Tumor mutational burden and immune infiltration as independent predictors of response to neoadjuvant immune checkpoint inhibition in early TNBC in GeparNuevo

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BACKGROUND
The predictive value of tumor mutational burden (TMB), alone or in combination with an immune gene expression profile (GEP), for response to neoadjuvant therapy in early triple negative breast cancer (TNBC) is currently not known, either for immune checkpoint blockade (ICB) or conventional chemotherapy.

PATIENTS AND METHODS
We obtained both whole exome sequencing and RNA-Seq data from pretreatment samples of 149 TNBC of the recent neoadjuvant ICB trial, GeparNuevo. In a predefined analysis, we assessed the predictive value of TMB and a previously developed immune GEP for pathological complete remission (pCR).

RESULTS
Median TMB was 1.52 mut/Mb (range 0.02-7.65) and was significantly higher in patients with pCR (median 1.87 versus 1.39; P = 0.005). In multivariate analysis, odds ratios for pCR per mut/Mb were 2.06 [95% confidence intervals (CI) 1.33-3.20, P = 0.001] among all patients, 1.77 (95% CI 1.00-3.13, P = 0.049) in the durvalumab treatment arm, and 2.82 (95% CI 1.21-6.54, P = 0.016) in the placebo treatment arm, respectively. We also found that both continuous TMB and immune GEP (or tumor infiltrating lymphocytes) independently predicted pCR. When we stratified patients in groups based on the upper tertile of TMB and median GEP, we observed a pCR rate of 82% (95% CI 60% to 95%) in the group with both high TMB and GEP in contrast to only 28% (95% CI 16% to 43%) in the group with both low TMB and GEP.

CONCLUSIONS
TMB and immune GEP add independent value for pCR prediction. Our results recommend further analysis of TMB in combination with immune parameters to

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individually tailor therapies in breast cancer.

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