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

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Poster #267095

Background

Background: The GeparNuevo trial is a randomized, double-blind, multi-center phase II trial of neoadjuvant therapy in patients with early-stage triple negative breast cancer (TNBC) investigating the role of durvalumab, an anti-PD-L1 antibody, which blocks PD-L1 binding to PD1 and CD80 in addition to standard anthracycline/taxane based chemotherapy (Loibl S et al. JCO 2018; 36.15_suppl.104).

Aim: Determination whether there exists a link between the tumor mutational burden (TMB) and composition, frequency and function of blood immune cells in patients of the GeparNuevo trial as well as with the pathological complete response (pCR).

See also poster 254765 „*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*"

Patients and Methods

Table 1. Data of patients evaluated by flow cytometry

	whole trial	current evaluation		
		TMB	blood monitoring	both
total patients	174	149	120	101
window treatment	117	101	63	53

Figure 1. Scheme of GeparNuevo treatment

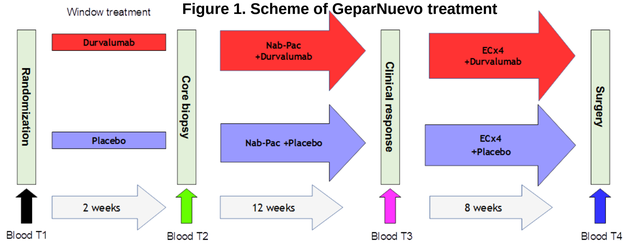


Table 2. Panel of antibodies used for blood immune monitoring

	Abs # (TruC tube)	subpopulations and phenotype						
		surface staining				intracellular staining		
Fitc	CD3	gd TCR	CD45	Tim3	CD45	CD25	CD3z	
Pe	CD16+56	CD56	CCR7	CXCR3	CTLA4	FoxP3	perforin	CTLA4
P5	CD45	CD4	CD4	CD4	CD4	CD4	CD4	CD4
Pe-Cy7	CD4	CD28	CD45RA	CCR6	CD19	CCR4	CD56	
APC	CD19	CD16	CD38	CD57	LIR1	CD127	CD19	CD19
APC-H7	CD8	CD8	CD8	CD8	CD8	CD45RO	CD8	CD8
BV421		CD45		CD45	PDL1	CD45	CD45	CD45
BV510			HLA-DR	PD1	PD1	HLA-DR		
BV605		CD3	CD3	CD3	CD3	CD3	CD3	CD3

Results

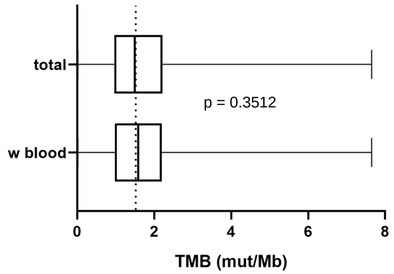


Figure 2. TMB of GeparNuevo patients and subcohorts
Tumor biopsies were evaluated for tumor mutation burden (TMB). Shown are the Wisker plot of the whole trial and of the patients who underwent immune monitoring on blood and the p value of the Wilcoxon test. The line at 1.52 represents the median of the whole group that is used to dichotomize the patients.

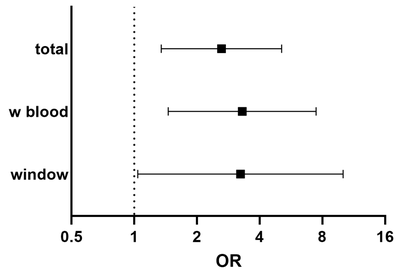
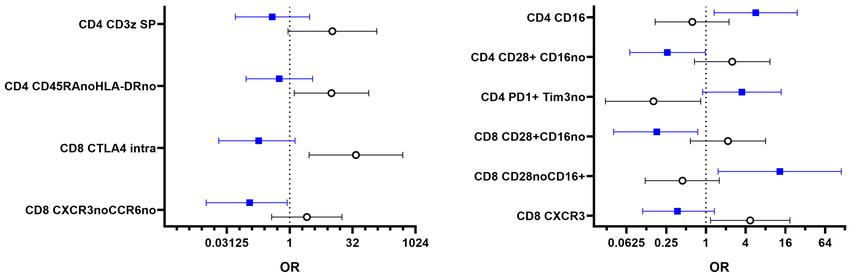


Figure 3. Association of TMB with clinical outcome
Univariate logistic regression models for pathological complete response (pCR) from the dichotomized TMB. Shown are the odds ratios (OR) with 95% CI for the different subsets of patients.



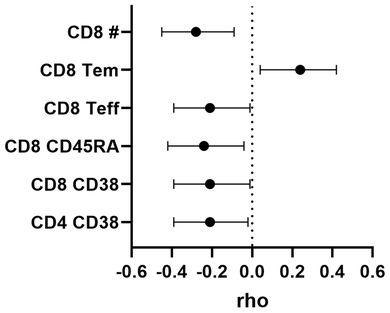


Figure 4. TMB correlates with different blood parameters at recruitment
Correlation between continuous TMB and T cell-related markers at recruitment was evaluated. Shown are the Spearman correlation coefficient (rho) and its 95%CI for selected variables having a significant correlation to TMB (#: cell number / µl blood; Tem: T effector memory; Teff: effector T cells).

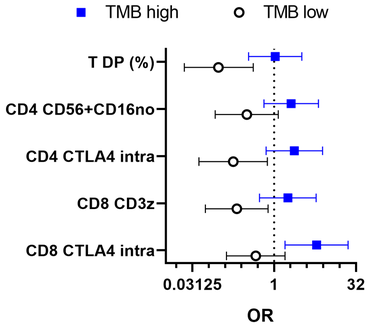


Figure 5. TMB and T cells´ biomarkers at recruitment correlate with pCR
Interaction of dichotomized biomarkers and TMB with pCR. Shown are the OR with 95% CI for the marker with a significant p value in the Wald test (DP: CD4 CD8 double positive; %: as % of PBMC; intra: intracellular stain).

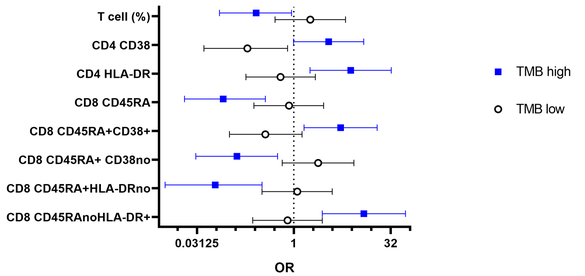


Figure 6. TMB and changes in T cells´biomarkers correlate with clinical outcome
Patients were divided into a "high" and "low" group based of the median of the TMB. Interaction of dichotomized changes in the biomarkers with pCR in the two groups was calculated. Shown are the OR with 95% CI for the marker with a significant p value in the Wald test for changes after T2 (*top left*), T3 (*top right*) and T4 (*bottom*); (%: as % of PBMC).

Conclusions

- The median TMB in patients from the GeparNuevo trial is 1.52 mut/Mb, the patients with immunomonitoring are a representative subcohort
- Patients with higher TMB have better pathological responses.
- TMB negatively correlates with the absolute number of $CD8^+$ T cells, but positively with the percentages of memory cells.
- Many T cell biomarkers interact with the TMB to predict pCR.
- Biomarkers changes along treatment have opposite effects in the TMB dichotomized cohort, except for CD45RA CD8+ T cells at endpoint (T4):
  - Changes in total population have the same role, but opposite effects when combined with CD38 or HLA-DR expression.

Presented at ASCO Annual Meeting 2019, May 31-June 4, 2019 Chicago, IL

The trial and translational research project were funded by AstraZeneca and Celgene