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Predicting benefit from maintenance durvalumab after first-line chemotherapy (1L CTx) in oesophagogastric adenocarcinoma (OGA) using a novel tumour microenvironment (TME) RNA assay

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BACKGROUND

- Predictive biomarkers beyond MSI-high/MMR deficiency and PD-L1 Combined Positive Score (CPS) are needed to improve patient selection for immune checkpoint inhibitors (ICIs) in OGA.
- Results from PLATFORM (NCT02678182), a phase II, multicentre, randomised adaptive study assessing maintenance therapies in advanced OGA reported that durvalumab did not prolong progression-free or overall survival (PFS or OS) over active surveillance in HER2-negative patients unselected for PD-L1 status following 18 weeks of 1L CTx[1].
- The Xerna™ TME RNA panel uses ≈100 genes to classify patients into dominant TME biologies along immune and angiogenic axes into 1 of 4 phenotypes (Figure 1):
  - Angiogenic (A)
  - Immune Active(IA)
  - Immune Desert (ID)
  - Immune Suppressed (IS)
- We hypothesise that a high immune score (IA + IS) is predictive of ICI benefit compared to a low immune score (A + ID).

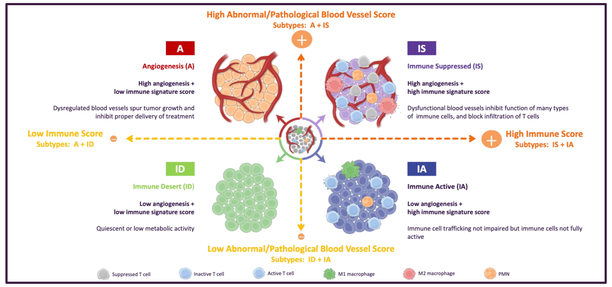

Figure 1. The Xerna™ panel TME phenotypes. PMN: polymorphonuclear neutrophils.

METHODS

- RNAseq and PD-L1 CPS (SP263) were performed on FFPE archival biopsies from patients randomised into active surveillance and durvalumab.
- Gene expression data was analysed using a machine learning artificial neural network algorithm to assign a TME subtype.
- PFS and OS analyses (median follow-up: 39 months) for the following biomarker-defined subgroups were compared using the Kaplan-Meier method:
  - IA + IS vs. A + ID;
  - PD-L1 CPS <5 vs. PD-L1 CPS ≥5;
  - Combinations of each TME and PD-L1 CPS subgroup.

RESULTS

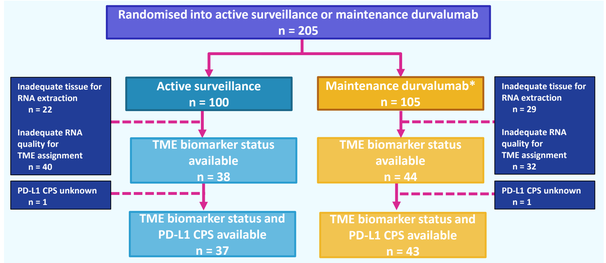

Figure 2. CONSORT diagram outlining patients with Xerna™ TME RNA panel and PD-L1 CPS results. *4-weekly cycles of 10mg/kg i.v. Q2W x 12 cycles. Patients who completed 12 cycles were eligible for a re-challenge on subsequent disease progression.

Patient characteristic		Active surveillance (n=38)		Durvalumab (n=44)	
Median age (years)		66	-	66	-
		n	**%**	**n**	**%**
Gender	Male	30	79	34	77
Primary tumour site	Oesophageal + GOJ	26	68	31	70
	Stomach	12	32	13	30
Disease extent	Metastatic*	35	92	38	86
TME RNA status	IA + IS	20	53	22	50
	A + ID	18	47	22	50
PD-L1 CPS	<5	18	47	17	39
	≥5	19	50	26	59
	Unknown	1	3	1	2
MMR status	Proficient[Y]	34	89	40	91

Table 1. Patient demographics. *Remainder of patients were locally advanced. [Y]MMR status unknown for remainder of patients. GOJ: gastro-oesophageal junction.

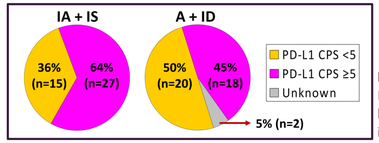

Figure 3. Distribution of PD-L1 CPS across patients with high (IA + IS) and low (A + ID) immune scores.

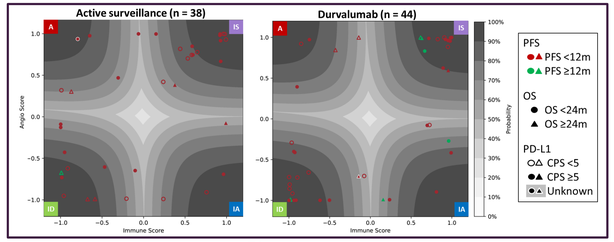

Figure 4. Latent space plot of Xerna™ TME calls. The contours represent the probability of individual TME subtypes as presented in Figure 1. Each glyph represents an individual patient according to length of PFS, OS and PD-L1 CPS status. m: months.

Survival function estimates (%)		Xerna™ TME Panel				PD-L1			
		IA + IS	97.5% CI	A + ID	97.5% CI	CPS ≥5	97.5% CI	CPS <5	97.5% CI
Active surveillance	**n**	20		18		19		18	
	6m PFS	17.5	3.5-40.4	27.8	8.3-51.8	18.4	3.7-42.1	27.8	8.3-51.8
	12m PFS	0	ND	5.6	0.2-25.7	0	ND	5.6	0.2-25.7
	12m OS	46.7	20.3-69.5	42.1	16.4-66.1	32.2	10.1-57.1	59.3	29.1-80.1
	24m OS	8.8	0.4-33.8	24.1	6.0-48.7	8.6	0.3-34.6	23.7	5.9-48.2
Durvalumab	**n**	22		22		26		17	
	6m PFS	35.0	13.4–57.8	27.3	9.4–49.0	28.0	10.7–48.5	31.3	9.3–56.6
	12m PFS	25.0	7.5–47.7	4.6	0.2–21.8	16.0	4.0–35.1	12.5	1.4–36.1
	12m OS	40.0	16.7–62.6	40.1	18.3–62.5	40.0	18.9–60.5	37.5	12.9–62.6
	24m OS	35.0	13.4–57.8	22.7	6.8–44.2	24.0	8.2–44.2	31.3	9.3–56.6

Table 2. Survival function estimates for patients according to treatment arm, TME and PD-L1 CPS status.
CI: confidence interval; m: months; ND: not determined.

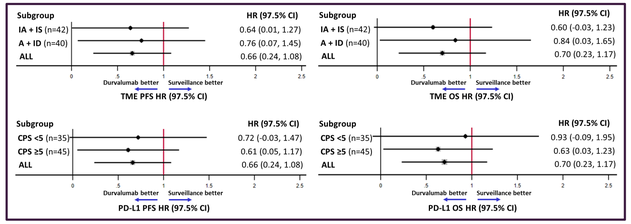

Figure 5. Forest plots of active surveillance vs. durvalumab. CI: confidence interval; HR: hazard ratio.

- IA + IS patients in surveillance had 6- and 12-month PFS and 24-month OS rates suggestive of poorer prognosis than A + ID patients. However, IA + IS patients had numerically higher 6- and 12-month PFS and 24-month OS rates than A + ID when treated with durvalumab (Table 2).
- In contrast, survival function estimates at all timepoints for PFS and OS were similar in A + ID patients across both treatment arms (Table 2).
- We observed numerically higher survival rates in PD-L1 CPS <5 patients randomised to surveillance compared to durvalumab. Survival benefit with durvalumab was limited to 12-month PFS and OS rates in PD-L1 CPS ≥5 compared to CPS <5 (Table 2).
- IA + IS showed a more pronounced treatment effect favouring durvalumab over active surveillance for both PFS and OS compared to A + ID. A similar trend was observed in CPS ≥5 compared to CPS <5 (Figure 5).
- In PD-L1 CPS ≥5 patients who received durvalumab, the IA + IS subgroup (n=17) had a numerical improvement in 12- and 24-month OS rates compared to those who were A + ID (n=9) (12-month: 44% vs. 33%; 24-month: 38% vs. 0%).
- In the surveillance arm, we observed longer survival in A + ID and CPS <5 patients (Figure 6).

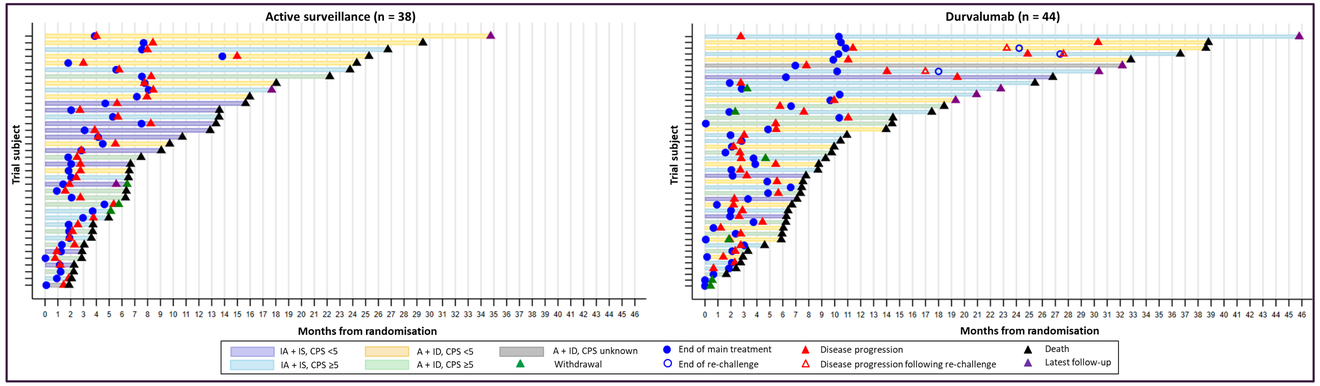

Figure 6. Swimmer plots showing patient survival with TME and PD-L1 CPS status.

CONCLUSIONS

- Our results suggest that IA + IS and CPS ≥5 patients had poorer prognoses with active surveillance compared to A + ID and CPS <5 patients respectively. When treated with durvalumab, IA + IS patients had improved survival with maintenance durvalumab. IA + IS may identify HER2-negative OGA patients who benefit from ICIs more consistently than PD-L1 CPS ≥5.
- Amongst CPS ≥5 patients, the Xerna™ panel may further distinguish a subgroup of patients who derive the most durable survival benefit from ICIs.
- A + ID and/or CPS <5 may be prognostic in HER2-negative OGA. The predictive and prognostic capabilities of the Xerna™ panel should be assessed in larger cohorts.

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