PIK3CA mutations predict resistance to trastuzumab/pertuzumab and nab-paclitaxel in primary HER2-positive breast cancer – massive parallel sequencing analysis of 293 pretherapeutic core biopsies of the GeparSepto study

Sibylle Loibl[1], Jan Budczies[2], Wilko Weichert[3,4], Jenny Furlanetto[1], Albrecht Stenzinger[3], Nicole Pfarr[4], Gunter von Minckwitz[1], Christian Jackisch[5], Andreas Schneeweiss[3], Peter Fasching[6], Sabine Schmatloch[7], Bahriye Aktas[8], Valentina Nekljudova[1], Karsten Weber[1], Michael Untch[9], Carsten Denkert[2]

[1]German Breast Group, Neu-Isenburg; [2]Institute of Pathology, Charité, Berlin; [3]Universitätsklinikum Heidelberg; [4]Institute of Pathology, TU Munich; [5]Sana Klinikum Offenbach; [6]Universitätsklinikum Erlangen; [7]Elisabeth Krankenhaus, Kassel; [8]Universitätsklinikum Essen; [9]Helios Kliniken Berlin-Buch; Germany

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Background

- Massive parallel sequencing (NGS) is a promising tool to investigate key molecular events in cancer.
- Genomic alterations, such as *PIK3CA* mutations, are important for response to therapy in HER2+ breast cancer (BC).
- *PIK3CA* mutations were shown to predict lower pathological complete response (pCR) to double blockade with trastuzumab/lapatinib in HER2+ primary BC.[1]

We investigated genomic alterations in 364 pretherapeutic core biopsies from two prospective clinical trials with or without anti-HER2 therapy.

Materials and Methods

- In GeparSepto (G7), patients with HER2+ BC received trastuzumab and pertuzumab in addition to nab-paclitaxel or solvent-based paclitaxel as part of neoadjuvant therapy. Significantly higher pCR rates were observed in patients receiving nab-paclitaxel.[2] Patients with HER2+ BC in GeparTrio (G3) received no anti-HER2 treatment in addition to neoadjuvant therapy.[3]
- 417 formalin-fixed paraffin embedded (FFPE) core biopsies taken before therapy from HER2+ tumors of G3 and G7 were analysed by deep targeted massive parallel sequencing.
- *PIK3CA* mutations were evaluated with a minimum coverage of 500 and a mean coverage of 6520 (exon 9) and 6346 (exon 20) per amplicon.
- Only non-synonymous mutations in the coding region that were called at variant allele frequency ≥10% and only cases with a tumor cell content of ≥20% were included.

The primary aim was to assess the predictive value of somatic *PIK3CA* mutations for pCR (ypT0 ypN0).

Secondary aims were to assess the predictive value of somatic *PIK3CA* mutations for pCR in subgroups of taxane and hormone receptor (HR) status.

Results

Table 1: Baseline patient and tumor characteristics

Parameter	no anti-HER2 treatment (G3; N=71) N (valid %)	dual HER2 blockade (G7; N=293) N (valid %)
Age, median (range), years	50 (27-78)	50 (22-75)
cT3-4	27 (38.6)	29 (10.1)
cN+	45 (64.3)	131 (45.6)
ER and/or PgR positive	48 (67.6)	204 (69.6)
Grade 3	20 (32.3)	158 (53.9)
Ductal/ductal-lobular invasive	63 (88.7)	260 (88.7)
LPBC, TILs >60%	17 (23.9)	49 (16.8)

Figure 1: Mutation frequencies overall and by HR status

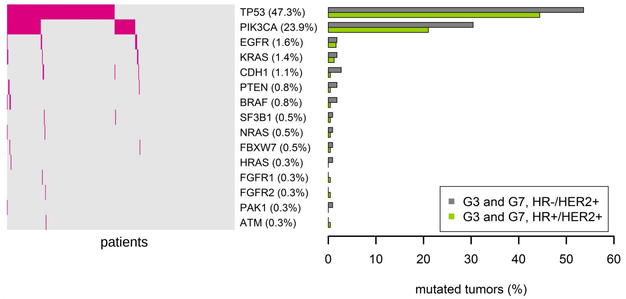
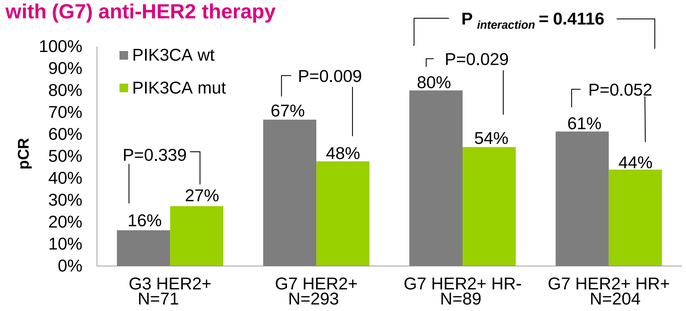


Figure 2: pCR rates according to *PIK3CA* mutation without (G3) or with (G7) anti-HER2 therapy



Analysis by NGS was successful in 364/417 tumors (87%), 293 from G7 and 71 from G3 (**Table 1**). A total of 291 non-synonymously mutated genes were detected. Mutation frequencies of *PIK3CA* and other genes analysed in the same panel are displayed in **Figure 1**.

In the double anti-HER2 treated group, the pCR rate was significantly lower in the *PIK3CA* mut vs wt group, overall and in the HR- cohort (**Figure 2**).

In the nab-paclitaxel cohort, pCR rates were significantly lower in the *PIK3CA* mut vs wt group, whereas in the paclitaxel cohort, no significant difference was observed between the *PIK3CA* mut and wt group (**Figure 3**). The respective interaction could be demonstrated in univariate (p=0.039) as well as multivariate regression analysis (p=0.010) after adjusting for known baseline factors.

Within the nab-paclitaxel treated group, significant differences between *PIK3CA* mut and wt could be observed in both the HR- and HR+ treated cohort (**Figure 4**).

Conclusions

Targeted NGS on FFPE core biopsies reliably identified the most common genomic alterations in HER2+ BC. *PIK3CA* mutation in HER2+ BC predicts resistance to anti-HER2 therapy. In addition, *PIK3CA* mutations were found to predict response to nab-paclitaxel in G7. The results show that mutational alterations are relevant for response in HER2+ BC.

References

1. Loibl et al. J Clin Oncol. 2014;32:3212-20. **2.** Untch et al. Cancer Res. 2015; 75;S2-07. **3.** Huober et al. Breast Cancer Res Treat. 2010;124:133-40.

Figure 3: pCR rates according to *PIK3CA* mutation in the trastuzumab/pertuzumab treated cohort (G7) overall and by taxane

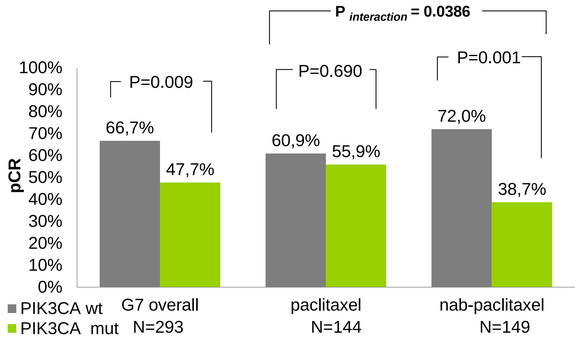
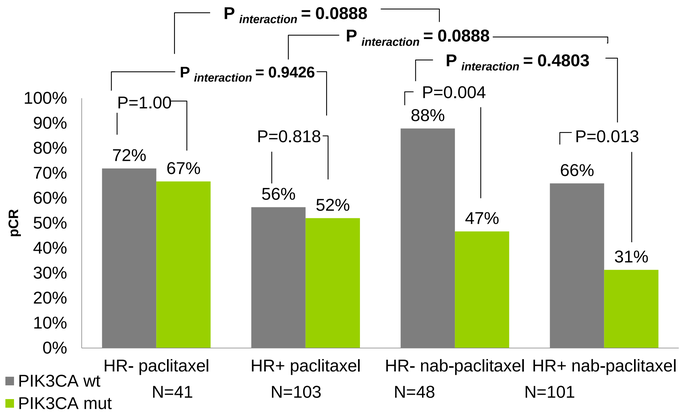


Figure 4: pCR rates according to *PIK3CA* mutation in the trastuzumab/pertuzumab treated cohort (G7) overall and by HR status and taxane



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