Exome analysis of oncogenic pathways and tumor mutational burden (TMB) in Triple Negative Breast Cancer (TNBC): Results of the Translational Biomarker Program of the neoadjuvant double-blind placebo controlled GeparNuevo trial

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Background

The GeparNuevo (G9) trial showed that an addition of anti-PD-L1 antibody durvalumab to neoadjuvant anthracycline-taxane based chemotherapy yielded to a numerical increased in pCR rate of 53% vs 44%; p=0.287 compared to placebo in primary TNBC[1] (**Figure 1, Table 1**). Somatic mutations in malignant cells manifest over the evolutionary history of a tumor. Reports in selected tumor types suggest that the tumor mutational burden (TMB) may predict clinical outcomes on immune-checkpoint inhibitors (ICI). The clinical relevance of TMB in breast cancer has not been studied widely. Here, we investigated the hypothesis that TMB predicts response to ICI.

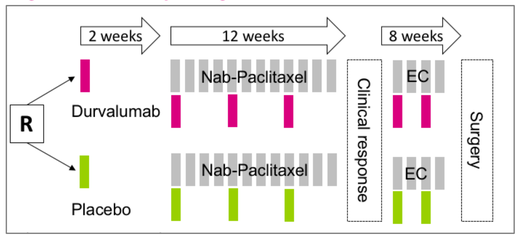
See also poster 267095 *"Correlation of the tumor mutational burden with the composition of the immune cell subpopulations in peripheral blood of triple negative breast cancer patients undergoing neoadjuvant therapy with durvalumab - results from the prospectively randomized GeparNuevo trial"*

Patients and Methods

Whole exome sequencing was conducted on patient-matched fresh-frozen core biopsies and blood samples with Illumina (n=149/174). SNVs and indels were called with Mutect; pureCN was used for copy number calls. Mutational signatures were identified as described by Alexandrov et al[2].

P-values are from two-sample Wilcoxon tests and from logistic regression models. Multivariate models included age, window, breast cancer staging, grading, stromal tumor infiltrating lymphocytes, and PD-L1 as covariates.

Figure 1: G9 study design



Patients with triple-negative (Stage I-III) primary breast cancer were randomized to receive anthracycline and taxane-based chemotherapy with or without the PD-L1 inhibitor durvalumab. The window phase (2 weeks) was closed after an amendment.

Results

Data from G9 were compared to The Cancer Genome Atlas (TCGA) TNBC cohort. A similar genomic landscape was observed between G9 and TCGA with primary genetic alterations in *TP53*, *c-MYC*, *BRCA1*, *PIK3CA* and *PTEN* (**Figure 2**).

Median TMB was 1.52 mut/MB in G9 which is slightly lower than in TCGA TNBC.

Results

Table 1. Baseline characteristics

Parameter	Category	n	%
Age	median	49.5 years	
	<40	47	27.0
	>=40	127	73.0
cT	cT1	78	44.8
	cT2	86	49.4
	cT3	6	3.4
	cT4	4	2.3
cN	cN0	120	69.0
	cN1	42	24.1
	cN2	8	4.6
	cN3	4	2.3
Breast cancer stage	0-I	61	35.1
	IIA+	113	64.9
Grade	G2	29	16.7
	G3	145	83.3
Histological tumor type	ductal	140	80.5
	lobular	2	1.1
	other	32	18.4
Stromal tumor infiltrating lymphocytes	0-10%	66	37.9
	11-59%	83	47.7
	60-100%	25	14.4
TMB	median	1.52 mut/MB	

Sign.: signature; Durva sign.: durvalumab-response related genes *BRCA2*, *NFE2L2*, *ARID1A*, *NOTCH1*; HRD sign.: 16 genes related to HRD; DDR sign.: 36 genes without *BRCA* from DDR pathway; GFR sign.: growth factor receptor genes *EGFR*, *FGFR1*, *FGFR2*, *FGFR4*, *IGF1R*, *KIT*, *c-MET*; BRCA/ATM: *BRCA1*, *BRCA2*, *ATM*; cell cycle sign.: *CDKN2A*, *RB1*, *CDK4*, *CDK6*, *CCNE1*, *c-MYC*; low: below median; high: above median; wt: wildtype; mut: mutated; m/d: mutated or deleted; m/a: mutated or amplified; m/a/d: mutated, amplified or deleted

Figure 2. Genomic landscapes of G9 and TCGA

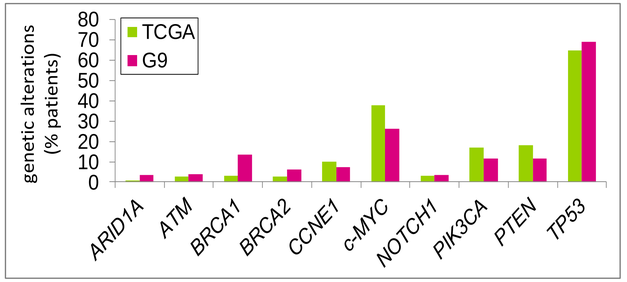
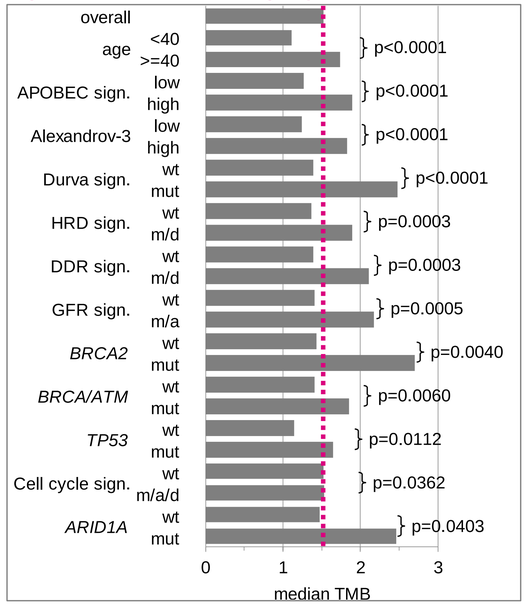


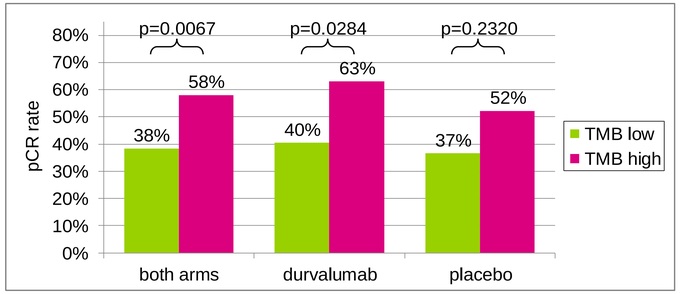
Figure 3. Median TMB in subgroups



TMB correlated with older age, higher mutation rates in *BRCA2*, *ARID1A*, and *TP53*, and higher burden in variant signatures such as DDR, HRD, GFRs, APOBEC and Alexandrov's signature 3 (**Figure 3**).

Continuous TMB predicted pCR in univariate (OR=1.62 referring to 1 mut/MB, 95%-CI: 1.20 - 2.20, p=0.0018) and multivariate (OR=2.06, 95%-CI: 1.33-3.20, p=0.0012) logistic regression models, but did not predict a durvalumab effect. After dichotomization of TMB at the top tertile, 50 patients had high TMB and 29 of them (58%) achieved a pCR, while 99 had low TMB and only 38 of them (38%) had a pCR (univariate p=0.0242, multivariate p=0.0067) (**Figure 4**).

Figure 4. Response to treatment



TMB low: below 66.7% percentile; TMB high: above 66.7% percentile;
p-values from multivariate logistic regression models

Conclusions

- The main genetic alterations were in *TP53*, *c-MYC, PTEN*
- Results were comparable between G9 and TCGA
- TMB may predict pCR in primary TNBC, but no dependency on ICI treatment was found

References

1. Loibl S et al. Annals Oncol 2019
2. Alexandrov LB et al, Nature 2013
3. Goodman AM et al. Mol Cancer Ther 2017

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