A Phase 1b Study of Navicixizumab & Weekly Paclitaxel in Heavily Pre-Treated Platinum Resistant Ovarian, Primary Peritoneal or Fallopian Tube Cancer

S. Fu[1], B. Corr[2], E. Hamilton[3], R.A. Burger[4], R. Wenham[5], R.W. Naumann[6], R. Stagg[7], K.N. Moore[3,8]

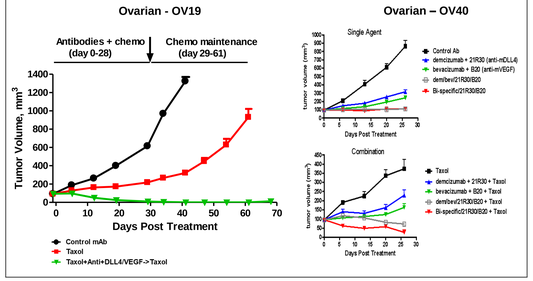
[1]Department of Investigational Cancer Therapeutics, MD Anderson Cancer Center, Houston, TX, US, [2]Gynecologic Oncology, University of Colorado Denver, Aurora, CO, US, [3]Gynecologic Oncology, Sarah Cannon at Tennessee Oncology, Nashville, TN, US, [4]Gynecologic Oncology, University of Pennsylvania Medical Center, Philadelphia, PA, US, [5]Gynecologic Oncology, Moffitt Cancer Center, Tampa, FL, US, [6]Gynecologic Oncology, Levine Cancer Institute, Charlotte, NC, US, [7]Clinical Research, OncoMed Pharmaceuticals, Redwood City, CA, US, [8]Gynecologic Oncology, Stephenson Cancer Center/University of Oklahoma, Oklahoma City, Oklahoma, US.

Background

Inhibition of tumor angiogenesis has proven to be a successful approach to treating cancer and two ligands responsible for tumor angiogenesis are vascular endothelial growth factor (VEGF) and delta-like ligand 4 (DLL4) which is one of the 5 ligands in the Notch pathway. In addition, inhibition of DLL4 reduces the tumorigenicity of a tumor in xenograft models by reducing the number of tumor initiating cells. Navicixizumab is an IgG_2 humanized bispecific monoclonal antibody directed against both human DLL4 and VEGF. Navicixizumab was carefully designed such that the anti-VEGF and anti-DLL4 arms have roughly equivalent affinity for their respective ligands. Navicixizumab was efficacious in all 11 of the human tumor xenograft models tested which included human breast, colon, gastric, glioblastoma, non-small cell lung cancer, pancreatic, ovarian and renal cell carcinomas. Finally, navicixizumab had a response rate of 25% (3/12) in heavily pretreated ovarian cancer pts who were treated in an earlier single agent Phase 1a trial.

Preclinical Xenograft Data

- Efficacious in ovarian xenograft models as a single agent and in combination with paclitaxel
- Reduces tumor growth and tumorigenicity



Methods

This is an ongoing Phase 1b study of paclitaxel & navicixizumab in platinum resistant ovarian cancer pts who have failed > 2 prior therapies &/or bevacizumab. Paclitaxel 80 mg/m2 was given on Days 1, 8 and 15 & navicixizumab was given on Days 1 & 15 of every 28 day cycle. This study was designed as a dose escalation trial testing navicixizumab doses of 3 or 4 mg/kg followed by an expansion cohort to enroll a total of 30-60 patients. The expansion cohort was undertaken with 3 mg/kg of navicixizumab as higher doses did not show increased activity, but did result in more pronounced chronic toxicity in the Phase 1a study. A standardized treatment algorithm for hypertension is being employed. Thirty-four patients have been enrolled of the study at 7 centers. Subjects were assessed for safety, immunogenicity, PK, biomarkers, and efficacy. Patients enrolled in the dose escalation cohort were assessed for DLTs from the time of the first dose through Day 28. The maximum tolerated dose (MTD) was defined as the highest dose level at which 0–1 of 6 subjects experienced a DLT (i.e., 6 patients will ultimately be treated at the MTD dose level). Three subjects were enrolled in cohort 1 and dosed at 3 mg/kg and 2 patients were enrolled in cohort 2 and dosed at 4 mg/kg. While there were no DLTs in these 5 pts, a decision was made to dose all further patients at 3 mg/kg based on the evolving single agent Phase 1a data which suggest that maximal efficacy was observed at a dose < 4 mg/kg. Subsequently, 29 patients were treated with 3 mg/kg in the expansion portion of the study. Data entered in the database through August 13, 2018 are presented. This study is sponsored by OncoMed Pharmaceuticals Inc.

Patient Demographics (n=34)

Navicixizumab Dose Level	3 mg/kg	4 mg/kg	Expansion 3 mg/kg	Total
N	3	2	29	34
Median age (years)	66	73	63	63
Ovarian Cancer Primary Peritoneal Cancer Fallopian Tube Cancer	2 0 1	2 0 0	20 2 4	24 2 5
Platinum Resistant* Yes No	 3 0	 2 0	 25 1**	 30 1
Median Number (range) Prior Therapies	3 (3-4)	4.5 (4-5)	4 (2-12)	4 (2-12)
Prior Paclitaxel***	3	2	27****	32/32 (100%)
Prior Bevacizumab***	1	1	20	22/32 (69%)

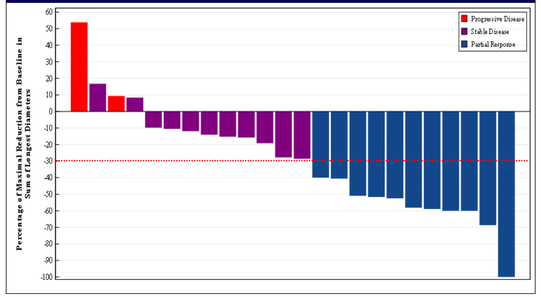
* Data on the platinum resistance status had been entered in the database on 31 of the 34 patients
** Protocol deviation.
*** Data on the prior chemotherapies had been entered in the database on 32 of the 34 patients
**** 1 patient received Abraxane®

RECIST Best Overall Response

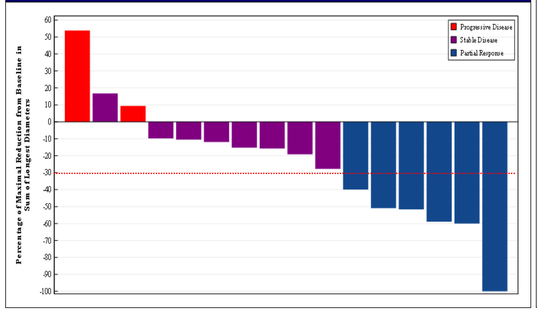
Dose	3 mg/kg	4 mg/kg	Expansion 3 mg/kg	Total	Bevacizumab Naïve Pts*	Bevacizumab Previously Treated Patients*
Treated	3	2	29	34	8	22
Partial Response	2	2	7	11/26 (42%)	4/7 (57%)	6/18 (33%)
Stable Disease	1	-	10	11/26 (42%)	3/7 (42%)	8/18 (44%)
Progressive Disease	-	-	2	2/26 (8%)	0/7 (0%)	2/18 (11%)
Not Evaluable	-	-	2	2/26 (8%)	0/7 (0%)	2/18 (11%)
Too Early	-	-	8	8	1	4
Clinical Benefit Rate	3	2	17	22/26 (85%)	7/7 (100%)	14/18 (78%)

* At the time of the data-cut, information on whether patients had or had not received prior bevacizumab was available for 30/34 patients evaluated for RECIST response

Best % Change in RECIST Target Lesion Size - All Patients



Best % Change in RECIST Target Lesion Size - Bevacizumab Treated Patients

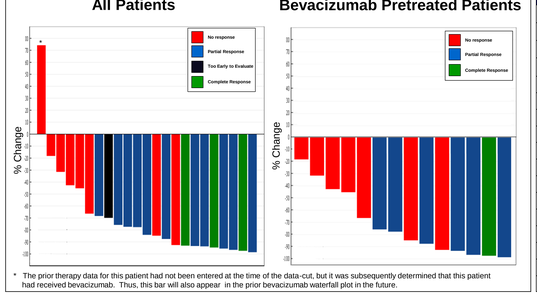


GCIG Best CA-125 Response

Dose	3mg/kg	4 mg/kg	Expansion 3 mg/kg	Total	Bevacizumab Naïve Pts*	Bevacizumab Previously Treated Patients*
Treated	3	2	29	34	10	22
Complete Response	0	1	2	3/23 (13%)	2/7 (29%)	1/15 (7%)
Partial Response	1	0	10	11/23 (48%)	5/7 (71%)	6/15 (40%)
Total Response	1	1	12	14/23 (61%)	7/7 (100%)	7/15 (47%)
No Response	1	0	8	9/23 (39%)	0/7 (0%)	8/15 (53%)
Not Evaluable	1	1	7	9	2	7
Too Early	0	0	2	2	1	0

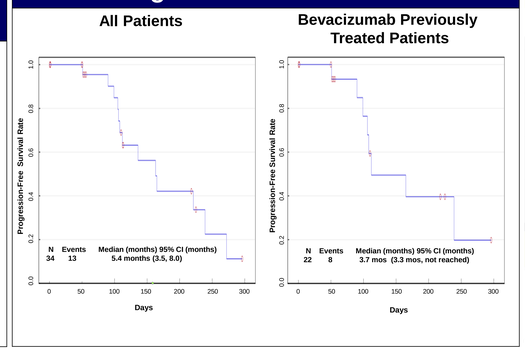
* At the time of the data-cut, information on whether patients had or had not received prior bevacizumab was available for 32/34 patients evaluated for CA-125 response

Best % Change in CA-125



* The prior therapy data for this patient had not been entered at the time of the data-cut, but it was subsequently determined that this patient had received bevacizumab. Thus, this bar will also appear in the prior bevacizumab waterfall plot in the future.

Progression-Free Survival



Treatment Emergent Adverse Events > 15% By Grade (n=34)

Grade	1	2	3	4	5	Total
Hypertension	1	3	14	0	0	19* (56%)
Fatigue	4	12	1	0	0	17 (50%)
Nausea	9	2	2	0	0	13 (38%)
Diarrhea	10	3	0	0	0	13 (38%)
Neutropenia	0	2	5	3	0	10 (29%)
Leukopenia	3	4	2	0	0	9 (27%)
Vomiting	6	2	1	0	0	9 (27%)
Decreased Appetite	7	1	0	0	0	8 (24%)
Headache	6	1	0	0	0	7 (21%)
Peripheral neuropathy	4	3	0	0	0	7 (21%)
GERD	5	1	0	0	0	6 (18%)
Peripheral edema	3	3	0	0	0	6 (18%)
Constipation	2	4	0	0	0	6 (18%)

*1 event ungraded

Treatment Related Adverse Events > 5% By Grade (n = 34)

Grade	1	2	3	4	5	Total
Hypertension	0	4	13	0	0	18* (53%)
Fatigue	4	7	0	0	0	11 (32%)
Diarrhea	7	1	0	0	0	8 (24%)
Headache	5	1	0	0	0	6 (18%)
GERD	3	1	0	0	0	4 (12%)
Nausea	2	0	1	0	0	3 (9%)
Decreased Appetite	3	0	0	0	0	3 (9%)
WBC decreased	1	2	0	0	0	3 (9%)
Neutrophil decreased	0	2	1	0	0	3 (9%)
BNP increased	3	0	0	0	0	3 (9%)
Dyspnea	1	2	0	0	0	3 (9%)
Proteinuria	1	1	0	0	0	2 (6%)
Back Pain	1	1	0	0	0	2 (6%)
Chills	2	0	0	0	0	2 (6%)
Thrombocytopenia	0	0	1	1	0	2 (6%)
Peripheral edema	1	1	0	0	0	2 (6%)

*1 event ungraded

Adverse Events of Special Interest

Adverse Event	# of Patients with Event (Grade)
Pulmonary Hypertension	1 related Grade 2 (reversible)
Heart Failure	1 related Grade 1 (reversible)
GI Perforation	1 related Grade 4
Thrombocytopenia	1 related Grade 4 (reversible) 1 unrelated Grade 4 (reversible)

Immunogenicity (n = 25)

ADA+ Patients (post-baseline)	ADA+ patients with impact on PK and an infusion reaction
4/25 (16%)	3*/25 (12%)

* 2 Grade 1, 1 Grade 2

Summary

- This is a Phase 1b dose escalation and expansion study of navicixizumab, a bispecific monoclonal antibody (targeting the DLL4 ligand in the Notch pathway and VEGF) plus paclitaxel in patients with the platinum resistant ovarian cancer who had failed > 2 prior therapies and/or received prior bevacizumab.
- Prior therapy data was available on 32 of 34 patients. Patients had received a median of 4 prior therapies,100% had previously received paclitaxel and 69% had received bevacizumab.
- The overall clinical benefit rate was 85%. Partial response was obtained in 11 of the 26 (42%) patients. The response rates in the bevacizumab naïve and bevacizumab pretreated patients were 57% and 33%, respectively.
- Fourteen of the 23 (61%) evaluable patients had a GCIG CA-125 response. The GCIG CA-125 response rates in the bevacizumab naïve and bevacizumab pretreated patients were 100% and 47%, respectively.
- The median PFS was 5.4 months (95% CI: 3.5 – 8 months). The median PFS for bevacizumab pretreated patients was 3.7 months (95% CI: 3.3 months – not reached).
- The most common related adverse events were hypertension (53%), fatigue (32%), diarrhea (24%) and headache (18%).
- The hypertension was managed with a protocol defined standardized anti-hypertensive treatment algorithm.
- Other rare adverse events of special interest were one Grade 2 related pulmonary hypertension, one Grade 1 related heart failure, one Grade 4 related gastrointestinal perforation & two (1 related, 1 unrelated) Grade 4 thrombocytopenia.
- Four of 25 (16%) patients were ADA positive and there was an impact on drug clearance and an associated infusion reaction in 3 of these patients.
- These efficacy data are encouraging in this heavily pretreated platinum resistant patient population and enrollment in the study is ongoing.

Corresponding author Siqing Fu, M.D.
(email address: siqingfu@mdanderson.org)