Correlative analyses of Phase 1b study of navicixizumab plus paclitaxel in patients with platinum-resistant ovarian cancer using Xerna™ TME Panel

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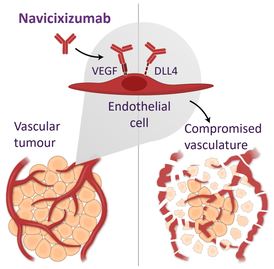
BACKGROUND

Mode of Action

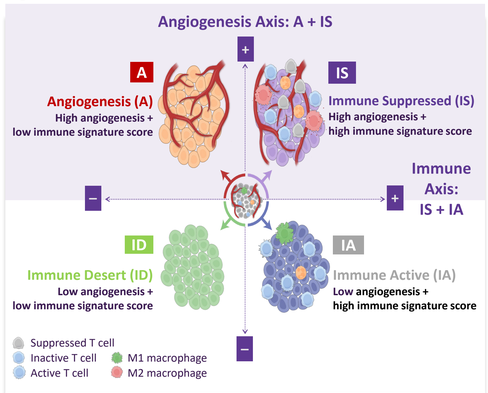
- Navicixizumab is a first-in-class, bispecific, anti-angiogenic antibody to vascular endothelial growth factor (VEGF) and delta-like ligand 4 (DLL4) in the Notch pathway[1]
- DLL4 and VEGF are central regulators of tumour angiogenesis
- Navicixizumab can localize to the tumour microenvironment (TME) to block cell-bound DLL4 and sequester locally secreted VEGF[1]
- Notch signalling regulates angiogenesis via a different mechanism to VEGF, making it a potential therapeutic target in overcoming anti-VEGF resistance[2,3]
- In preclinical tumour studies, dual DLL4 and VEGF blockade was additive and superior to inhibiting DLL4 or VEGF alone[4]



Xerna™ TME Panel: Novel Biomarker Assay

- The Xerna TME Panel evaluates RNA expression of ~100 genes defining the angiogenic and immune biologies that dominate the TME[5]
- A machine-learning model classifies patient tumour samples into one of four subtypes based on the gene signatures of the angiogenic and immune processes that dominate TME biology: angiogenic, immune-active, immune-desert, and immune-suppressed[5]

Biomarker Panel Subtypes Based on Angiogenesis and Immune Signatures



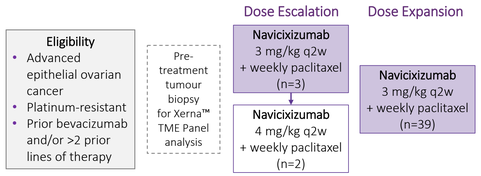
AIM

- To test the biomarker hypothesis that tumours with high angiogenesis or immune-suppressed TME subtypes (**biomarker-positive**) are more likely to respond to navicixizumab treatment than those with immune-active and immune-desert phenotypes (**biomarker-negative**) in patients with platinum-resistant ovarian cancer (PROC)

METHODS

Study Design

- Phase 1b open-label, non-randomised, dose-escalation and -expansion study of the safety, tolerability and efficacy of navicixizumab plus paclitaxel (NCT03030287)



Biomarker Analyses

- Pre-treatment formalin-fixed, paraffin-embedded tumour samples were retrospectively analysed for RNA expression by total RNA sequencing
- Gene expression data were quantified by standard bioinformatics processing, and expression values were used as input for the TME Panel algorithm
  - The algorithm takes as input normalized gene expression values for the biomarker panel genes, analysed per patient, and returns as output a TME phenotype assignment
  - Patients whose tumours had high angiogenesis (A or IS) TME subtypes per the TME Panel were classified as '**biomarker-positive**' and those with IA or ID TMEs were classified as '**biomarker-negative**'
- Patients' TME profiles were retrospectively analysed against their objective responses as assessed per RECIST 1.1
- Cox proportional hazards models were used in univariate and multivariate analyses of progression-free survival (PFS) to evaluate the prognostic and predictive utility of the TME Panel and other clinicopathological factors

REFERENCES

1. Jimeno A, et al. *Invest New Drugs* 2019;37:461-472; 2. Xie Q, et al. *J Ovarian Res* 2017;10:13; 3. Noguera-Troise I, et al. *Nature* 2006;444:1032-1037; 4. Yen W-C, et al. *Mol Can Ther* 2015;14:C164; 5. Strand-Tibbitts K, et al. *J ImmunoTher Can* 2020;8:A155-A156.

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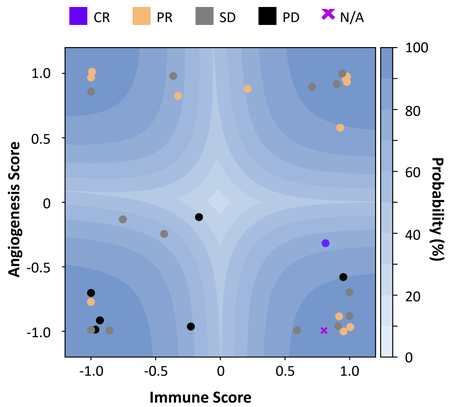
RESULTS

TME Panel Findings

- This study enrolled 44 patients in the intent-to-treat (ITT) population
- Samples from 33 of these patients were available for TME Panel testing
  - 13 (39%) were biomarker-positive
  - 20 (61%) were biomarker-negative

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 TME Panel are shown as blue contours. Filled circles represent individual patient samples and are coloured by best response.
CR, complete response; N/A, response data not available; PD, progressive disease; PR, partial response; SD, stable disease.

Anti-Tumour Activity by Biomarker Status

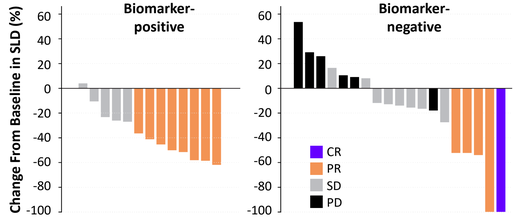
- Among biomarker-positive patients, the objective response rate (ORR) was 62% and disease control rate (DCR) was 100%, compared to 25% and 65%, respectively, in biomarker-negative patients
- PD as best response was observed only in biomarker-negative patients
- The biomarker-positive group had a median PFS gain of 5.3 months (HR 0.43 [95% CI 0.188–0.999]) over the biomarker-negative group

Best Overall Response per RECIST 1.1

n (%)	ITT		Biomarker Status	
	Overall (N=44)	Bev-treated (n=30)	Positive (n=13)	Negative (n=20)
ORR (CR+PR)	**19 (43)**	**10 (33)**	**8 (62)**	**5 (25)**
CR	1 (2)	0	0	1 (5)
PR	18 (41)	10 (33)	8 (62)	4 (20)
SD	15 (34)	10 (33)	5 (38)	8 (40)
DCR (CR+PR+SD)	**34 (77)**	**20 (67)**	**13 (100)**	**13 (65)**
PD	7 (16)	7 (23)	0	6 (30)
Not evaluable	3 (7)	3 (10)	0	1 (5)

Bev, bevacizumab; CR, complete response; DCR, disease control rate; PD, progressive disease; PR, partial response, SD, stable disease.

Best Change from Baseline in Sum of Longest Target Lesion Diameters (SLD)



Link Between TME Panel Classification and PFS

- Univariate analysis of PFS showed a significant association with:
  - Biomarker-positive status per TME Panel (p=0.044)
  - Measurable disease ≥50 mm at baseline (p=0.014)
- Multivariate analysis showed an overall significant effect on PFS driven largely by measurable disease at baseline (p=0.010)
  - The association between PFS and biomarker-positive status was not significant (p=0.074), but the HR was 0.45

Univariate Analysis of PFS using Cox Proportional Hazards Model

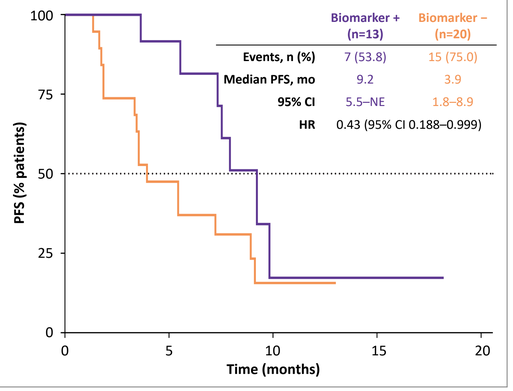
Variable	HR (95% CI)	P-value
Age (≥65 vs <65 years)	1.19 (0.568–2.51)	0.641
Ascites (yes vs no)	2.05 (0.593–5.46)	0.229
Current disease stage (IV vs III)	1.63 (0.760–3.59)	0.208
Measurable disease, mm (≥50 vs 10–<50)	**0.34 (0.137–0.801)**	**0.014**
PFI, months (<3 vs ≥3)	2.23 (0.740–5.50)	0.142
Prior bevacizumab (no vs yes)	1.93 (0.884–4.65)	0.101
Stage at diagnosis stage (IV vs III)	2.10 (0.965–4.50)	0.064
TME Panel (positive vs negative)	**0.41 (0.154–0.978)**	**0.044**

HR, hazard ratio; CI, confidence interval; PFI, platinum-free interval.

Multivariate Analysis of PFS using Cox Proportional Hazards Model

Variable	HR (95% CI)	P-value
TME Panel (positive vs negative)	0.45 (0.167–1.08)	0.074
Measurable disease, mm (≥50 vs 10–<50)	0.26 (0.087–0.726)	0.010

PFS by Biomarker Status



CONCLUSIONS

- Navicixizumab + paclitaxel demonstrated promising clinical activity in patients with heavily pre-treated PROC
- Clinical benefit was greater in TME Panel-classified biomarker-positive than biomarker-negative patients
- A 5-month PFS gain among biomarker-positive vs -negative patients with PROC is clinically meaningful in the 4th-line setting
- A consistent correlation was seen between biomarker-positive TME Panel phenotype and improved PFS
- Taken together, these results show the TME Panel can select patients with ovarian cancer who are more likely to respond to navicixizumab treatment
- A phase 3 study of navicixizumab ± paclitaxel vs paclitaxel monotherapy (NCT05043402) is planned to confirm these findings in patients with pre-treated PROC stratified by biomarker status using the TME Panel

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