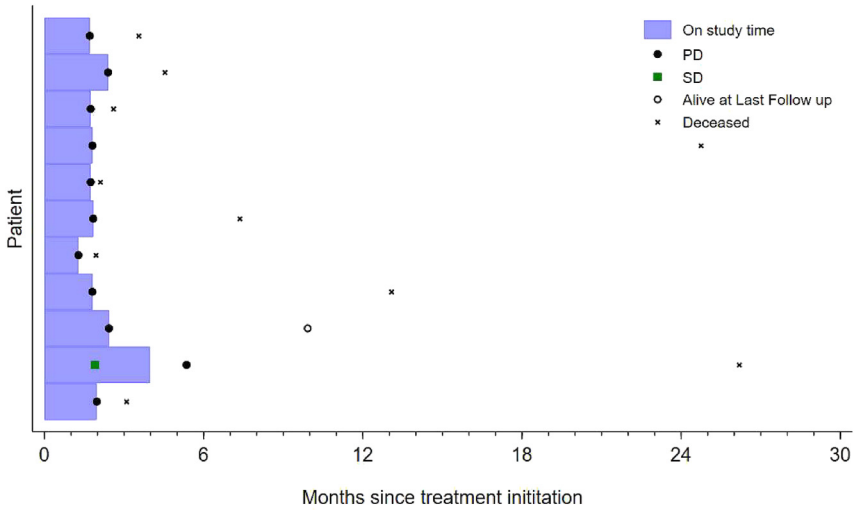


**Figure 2. Swimmer plot**

Disease status (stable disease [SD] or progressive disease [PD]) based on response evaluation criteria in solid tumors (RECIST v1.1) for the study population (N = 11). Each bar represents one patient in the study.

had positive GAS6 expression. The patient who exhibited stable disease had negative AXL and GAS6 expression. Median pre-treatment serum AXL and GAS6 concentrations were 26.0 ng/mL (range 12.3–112.0 ng/mL) and 30.5 ng/mL (range 5.6–45.1 ng/mL), respectively. Post cycle 1 day 1 batiraxcept levels ranged from 313,000 ng/mL to 749,000 ng/mL with a median of 453,000 ng/mL. Batiraxcept trough levels were available for 9 patients with a median of 16,000 ng/mL ($n$ = 8; range 134–26,200 ng/mL) and one too low to quantify by 1-h post-treatment. Serum GAS6 levels at trough (day 15) were too low to quantify in all cases except for one patient, who had a trough level of 42.9 ng/mL. See Table 3 for detailed PK/pharmacodynamics and biomarker data.

## DISCUSSION

In this phase 1b study of batiraxcept and durvalumab in patients with recurrent, platinum-resistant epithelial ovarian cancer, the drug combination was safe and tolerable at all dose levels tested but did not produce any objective responses. One patient exhibited stable disease for 3 months, and the rest of the patients demonstrated progression soon after starting therapy. There are several potential reasons for the demonstrated lack of efficacy for this combination in this specific trial. First, the study population was highly heterogenous with many patients with non-high grade serous histology included (e.g., 55% clear cell histology), and high-grade serous histology specifically has been found to be associated with high AXL expression.[21] However, even patients with high grade serous cancer did not respond to the combination therapy, highlighting the potential involvement of other factors. Additionally, almost half (45%) of patients enrolled on this trial had platinum refractory disease, which represents an exceptionally poor prognostic group with very limited responses to traditional chemotherapy agents.[22] Prior exposure to bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor, for the majority of patients (73%) could have also impacted response to batiraxcept. In the previous phase 1b trial of batiraxcept with chemotherapy in PROC, patients

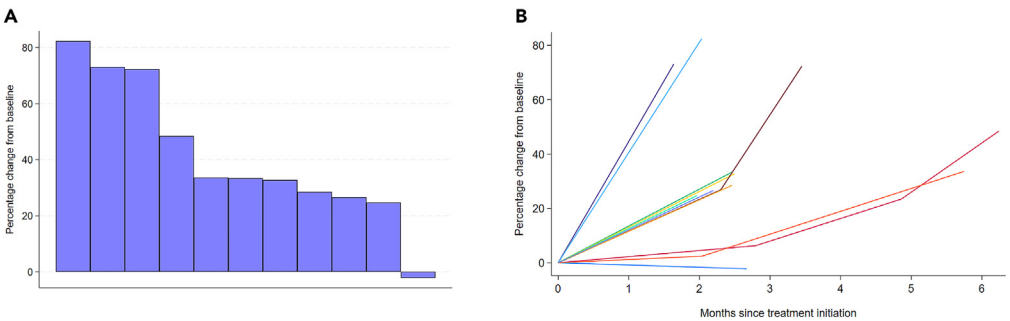


**Figure 3. Waterfall (A) and spider plots (B)**

Best response change from baseline (% change; N = 11) per response evaluation criteria in solid tumors (RECIST v1.1), calculated based on sum of diameters for target lesions.

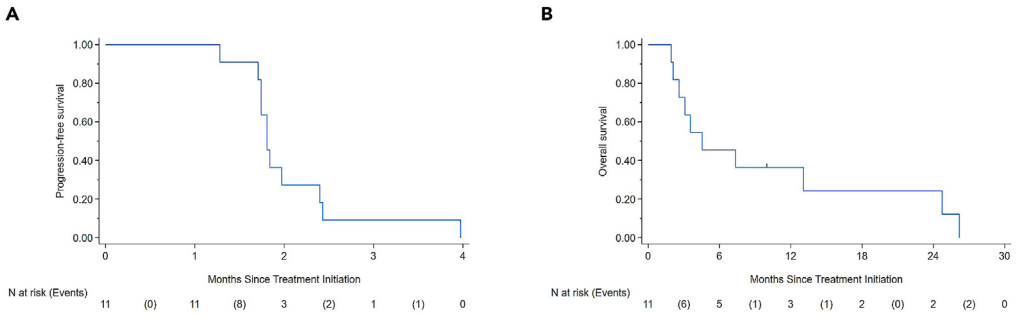


**Figure 4. Kaplan and Meier survival curves**

(A) Progression-free survival (PFS) and (B) overall survival (OS) were defined as the date of treatment start to the earliest date of progression or death due to any cause, respectively.

with prior bevacizumab treatment had significantly worse clinical outcomes.[21] Finally, it is worth noting that dose delays impacted 55% of patients.

Aside from these poor patient prognostic factors, it is also plausible that batiraxcept may just not have significant anti-tumor activity in all subtypes of ovarian cancer. To this end, the objective response rate of 34.8% for those with PROC who received batiraxcept with weekly paclitaxel in the previous phase 1b trial is not appreciably different from that of weekly paclitaxel alone (approximately 30%) in the platinum-resistant setting.[23,24] A large, randomized phase 3 trial of paclitaxel with or without batiraxcept (AXLerate-OC, NCT04729608) aimed to answer this question and found no significant difference in progression free survival (PFS) between the two arms (5.1 versus 5.5 months for the combination and paclitaxel alone arms, respectively).[25] Although AXL has been shown to play a role in chemoresistance in pre-clinical ovarian cancer models,[26] there are likely other mechanisms contributing more to therapy resistance, including tumoral heterogeneity and immunosuppressive microenvironment factors.[27]

Another notable factor to consider is that the AXL receptor can also be activated by mechanisms aside from GAS6 binding, including ligand-independent homo-dimerization and activation by other receptor tyrosine kinase ligands.[11] Therefore selective inhibition of GAS6 with batiraxcept may still result in clinically significant AXL-mediated signaling and downstream pro-tumorigenic effects, limiting efficacy of this therapy. For this reason, it may be more efficacious to target AXL directly. This target specific modality is being evaluated via the use of bemcentinib (BG324), a small molecule AXL-specific kinase inhibitor, in a number of ongoing phase 1 and 2 clinical trials in multiple advanced solid tumors including melanoma (NCT02872259), non-small cell lung cancer (NCT02922777 and NCT03184571), and glioblastoma (NCT03965494).[28]

In conclusion, this study demonstrates that the combination of batiraxcept and durvalumab is safe at the dose levels tested but does not appear to induce anti-tumor immunity in a heterogenous group of patients with platinum resistant ovarian cancer. Further research is needed to identify novel targets for therapeutic intervention to benefit these at need patients.

## Limitations of the study

A key limitation of this study is the single-arm study design, which limits our understanding of how this combination may fare in comparison to standard of care chemotherapy is this particularly poor prognostic group. Additionally, the study is limited by a small sample size of only 11 patients with multiple histological subtypes, making it difficult to draw any definitive conclusions. Specifically, it is not well understood which subtypes, if any, respond most favorably to anti-AXL therapy.

## STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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- RESOURCE AVAILABILITY
  - Lead contact
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- EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS
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  - Patient selection
- METHOD DETAILS
  - Study design
  - Study assessments
  - Pharmacokinetic/Pharmacodynamic (PK/progressive disease) studies and biomarker assessments

**Table 3. Pharmacokinetics/pharmacodynamics and biomarker assessments for the study population**

| Patient ID | Dose level | Response (Cycle #) | Histology | PD-L1 status | Tumor AXL | Tumor GAS6 | Serum AXL (ng/mL) | Serum GAS6 (ng/mL) | sAXL/GAS6 Ratio | Batiraxcept at trough (ng/mL) | Serum GAS6 at trough (ng/mL) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | PD (2) | HGS | 76 | ++ | + | 18.8 | 28.4 | 0.66 | 2570 | BLQ |
| 2 | 1 | PD (5.5) | CC | 100 | – | – | 31.1 | 5.6 | 5.55 | 134 | 42.9 |
| 3 | 1 | PD (2) | Endo | 22 | – | + | 26.0 | 39.8 | 0.65 | 9050 | BLQ |
| 4 | 2 | PD (3.5) | CC | 3[a] | – | – | 20.2 | 30.5 | 0.66 | 18100 | BLQ |
| 5 | 2 | PD (1) | HGS | 4 | – | – | 29.8 | 30.7 | 0.97 | NA | NA |
| 6 | 2 | PD (5) | CC | 10 | + | – | 12.3 | 27.5 | 0.45 | 13900 | BLQ |
| 7 | 3 | PD (1.5) | CC | 43 | – | – | 112.0 | 37.6 | 2.98 | 25900 | BLQ |
| 8 | 3 | PD (3) | HGS | 12 | + | – | 102.0 | 37.2 | 2.74 | NA | NA |
| 9 | 3 | PD (2) | CC | 11 | – | – | 28.5 | 45.1 | 0.63 | 26200 | BLQ |
| 10 | 3 | PD (2) | HGS | 2[a] | ++ | – | 19.5 | 13.9 | 1.40 | 20800 | BLQ |
| 11 | 3 | PD (2) | CC | 12 | – | + | 15.2 | 18.5 | 0.82 | BLQ | NA |

Dose levels: 1 = 10 mg/kg; 2 = 15 mg/kg; 3 = 20 mg/kg.
PD, progressive disease; HGS, high-grade serous; CC, clear cell; endo, endometrioid; BLQ, below limit of quantitation; NA, not assessed.
[a]Tumor evaluated at visit 3.



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## AUTHOR CONTRIBUTIONS

Conceptualization, E.M.H., E.G., and A.A.J.; methodology, E.M.H., B.F., Y.Y., and A.A.J.; formal analysis, B.F. and Y.Y.; investigation, E.M.H., S.N.W., A.K.S., K.L., and A.A.J.; resources, E.M.H., K.H.L., and A.A.J.; data curation, E.M.H., A.K., B.F., and Y.Y.; writing – original draft, A.K. and E.M.H.; writing – review and editing, A.K., E.M.H., E.G., B.F., Y.Y., R.R., A.K.S., K.L., S.N.W., A.K.S., K.H.L., and A.A.J.; visualization, A.K., B.F., and Y.Y.; supervision, A.A.J.; project administration, R.R., K.L., and A.A.J.; funding acquisition, A.A.J and E.M.H.

## DECLARATION OF INTERESTS

E.G. is an Expert in Residence at General Inception and provides guidance for oncology programs. R.R. was previously the chief medical officer at Aravive and is currently the chief medical officer at Karyopharm. A.K.S. reports consulting for KIYATEC, Merck & Co., GSK, Onxeo, ImmunoGen, Iylon, and AstraZeneca; being a stockholder in Bio-Path Holdings. S.N.W. reports consulting for AstraZeneca, Caris, Clovis Oncology, Eisai, EQRX, Gilead, GSK, Immunocore, ImmunoGen, Lilly, Merck, Mereo, Mersana, NGM Bio, Nuvectis, Roche/Genentech, SeaGen, Verastem, Vincerx, Zentalis, ZielBio and research funds to institution from Astra Zeneca, AvengeBio, Bayer, Bio-Path, Clovis Oncology, GSK, Jazz Pharmaceuticals, Mereo, Novartis, Nuvectis, Roche/Genentech, Zentalis. A.A.J. reports consulting for Guidepoint, Gerson Lehrman Group, Macrogenics, Xencor, Theolytics, Avenge Bio, and Green Fire Bio, and clinical trial funding to the Institution from Merck, AstraZeneca, Bristol Myers Squibb, Iovance, Macrogenics, Eli Lilly, Alaunos, Immatics, Xencor, Break Through Cancer, and Imunon. Y.Y. reports consulting for AbbVie, Amgen, Bexion, Boehringer Ingelheim Pharmaceuticals, Bristol Myers Squibb, Century, Enliven, GT Medical, NeoImmueTech, Merck, NGM, Repare, Servier, Transthera, Xinthera, and Vertex.

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## STAR★METHODS

### KEY RESOURCES TABLE

| REAGENT or RESOURCE | SOURCE | IDENTIFIER |
|---|---|---|
| Antibodies | | |
| Recombinant Anti-PD-L1 Antibody | Abcam | Cat#205921; RRID: AB_2687878 |
| Human Gas6 Antibody | R&D Systems | Cat#AF885; RRID: AB_2108079 |
| GAS6 Rabbit anti-Human Polyclonal Antibody | LSBio | Cat#LS-B13094; RRID: AB_3096951 |
| Human Axl Antibody | R&D Systems | Cat#AF154; RRID: AB_354852 |

### RESOURCE AVAILABILITY

#### Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Amir A. Jazaeri (aajazaeri@mdanderson.org).

#### Materials availability

This study did not generate new unique reagents.

#### Data and code availability

- Clinical data from this trial is available from the lead contact upon request.
- This paper does not report original code.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

### EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

#### Study approval

This investigator-initiated study was approved by the United States Food and Drug Administration and the Institutional Review Board of the University of Texas MD Anderson Cancer Center (#2019-0149, NCT04019288). The study monitoring was performed by the MD Anderson Investigational New Drug Office. This study was conducted in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent prior to the initiation of treatment.

#### Patient selection

Patients over 18 years of age with high grade epithelial ovarian/fallopian tube/primary peritoneal carcinoma (with serous, endometrioid, or CC histology) were required to meet eligibility criteria including platinum resistant or refractory disease, defined as a platinum-free interval of less than 6 months or progression on platinum-based therapy. There were no limitations with regards to number of prior treatment regimens, and prior immune checkpoint therapy was allowed. All patients were required to have measurable disease based on modified Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)[29] and an Eastern Cooperative Oncology Group performance status of 0 or 1 with adequate organ and bone marrow function. Participants' information on race and ethnicity was self-reported. Information on gender and socioeconomic status was not collected. Additional inclusion and exclusion criteria can be found on the NCI website under clinical trial (NCT04019288).

### METHOD DETAILS

#### Study design

NCT04019288 is an open-label phase 1b trial that enrolled patients via a Bayesian optimal interval design.[30] Durvalumab 1500 mg was administered every 4 weeks. Based on safety data from a phase 1 study with healthy volunteers (NCT03401528), a starting dose of Batiraxcept 10 mg/kg every two weeks was selected and a dose escalation study design was implemented with additional dose levels of 15 mg/kg and 20 mg/kg (Figure 1). Initially, there was a planned dose expansion cohort; however, given lack of an efficacy signal, it was mutually agreed between investigators and pharmaceutical supporters that the study would be terminated.

#### Study assessments

RECIST v1.1 modified for immunotherapy[31] was used to assess response. Disease was assessed with imaging every 6 weeks of therapy; any subject who developed PD during investigational agent treatment cycles was required to undergo confirmatory imaging (no earlier than

5 weeks from the initial assessment of PD, in the absence of clinically significant deterioration) in order to verify the reliability of the radiologic finding per immune-related response guidelines. Progression-free survival was calculated using the time of first documented progression. OS was calculated from the time of study registration to the earliest date of death or last follow up. AEs and serious adverse events were recorded from time of first protocol-specific intervention, throughout the treatment period and including the follow-up period (30 days after the last dose of study drug). All toxicities were graded according to NCI CTCAE v5.0.

### Pharmacokinetic/Pharmacodynamic (PK/progressive disease) studies and biomarker assessments

Pre-treatment biopsies were required for histological confirmation of recurrence. Archival tissue $\leq$3 years old was also eligible for use for biomarker studies when necessary. Tissue was analyzed using validated methods for AXL and GAS6 expression using commercially available antibodies. PD-L1 expression was also measured using immunohistochemistry (Dako) with the 28-8 antibody (Abcam) (Discovery Life Sciences, Philadelphia, PA). Serum was collected by patient blood draw for PK/PD studies at three time points on the day of cycle 1 day 1: immediately prior to initiation of combination therapy, 1-h post-treatment, and 4 h post-treatment. Serum was also collected pre-treatment on cycle 2 days 1 and at 90-day follow up, when feasible. Soluble AXL protein (sAXL) and soluble GAS6 protein (sGAS6) were analyzed by a proprietary validated ELISA under GLP conditions for all available time points (Atlasciences, Everett, WA).

## QUANTIFICATION AND STATISTICAL ANALYSIS

The primary objective of the study was to determine the toxicity profile of the combination of Batiraxcept and durvalumab therapy. Secondary objectives were to determine ORR for the combination, to estimate PFS and OS, and to investigate molecular and immunological changes associated with the combination treatment. Standard summary statistics were used to describe the demographic and clinical characteristics of the study population. PFS and OS were estimated using the Kaplan Meier method. AEs were tabulated by grade and relationship to study drug. Molecular/immunological changes were summarized with standard descriptive statistics. All statistical analyses were performed using Stata/MP v17.0 (College Station, TX).

## ADDITIONAL RESOURCES

Additional information regarding this trial can be found on the NCI website under clinical trial NCT04019288.