A phase II clinical trial of the phosphatidylserine targeting antibody, bavituximab in combination with pembrolizumab in patients with advanced hepatocellular carcinoma

David Hsieh[1], Radhika Kainthla[1], Hao Zhu[1], Amy Jones[1], Adam Yopp[1], Hagop Youssoufian[2], Colleen Mockbee[2], Kerry Culm[2], Mark Uhlik[2], Laura Benjamin[2], M Shaalan Beg[1]

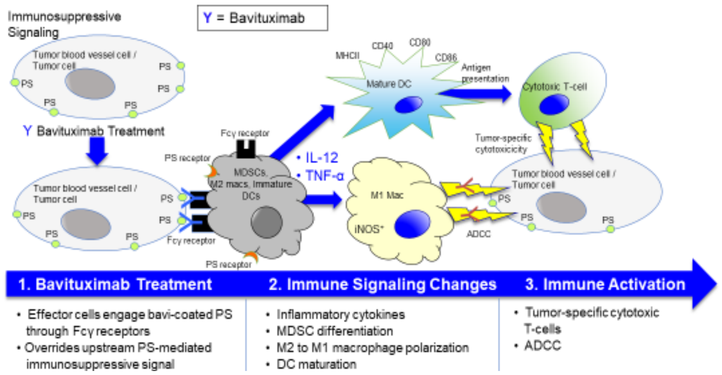
[1] Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX; [2]OncXerna Therapeutics, Waltham, MA, USA

BACKGROUND

- Phosphatidylserine is a highly immunosuppressive molecule typically expressed on the inner leaflet of the plasma membrane of normal cells.
- Phosphatidylserine and becomes externalized to the outer leaflet of the plasma membrane on cells that line tumor blood vessels, tumor cells, and exosomes in the tumor microenvironment creating a specific target for anticancer treatments.

Bavituximab

- First-in-class chimeric monoclonal antibody in clinical development for cancer.
- Complexes with β2-glycoprotein 1 to inhibit immunosuppressive phosphatidylserine signalling.
- Can modulate the tumor microenvironment (TME) by driving innate and adaptive immunitv.



STUDY DESIGN & HYPOTHESIS

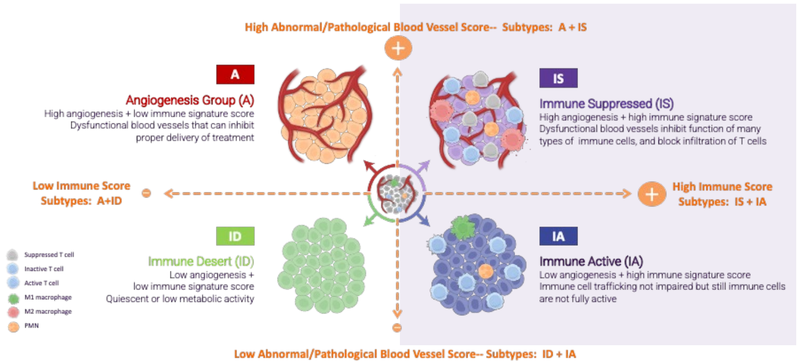
- Phase 2, single arm, clinical trial
- Sample size:
  - 28 evaluable patients
  - 3 or more of the first 15 patients should have a complete or partial response
- Hypothesis: the addition of bavituximab can increase the clinical activity of pembrolizumab for patients with advanced HCC

Locally advanced or metastatic HCC not amenable to locoregional therapy → Pembrolizumab: 200 mg IV once every 3 weeks; Bavituximab: 3 mg/kg IV weekly → Endpoints:
Primary
ORR
Secondary
OS
6-months PFS
DOR
Safety
Exploratory
Correlative

Xerna™ TME PANEL

- Pre-treatment tumor 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 tumor 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 retrospective analysis was conducted to test the hypothesis that tumors with high immune score (immune active [IA] or immune-suppressed [IS] TME subtypes [biomarker-positive]) are more likely to respond to bavituximab + pembrolizumab than those with angiogenic (A) or immune-desert (ID) TME subtypes (biomarker-negative).

Biomarker Panel Subtypes Based on Angiogenesis and Immune Signature Score



PATIENT CHARACTERISTICS (N=28)

Age, median, y (IQR)	64 (60-67)
Sex	
Female no. (%)	4 (14.3)
Male no. (%)	24 (85.7)
Race	
Asian no. (%)	0 (0)
Black no. (%)	14 (50)
White no. (%)	14 (50)
Ethnicity	
Hispanic no. (%)	2 (7.1)
Non-Hispanic no. (%)	26 (92.9)

SAFETY

Treatment-related Adverse Events

Adverse Event	Grade ≥ 3 No. (%)	All No. (%)
Rash	1 (3.6)	3 (10.7)
AST increase	1 (3.6)	3 (10.7)
Chills	0 (0)	2 (7.1)
Diarrhea	1 (3.6)	5 (17.9)
Fatigue	0 (0)	3 (10.7)
Platelet count decrease	0 (0)	2 (7.1)
Pruritus	0 (0)	3 (10.7)
ALT increase	0 (0)	2 (7.1)

EFFICACY

Best Overall Response N (%)	All Patients[1] N =28	Patients with Biomarker Data[2]		
		All N =19	Biomarker + N = 8	Biomarker - N =11
Complete response[3]	2 (7.1)	1 (5.3)	1 (12.5)	0 (0)
Partial response[3]	7 (25.0)	5 (26.3)	4 (50.0)	1 (9.1)
Stable disease	5 (17.9)	3 (15.8)	1 (12.5)	2 (18.2)
Progressive disease	14 (50.0)	10 (52.6)	2 (25.0)	8 (72.7)
Objective response rate	9 (32.1)	6 (31.6)	5 (62.5)	1 (9.1)
Disease control rate	14 (50.0)	9 (47.4)	6 (75.0)	3 (27.3)

[1]Analysis based on evaluable patients per protocol; [2]All patients with available biomarker results; 9 patients did not have tissue available for testing and biomarker status could not be determined. [3]Responses were confirmed by radiographic assessment no sooner than 4 weeks from the time of initial response.

CONCLUSIONS

- Bavituximab plus pembrolizumab is well tolerated with no new safety signals.
- Bavituximab plus pembrolizumab induces objective tumor responses in a meaningful subset of HCC in the frontline setting.
- Retrospective analysis of tumor biopsies showed that responses were enhanced in Xerna TME biomarker-positive patients while higher PD rates were observed in biomarker-negative patients.

ACKNOWLEDGEMENTS & DISCLOSURES

- Almac Group for contributions to RNA sequencing
- Genialis, Inc. for contributions to Xerna™ TME Panel classifications
- This study was sponsored by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA and OncXerna Therapeutics, Inc.
- David Hsieh declares no conflicts of interest.

American Society for Clinical Oncology Gastrointestinal Cancers Symposium (ASCO GI) 2023; January 19-21, 2023. Abstract 584. Poster E16.

ClinicalTrials.gov NCT03519997