# INITIAL SAFETY AND EFFICACY FINDINGS WITH BAVITUXIMAB PLUS PEMBROLIZUMAB IN PATIENTS WITH ADVANCED GASTRIC OR GASTROESOPHAGEAL CANCER

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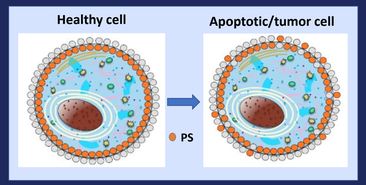
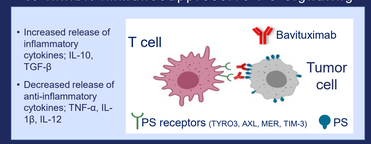
## BACKGROUND

- Phosphatidylserine (PS), an amino-phospholipid translocated to the outer leaflet of the plasma membrane in apoptotic tumor cells, exerts a global, powerful immunosuppressive signal




## BAVITUXIMAB

- First-in-class chimeric monoclonal antibody (MAb) currently in clinical development for cancer
- Complexes with β2-glycoprotein 1 (β2-GP1) to inhibit immunosuppressive PS signaling




- In a post-hoc analysis of Ph III SUNRISE 2nd line NSCLC study data, patients who progressed on bavituximab plus docetaxel and who subsequently received a checkpoint inhibitor (CPI) showed improved overall survival[1]

## PEMBROLIZUMAB

- High-affinity IgG4 MAb to programmed cell death 1 (PD-1) receptor
- Potently inhibits binding of programmed cell death ligand 1 (PD-L1) and PD-L2 to PD-1, thereby blocking PD-1/PD-L- mediated immunosuppression
- One mechanism of resistance to CPI in treatment relapsed patients includes T-cell exhaustion and the presence of myeloid suppressive cells
- In 2nd and 3rd line patients, the ORR for pembrolizumab monotherapy was 16% (Keyonote-061, CPS≥1) and 11.6% (Keynote-059, PD-L1 agnostic), respectively.

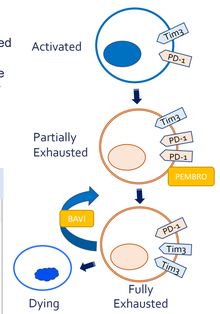
## BAVITUXIMAB IN COMBINATION WITH PEMBROLIZUMAB

- Clear biologic rationale for combination of dual PS and PD-(L)1 inhibition
- Inhibition of PS receptor mediated (TIM-3/TYRO3, AXL, MER) activation in exhausted myeloid and lymphoid immune cells with bavituximab may inhibit immunosuppressive myeloid cells, re-stimulate T cells or render exhausted T cells susceptible to checkpoint inhibition
- Supported by both nonclinical and clinical data

PD-1 & Tim3 Drive Progressive Stages of T cell Exhaustion

| | Receptor Expression | | Cytokine Production |
|---|---|---|---|
| T Cell Activity: | PD-1 | Tim-3 | IFNγ, TNFα, IL-2 |
| Activated | + | + | +++ |
| Partially Exhausted | +++ | + | + |
| Fully Exhausted | + | +++ | - |

CYTOTOXIC T CELL STAGES




## STUDY DESIGN & OBJECTIVES

- Phase 2, multicenter, open-label, single arm, global study (NCT0409641) in checkpoint inhibitor naïve, advanced gastric or gastroesophageal junction patients
  - Patients with known MSI-H were excluded from the study
- Safety run-in phase, 21-day dose-limiting toxicity observation period, followed by an expansion phase
- Study objectives:
  - Primary: Assess safety, tolerability and anti-tumor activity (using RECIST) v1.1 of bavituximab in combination with pembrolizumab in patients with advanced gastric/gastroesophageal junction cancer
  - Secondary: Assess bavituximab concentrations and immunogenicity
  - Tertiary: Evaluate novel biomarker signatures and explore relationships among patient subgroups with efficacy outcomes
- Patient subgroup analyses were explored using for microsatellite stability (MSS) status, PD-L1 status, neutrophil to lymphocyte ratio (NLR), and TME-1 panel, a proprietary RNA expression signature panel characterized using patient tumor biopsies.
- Preliminary results reflect both central and local laboratory values based upon data availability.

## STUDY STATUS

- Safety run-in phase: 3 patients enrolled; recommend dose for expansion confirmed at 3 mg/kg bavituximab QW, 200 mg pembrolizumab Q3W
- Extension phase opened: enrolled an additional 37 patients
- 32 patients discontinued treatment due to: disease progression (24), adverse events (5), other (3)
- 8 patients still on treatment at data cut off date of Aug 14, 2020

## BASELINE PATIENT CHARACTERISTICS

| | Patients (N=40) |
|---|---|
| Age, years | |
| Mean (SD) | 60.9 (13.16) |
| Median | 62.5 |
| Sex, n (%) | |
| Male | 30 (75.0) |
| Female | 10 (25.0) |
| ECOG performance, n (%) | |
| 0 | 12 (30.0) |
| 1 | 28 (70.0) |
| Primary site | |
| Gastric | 25 (62.5) |
| GEJ | 15 (37.5) |
| Previous lines of therapy, n (%) | |
| 1 | 28 (70.0) |
| 2 | 12 (30.0) |
| Race, n (%) | |
| Non-Asian | 22 (55.0) |
| Asian | 18 (45.0) |
| Molecular characteristics, n (%) | |
| HER2 positive | 6 (15.0) |
| HER2 negative | 34 (85.0) |
| | |
| EBV positive | 0 |
| EBV negative | 4 (10.0) |
| EBV unknown | 36 (90.0) |
| | |
| MSI-H | 0 |
| MSS | 24 (60.0) |
| UNK | 16 (40.0) |
| | |
| PD-L1 CPS < 1 | 10 (25.0) |
| PD-L1 10 > CPS ≥ 1 | 10 (25.0) |
| PD-L1 CPS ≥ 10 | 11(27.5) |
| Unknown | 9 (22.5) |
| | |
| TME-1 biomarker positive* | 14 (60.8) |
| TME-1 biomarker negative* | 9 (39.1) |
| | |
| NLR ratio <4 | 22 (55) |
| NLR ratio ≥ 4 | 18 (45) |


## REFERENCES

1. Gerber DE, Horn L, Boyer M., et al. Randomized phase III study of docetaxel plus bavituximab in previously treated advanced non-squamous non-small-cell lung cancer. Annals Oncology. 2018; 29: 1548-1553.
2. Gray MJ, Gong J, Hatch MM., et al. Phosphatidylserine-targeting antibodies augment the anti-tumorigenic activity of anti-PD-1 therapy by enhancing immune activation and downregulating pro-oncogenic factors induced by T-cell checkpoint inhibition in murine triple-negative breast cancers. Breast Cancer Res. 2016; 18: 50



## ACKNOWLEDGEMENTS

- Almac Group for their contributions on RNA sequencing
- Genialis, Inc. for their contributions on TME-1 classifications
- Merck for collaboration


## *AUTHOR DISCLOSURES

- Lilly; Astra Zeneca; Bayer; Bristol-Myers Squib; Janssen-Cilag; Merck Serono; MSD Oncology; Oncologie, Inc; Pierre Fabre; Roche/Genentech; Sanofi.

## SAFETY: OVERALL

- There were no dose limiting toxicities observed during the 3 patient safety run-in phase.
- Gastrointestinal and general disorders were the most commonly affected system organ classes.
- Based on a data cut of 6 July 2020 the most common treatment emergent adverse events (TEAEs, occurring in ≥ 20% of patients) included decreased appetite, nausea, fatigue, constipation, vomiting, anemia and decreases in weight.
  - 90% of TEAEs were Grade 1-3.
  - Five TEAEs( 10%) were Grade 5 and included disease progression (n=3), aspiration pneumonia (n=1) and respiratory failure (n=1)
- Fourteen (14) patients had at least one serious adverse event (SAE)
  - All SAEs were reported as not related to the combination; except for pneumonitis (n=1, recovered/resolved), which was reported as related to both bavituximab and pembrolizumab
- No new safety signals have emerged with the treatment combination.

## TREATMENT-RELATED ADVERSE EVENTS OCCURING IN >5% OF PATIENTS

| Patients with at least one Treatment Emergent Adverse Event, n (%) | 40 (100) |
|---|---|
| Preferred Term | |
| Decreased appetite | 16 (40.0) |
| Nausea | 15 (37.5) |
| Fatigue | 12 (30.0) |
| Constipation | 10 (25.0) |
| Vomiting | 10 (25.0) |
| Anaemia | 8 (20.0) |
| Weight decreased | 8 (20.0) |
| Abdominal pain | 7 (17.5) |
| Oedema peripheral | 7 (17.5) |
| Pyrexia | 7 (17.5) |
| Arthralgia | 6 (15.0) |
| Chills | 6 (15.0) |
| Dyspnoea | 6 (15.0) |
| Back pain | 5 (12.5) |
| Diarrhoea | 5 (12.5) |
| Dysphagia | 5 (12.5) |
| Depression | 4 (10.0) |
| Dizziness | 4 (10.0) |
| Hypothyroidism | 4 (10.0) |
| Myalgia | 4 (10.0) |
| Rash | 4 (10.0) |
| Abdominal distension | 3 (7.5) |
| Abdominal pain upper | 3 (7.5) |
| Alanine aminotransferase increased | 3 (7.5) |
| Aspartate aminotransferase increased | 3 (7.5) |
| Asthenia | 3 (7.5) |
| Dehydration | 3 (7.5) |
| Headache | 3 (7.5) |
| Hypertension | 3 (7.5) |

## ANTI-TUMOR ACTIVITY: OVERALL

| Best Response | Evaluable patients (n=36) |
|---|---|
| ORR (CR+PR), n (%) | 7 (19.4) |
| Complete response, n (%) | 2 (5.5) |
| Partial response, n (%) | 5 (13.9) |
| Stable disease, n (%) | 7 (19.4) |
| DCR (CR+PR+SD), n (%) | 14 (38.9) |
| Disease progression, n (%) | 22 (61.1) |

- Objective responses were observed in 7 evaluable patients for an overall response rate (ORR) of 19.4%.
  - Duration of treatment in responding patients ranges from approximately 63 to 315 days (3 to 15 cycles respectively).
- In patient subset analyses based upon biomarkers of interest for the treatment combination:
  - Out of the 23 MSS patients with outcome data, the ORR was 17.4% (n=4)
  - 20% of patients with a combined positive score (CPS) <1 responded to treatment (2 out of 10), where both patients were complete responses (CRs)
  - 21.4% of TME-1 biomarker panel positive patients responded (3 out 14)
  - 100% of the responding patients had an NLR of <4; the ORR in patients with <4 was 33% (7 out of 21)

## ANTI-TUMOR ACTIVITY BY PATIENT SUBGROUP

| Microsatellite Stability Status (MSS, n= 36) | | | |
|---|---|---|---|
| | MSS (n=23) | MSI-H | Unknown (n=13) |
| ORR (CR + PR), n (%) | 4 (17.4) | 0 | 3 (23.1) |
| Complete response, n (%) | 2 (8.7) | 0 | 0 |
| Partial response, n (%) | 2 (8.7) | 0 | 3 (23.1) |
| Stable disease, n (%) | 4 (17.4) | 0 | 3 (23.1) |
| Disease progression, n (%) | 15 (65.2) | 0 | 7 (53.8) |

| Programed Death Ligand 1 (PD-L1) Expression (n=36) | | | | |
|---|---|---|---|---|
| | CPS <1 (n=10) | 10 > CPS ≥ 1 (n=9) | CPS ≥10 (n=10) | Unknown (n=7) |
| ORR (CR + PR), n (%) | 2 (20.0) | 0 | 2 (20.0) | 3 (42.9) |
| Complete response, n (%) | 2 (20.0) | 0 | 0 | 0 |
| Partial response, n (%) | 0 | 0 | 2 (20.0) | 3 (42.9) |
| Stable disease, n (%) | 0 | 3 (33.3) | 4 (40.0) | 0 (0) |
| Disease progression, n (%) | 8 (80.0) | 6 (66.7) | 4 (40.0) | 4 (57.1) |

| | Tumor Microenvironment (TME-1) Biomarker Panel (n=23) | | Neutrophil to Lymphocyte Ratio (NLR, n=36) | |
|---|---|---|---|---|
| | Positive (n=14) | Negative (n=9) | <4 (n=21) | ≥4 (n=15) |
| ORR (CR + PR), n (% | 3 (21.4) | 1 (11.1) | 7 (33.3) | 0 |
| Complete response, n (%) | 2 (14.3) | 0 | 2 (9.5) | 0 |
| Partial response, n (%) | 1 (7.1) | 1 (11.1) | 5 (23.8) | 0 |
| Stable disease, n (%) | 4 (28.6) | 1 (11.1) | 4 (19.0) | 3 (20.0) |
| Disease progression, n (%) | 7 (50.0) | 7 (77.8) | 10 (47.6) | 12 (80.0) |

## CONCLUSIONS

- The combination of bavituximab and pembrolizumab appears to be well tolerated in this patient population.
- Anti-tumor activity was observed in this high unmet need patient population of both second- and third-line patients with lower historical CPI response rates, such as MSS (17.4% ORR) and CPS<1 (20% ORR)
- These data support the proposed hypothesis that inhibition of immunosuppressive cells with bavituximab can potentiate CPI activity.
- In addition, anti-tumor activity was enhanced in patients with reduced NLR (33% ORR) and in patients whose TME RNA expression profile displayed hallmarks of either an active or suppressed immune response (21.4% ORR).
- Overall, the bavituximab/pembrolizumab combination in advanced gastric cancer patient appears promising, especially in TME-1 biomarker positive patients with NLR values < 4 where the combined ORR is 42.9% (3 out of 7).

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