# Phase 2 Study of Bavituximab, a First-in-class Antibody Targeting Phosphatidylserine, Plus Pembrolizumab in Advanced Gastric or Gastroesophageal Junction Cancer

**1386P**


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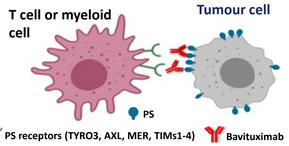
## BACKGROUND

- In tumour cells, phosphatidylserine (PS), an amino-phospholipid, relocates to the outer surface of the cell membrane and acts as an immunosuppressive ligand for multiple immune receptors, including TIM and TAM receptors.[1]

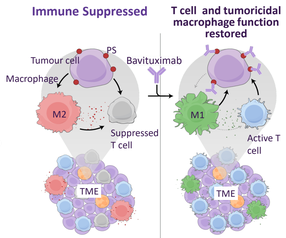
### Bavituximab

- First-in-class chimeric monoclonal antibody (MAb) in clinical development for cancer.
- Complexes with β2-glycoprotein 1 to inhibit immunosuppressive PS signalling.[2]
- Leads to:
  - Increased release of inflammatory cytokines IL-10, TGF-β
  - Decreased release of anti-inflammatory cytokines TNF-α, IL-1β, IL-12.[1,2]




### Mechanism of Action

- Bavituximab reverses immune suppression by inhibiting PS (TIM/TAM) signalling, activating immune cells.
- In a *post hoc* analysis of 2L data from the Phase III SUNRISE NSCLC study, patients who progressed on bavituximab plus docetaxel and who subsequently received a checkpoint inhibitor (CPI) had improved overall survival.[3]



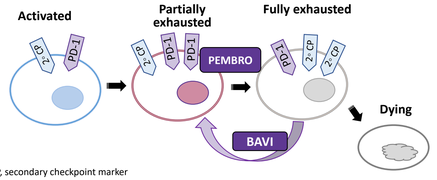

### Pembrolizumab

- High-affinity IgG4 MAb to programmed cell death 1 (PD-1) receptor inhibits binding of programmed cell death ligand 1 (PD-L1) and PD-L2 to PD-1, blocking PD-1/PD–L1-mediated immunosuppression.
- After 2L and 3L treatment, the objective response rate (ORR) for pembrolizumab monotherapy was 16% (Keynote-061, PD-L1 combined positive score [CPS] ≥1)[4] and 11.6% (Keynote-059, PD-L1 agnostic),[5] respectively.

### Rationale for Bavituximab in Combination with Pembrolizumab

- One mechanism of resistance to CPI in treatment-relapsed patients includes T cell exhaustion and the presence of myeloid suppressive cells.[6]
- Inhibition of TIM/TAM pathways in exhausted immune cells with bavituximab may re-stimulate T cells or make exhausted T cells susceptible to checkpoint inhibition.
- PS-targeting antibodies like bavituximab can enhance the anti-tumour activity of anti-PD–(L)1 treatments by inhibiting cytokines stimulated by anti-PD-1 therapy that suppress immune response.[7]

**Cytotoxic T Cell Stages**

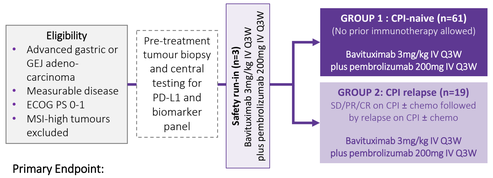



2° CP, secondary checkpoint marker

## METHODS

### Study Design & Objectives

- Phase 2, multicentre, open-label, two-cohort, global study (NCT0409641) in patients with advanced gastric or gastroesophageal junction (GEJ) cancer regardless of PD-L1 status, who have progressed on ≥ 1 prior standard therapy.
- Safety run-in phase, 21-day dose-limiting toxicity observation period, followed by an expansion phase




Primary Endpoint:

- Safety, tolerability, investigator-assessed ORR per RECIST 1.1

Key Secondary Endpoints:

- Bavituximab concentrations and immunogenicity

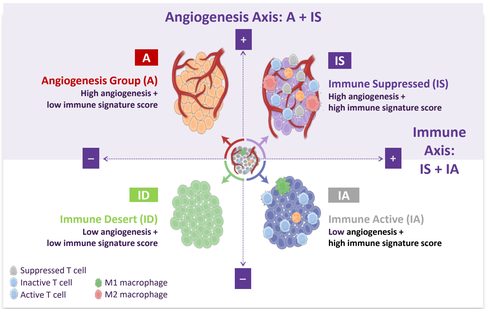
Tertiary endpoints:

- Evaluate novel biomarker signatures and explore relationships between patient subgroups and efficacy outcomes
  - Microsatellite stability (MSS) status, PD-L1 status, neutrophil to lymphocyte ratio (NLR), and tumour microenvironment (TME) in tumour biopsies characterised using a proprietary RNA expression signature panel (biomarker panel)

### Biomarker Panel Assay (Xerna™ TME Panel)

- Pre-treatment tumour biopsies were analysed for RNA expression using a biomarker panel (Xerna™ TME Panel [OncXerna Therapeutics, Inc.]) to determine the dominant angiogenic and immunogenic biology in the patient's TME, and the findings were correlated with tumour response.
  - Xerna™ TME Panel is a qualitative *in vitro* diagnostic assay that uses next-generation sequencing to determine a gene expression profile from formalin-fixed paraffin-embedded samples.
  - The assay has been validated for Total RNA-Seq chemistry (Roche Kapa) in combination with the Illumina NextSeq 500/550 sequencer.
- A prospective-retrospective analysis was conducted to test the hypothesis that tumours with high immune score (immune active [IA] or immune-suppressed [IS] TME subtypes [**biomarker-positive**]) are more likely to respond to bavituximab than those with angiogenic (A) or immune-desert [ID] TME subtypes (**biomarker-negative**).

**Biomarker Panel Subtypes Based on Angiogenesis and Immune Signature Score**




## RESULTS

### Patients, Enrolment and Disposition

- **Safety run-in phase:** 3 patients were enrolled; recommended dose for expansion was confirmed at 3 mg/kg bavituximab QW plus 200 mg pembrolizumab Q3W.
- **Extension phase:** 77 patients were enrolled.
  - Overall, Group 1 had 61 patients and Group 2 had 19 patients.
- Patient disposition at the data cutoff on 15 July 2021:
  - **Group 1:** 58 patients discontinued treatment due to disease progression (48), adverse events (AEs; 6), other (4); 3 patients were still on treatment.
  - **Group 2:** 15 patients discontinued treatment due to disease progression (13), AE (1), other (1); 4 patients were still on treatment.
- Demographic and safety data are presented for Group 1 and Group 2.
- Most Group 2 patients enrolled within the last 3 months and the corresponding efficacy data are not mature; hence only Group 1 efficacy data are presented.

**Baseline Demographics and Disease Characteristics**

| | Group 1 (n=61) | Group 2 (n=19) |
|---|---|---|
| **Mean (SD) age, years** | 60.2 (12.8) | 61.2 (11.7) |
| **Male, n (%)** | 45 (73.8) | 15 (78.9) |
| **ECOG performance, n (%)** | | |
| 0 \| 1 | 22 (36.1) \| 39 (63.9) | 3 (15.8) \| 16 (84.2) |
| **Primary site** | | |
| Gastric\| GEJ | 43 (70.5) \| 18 (29.5) | 14 (73.7) \| 5 (26.3) |
| **Previous lines of therapy, n (%)** | | |
| 1 \| ≥2 | 35 (57.4) \| 26 (42.6) | 2 (10.5) \| 17 (89.5) |
| **Race, n (%)** | | |
| Non-Asian \|Asian | 29 (47.5) \| 32 (52.5) | 7 (36.8) \| 12 (63.2) |
| **Molecular characteristics, n (%)** | | |
| HER2-positive \| -negative \|unknown | 10 (16.4) \| 51 (83.6) \|0 | 3 (15.8) \| 15 (78.9) \|1 (5.3) |
| MSS\|unknown | 43 (70.5) \| 18 (29.5) | 16 (84.2) \| 3 (15.8) |
| PD-L1 CPS <1\|≥ 1\| Unknown | 17 (27.9) \| 40 (65.6) \| 4 (6.6) | 6 (31.6) \| 9 (47.4) \| 4 (21.1) |
| Biomarker positive\| -negative \| Unknown | 32 (52.5) \| 25 (41) 4 (6.6) | 13 (68.4) \| 3 (15.8) \| 3 (15.8) |
| NLR <4\|≥4 | 39 (64) \|22 (36) | 12 (63.2) \|7 (36.8) |

**Baseline Biomarker Status Distribution and PD-L1 Status**

| | Group 1 (n=57)[a] | Group 2 (n=16)[b] |
|---|---|---|
| **Biomarker-positive, n/N (%)** | **32/57 (56)** | **13/16 (81)** |
| Immune active | 22/32 (69) | 6/13 (46) |
| Immune suppressed | 10/32 (31) | 7/13 (54) |
| PD-L1 CPS <1 | 5/32 (16) | 3/13 (23) |
| PD-L1 CPS ≥1 | 26/32 (81) | 9/13 (69) |
| **Biomarker-negative, n/N (%)** | **25/57 (44)** | **3/16 (19)** |
| Angiogenic | 11/25 (44) | 1/3 (33) |
| Immune desert | 14/25 (56) | 2/3 (67) |
| PD-L1 CPS <1 | 11/25 (44) | 3/3 (100) |
| PD-L1 CPS ≥1 | 13/25 (52) | 0/3 (0) |

[a]4 patients did not have biomarker panel results: 1 patient did not have samples collected and 3 patients' samples failed QC. [b]3 patients' samples are pending analysis.


## Acknowledgements

- Almac Group for contributions to RNA sequencing
- Genialis, Inc. for contributions to Xerna™ TME Panel classifications
- Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA for collaboration
- This study was funded by OncXerna Therapeutics, Inc.


## Author Disclosures

Advisory Board, personal: Astellas, Astra-Zeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Incyte, Merck-Serono, MSD, OncXerna, Pierre Fabre, Roche. Invited speaker, personal: Eisai, Eli Lilly. DMC chairman, personal: Five Prime Therapeutics. Coordinating PI, institutional, financial interest: Janssen-Cilag, Eli Lilly.

### Overall Safety

- No dose-limiting toxicities were observed during the safety run-in phase.
- At the data cut on 28 April 2021 (involving 77 patients), 96% of treatment-emergent adverse events (TEAEs) were CTCAE grades 1-3.
- Fatal AEs were injury, upper gastrointestinal haemorrhage, COVID-19, and "death, cause unknown", none of which were considered related to bavituximab or pembrolizumab.
- Thirty-four patients had ≥1 SAE; only pneumonitis (n=1), transient ischaemic attack (n=1) and encephalopathy (n=1) were related to both bavituximab and pembrolizumab.
- Serious AEs experienced by >1 patient were gastric cancer (9 patients, 11.7%), pleural effusion (3 patients, 3.9%), and ascites, dehydration, dysphagia, pyrexia, respiratory failure, and upper gastrointestinal haemorrhage (2 patients each, 2.6%).
- No new safety signals emerged with this treatment combination.

**Cumulative TEAEs[a] Occurring in >10% of All Patients**

| Preferred Term, n (%) | N=77 |
|---|---|
| Decreased appetite | 24 (31.2) |
| Fatigue | 24 (31.2) |
| Constipation | 22 (28.6) |
| Nausea | 20 (26.0) |
| Diarrhoea | 18 (23.4) |
| Anaemia | 15 (19.5) |
| Abdominal pain | 14 (18.2) |
| Vomiting | 14 (18.2) |
| Dyspnoea | 13 (16.9) |
| Oedema peripheral | 12 (15.6) |
| Weight decreased | 11 (14.3) |

| Preferred Term, n (%) | N=77 |
|---|---|
| Aspartate aminotransferase increased | 10 (13.0) |
| Arthralgia | 9 (11.7) |
| Ascites | 9 (11.7) |
| Dizziness | 9 (11.7) |
| Headache | 9 (11.7) |
| Myalgia | 9 (11.7) |
| Pyrexia | 9 (11.7) |
| Abdominal pain upper | 8 (10.4) |
| Alanine aminotransferase increased | 8 (10.4) |

[a] Related and unrelated to treatment.

### Anti-Tumour Activity in Group 1 (CPI-Naive)

- Objective responses were observed in 8 of 61 patients (ORR 13%).
- Duration of treatment in patients who responded was ~0.03 to 15.2 months (1 to 23 cycles, respectively).
- Subgroup analyses showed antitumour activity as follows:
  - **MSS:** Among 43 patients with available outcomes, ORR was 14%
  - **PD-L1 CPS <1:** 3 of 17 patients (18%) responded to treatment
  - **Biomarker-positive:** 7 of 32 patients (22%) responded to treatment
    - Of these, 5 patients had IA phenotype, 2 had IS phenotype
  - **NLR <4:** 90% of patients with response had NLR <4; ORR in these patients was 18%.

**Anti-Tumour Activity in Group 1: Overall and by Biomarker Status**

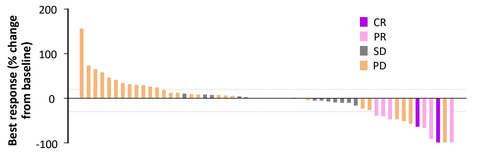
| Best Overall Response, n (%) | Overall (n=61) | Biomarker Panel (n=57) | |
|---|---|---|---|
| | | Positive (n=32) | Negative (n=25) |
| **ORR (CR + PR)** | **8 (13)** | **7 (22)** | **1 (4)** |
| Complete response (CR) | 2 (3) | 2 (6) | 0 |
| Partial response (PR) | 6 (10) | 5 (16) | 1 (4) |
| Stable disease (SD) | 18 (30) | 8 (25) | 8 (32) |
| **DCR (CR+PR+SD)** | **26 (43)** | **15 (47)** | **9 (36)** |
| Progressive disease (PD) | 30 (49) | 13 (41) | 16 (64) |
| Not evaluable/Not assessed | 5 (8) | 4 (13) | 0 |

**Best Overall Response by Demographic or Disease Characteristic**

| | ORR in Group 1, n/N (%) |
|---|---|
| **Tumour location:** Gastric \| GEJ | 2/18 (11%) \| 6/43 (14%) |
| **Region:** US \| EU \| Asia | 4/27 (15%) \| 1/2 (50%) \| 3/32 (9.4%) |
| **MSS status[a]:** MSS \| Unknown | 6/43 (14%) \|2/18 (11%) |
| **PD-L1 CPS[a]:** <1\|≥ 1\|unknown | 3/17 (17.6%) \| 5/40 (12.5%) \| 0/4 (0%) |
| **Line of therapy:** 2\|3\|≥4 | 4/35 (11%) \| 2/17 (12%) 2/9 \| (22%) |
| **ECOG:** 0 \| 1 | 2/22 (9%)\| 6/39 (15%) |
| **NLR:** <4\|≥4 | 7/39 (18% ) \|1/22 (4.5%) |

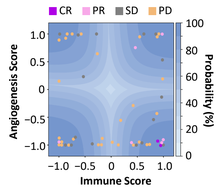
[a]The preliminary results used central laboratory values, if available. Local laboratory values were used if central laboratory results were not available.

**Best Change from Baseline in Sum of Longest Target Lesion Diameters**

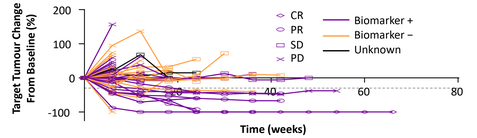



**Latent Space Plot Showing Decision Boundaries Between Biomarker Panel TME Subtypes**

Immune scores are shown on the x-axis from -1 to 1, while angiogenesis scores are shown on the y-axis. Classification probabilities derived from the biomarker panel are shown as blue contours. Filled circles represent individual patient samples from Group 1 and are coloured by best response.




**Longitudinal Change in Sum of Longest Target Lesion Diameters by Biomarker Status (N=55)**




## CONCLUSIONS

- The combination of bavituximab and pembrolizumab is well tolerated and shows clinical activity in gastric cancer.
  - No additional toxicities to those expected with pembrolizumab alone were seen.
- In Group 1 (CPI-naïve) , 68% of patients were biomarker-positive and 32% were biomarker-negative compared with Group 2 (CPI relapse): 82% positive and 18% negative.
  - The higher proportion of biomarker-positive patients in Group 2 likely reflects a selection bias since Group 2 was limited to patients who had prior clinical benefit on CPI treatment.
- The biomarker panel may be predictive of treatment response, with higher response rates observed in biomarker-positive patients in MSS, CPS>1, and CPS <1 subgroups.
- Retrospective analysis suggests baseline NLR may have a prognostic or predictive role.
- The anti-tumour activity of bavituximab plus pembrolizumab across high and low PD-L1 CPS, as well as in patients with MSS tumours, suggests that bavituximab sensitises cancers to CPI activity, potentially expanding the use of this combination to patients whose disease is typically less responsive to CPI.
- Further studies to confirm the activity of bavituximab in combination with immune CPIs and the predictive role of the Xerna™ TME Panel are planned.

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