Biomarkers for response to immunotherapy in triple-negative breast cancer – differences between survival and pCR biomarkers

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Background

Immunotherapy is entering clinical practice as a promising new neoadjuvant therapeutic approach in triple-negative breast cancer, and it is important to identify biomarkers to focus this therapy on those patients that have the highest benefit. Interestingly, an improved survival outcome is observed in pCR and non-pCR patients, which raises the hypothesis that biomarkers might also be different for pCR prediction as well as prognosis. In this study, we investigated this hypothesis in the neoadjuvant GeparNuevo trial.

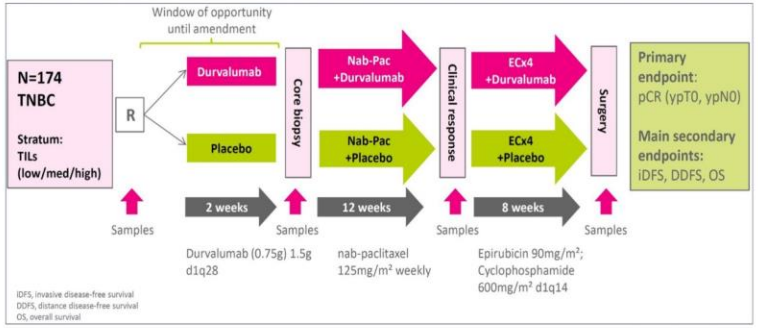
Patients and Methods

A total of 174 patients were randomized to receive neoadjuvant chemotherapy with durvalumab vs. placebo. HTG EdgeSeq mRNA analysis was performed retrospectively for a total of 2549 genes in 162 pretherapeutic core biopsies collected before randomization. In addition, tumor-infiltrating lymphocytes (stromal and intratumoral) as well as PD-L1 protein expression by IHC was evaluated. We systematically compared the distant disease-free survival (DDFS) of 6 predefined gene signatures (including the GeparSixto immune signature) as well as 12 single mRNA markers identified in previous projects between treatment arms using univariate Cox proportional-hazard regression analyses.

Table 1: Description of signatures

Signature name	Genes in signature	Reference
11-gene-prolif-sig	BIRC5, CCNB1, CDC20, NUF2, CEP55, NDC80, MKI67, PTTG1, RRM2, TYMS, UBE2C	Metzger Filho O, et al.J Clin Oncol 2019
10-gene-G6-sig	CXCL9, CCL5, CD8A, CD80, CXCL13, IDO1, PDCD1, CD274, CTLA4, FOXP3	Denkert et al, JCO 2015, modified in Sinn et al, 2021
2-gene-CYT-sig	PRF1, GZMA	Rooney et al, Cell 2015
4-gene-IFN-sig	IFNG, CD274, LAG3, CXCL9	Higgs et al, CCR 2018
4-gene-G6-sig	CXCL9, CCL5, IDO1, CXCL13	based on Denkert et al, JCO 2015, modified
12-gene_G9-sig	ITGA2, TAP1, HLA-A, HLA-B, GBP1, STAT1, CXCL10, CD38, CD274, PSIP1, THBS4, HEY2	based on Sinn et al, 2021; additional genes added

Figure 1: GeparNuevo clinical trial design



Main results

- In the GeparNuevo cohort, immune biomarkers are predictive for increased pCR and improved survival with neoadjuvant durvalumab therapy.
- Significant signatures for survival (DDFS) were observed only in the durvalumab arm, but not in the placebo arm.

Figure 2: Clinical results of GeparNuevo A: pCR differences are not significant; B: significant DDFS differences; C: DDFS stratified by pCR

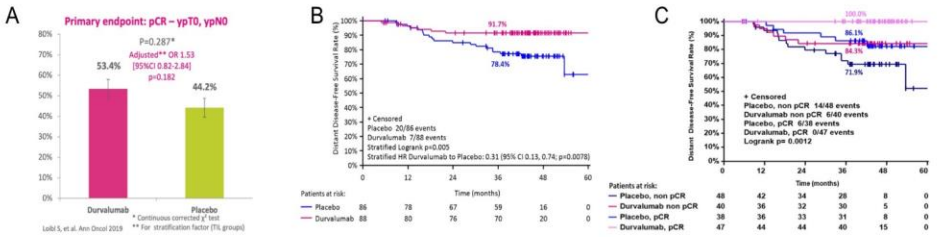


Table 2: Gene signatures associated with pCR and DDFS in the complete cohort, the durvalumab arm and the placebo arm

	complete cohort – both therapy arms (n=162)				Durvalumab therapy arm (n=83)				Placebo therapy arm (n=79)			
Signature	OR for pCR	p-value	HR for DDFS	p-value	OR for pCR	p-value	HR for DDFS	p-value	OR for pCR	p-value	HR for DDFS	p-value
11-gene-prolif-sig	2.22 (1.25-3.92)	0.0063	1.20 (0.60-2.39)	0.5992	1.88 (0.84-4.21)	0.1252	1.28 (0.33-4.96)	0.7193	2.64 (1.16-6.02)	0.0204	1.14 (0.52-2.50)	0.7433
10-gene-G6-sig	1.69 (1.23-2.31)	0.0011	0.75 (0.53-1.06)	0.0983	1.87 (1.21-2.88)	0.0049	0.51 (0.27-0.97)	0.0411	1.54 (0.97-2.46)	0.0677	0.87 (0.57-1.34)	0.5299
2-gene-CYT-sig	1.37 (1.04-1.82)	0.0274	0.75 (0.55-1.03)	0.0730	1.56 (1.06-2.30)	0.0252	0.62 (0.36-1.08)	0.0918	1.21 (0.80-1.84)	0.3724	0.80 (0.54-1.18)	0.2654
4-gene-IFN-sig	1.78 (1.30-2.44)	0.0003	0.77 (0.55-1.09)	0.1378	1.84 (1.20-2.80)	0.0048	0.47 (0.24-0.89)	0.0209	1.77 (1.10-2.84)	0.0182	0.97 (0.63-1.50)	0.8971
4-gene-G6-sig	1.52 (1.19-1.92)	0.0006	0.79 (0.61-1.02)	0.0730	1.66 (1.19-2.32)	0.0031	0.61 (0.37-0.99)	0.0477	1.41 (1.00-2.00)	0.0502	0.85 (0.62-1.17)	0.3198
12-gene_G9-sig	2.63 (1.53-4.53)	0.0005	0.63 (0.36-1.13)	0.1230	3.40 (1.58-7.34)	0.0018	0.38 (0.15-0.99)	0.0478	2.16 (0.97-4.80)	0.0596	0.73 (0.33-1.62)	0.4442

Results

Figure 3: A: Overview on gene signatures for pCR and DDFS in the complete GeparNuevo cohort and the two therapy arms; B, C: KM-Plots for selected signatures

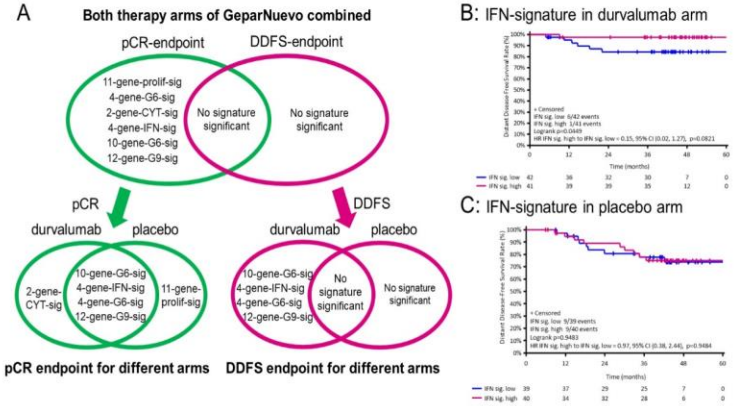
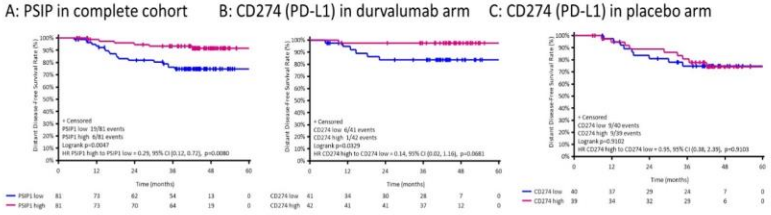


Figure 4 A-C: Selected KM-Plots for indivdual genes



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