Molecular Testing in Breast Cancer: The Key to More Personalized and Effective Therapies

Sibylle Loibl[1,2], Marcus Schmidt[3], Thomas Decker[4], Valentina Nekljudova[1], Julia Teply-Szymanski[5], Marc Thill[6], Kristina Lübbe[7], Christoph Mundhenke[8], Nader Hirmas[1], Volkmar Müller[9], Bärbel Felder[1], Kerstin Rhiem[10], Johannes Holtschmidt[1], Carsten Denkert[5]

[1]GBG c/o GBG Forschungs GmbH, Neu-Isenburg, Germany; [2]Goethe University Frankfurt, Frankfurt/Main, Germany; [3]University Medical Center Mainz, Germany; [4]Haematologie-Onkologie Praxis, Augsburg, Germany; [5]Institute of Pathology, Philipps University Marburg and University Hospital Marburg (UKGM), Marburg, Germany; [6]Agaplesion Markus Hospital Frankfurt, Frankfurt/Main, Germany; [7]Breast Center, department of Gynecology, Diakovere Hospital, Henriettenstift, Hannover, Germany; [8]Breast Unit, Center for Gynecological Cancer, Center for High-Risk Obstetrics, Bayreuth, Germany; [9]University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [10]Zentrum Familiärer Brust- und Eierstockkrebs, Universitätsklinikum Köln, Germany

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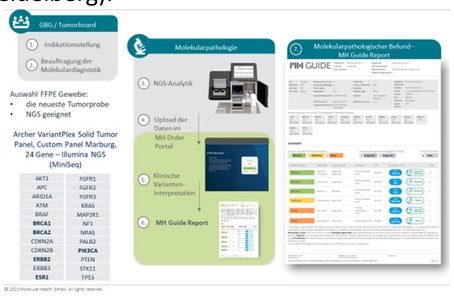
Background

- Modern breast cancer treatment is shifting from standardized therapeutic concepts to individualized approaches based on molecular and genetic testing. These allow for a more precise selection of treatment options, yet they frequently remain underutilized in clinical practice despite their high potential.
- Analyses of tumor tissue enable identification of genetic alterations relevant for guiding targeted therapies through predicting treatment efficacy and can indicate potential resistances.
- Particularly important are tests for pathogenic variants in *BRCA1*, *BRCA2*, *PIK3CA*, *AKT*, *PTEN, ESR1, ERBB2* and *PALB2*, which can have direct therapeutic consequences for patients.
- Among others, we retrospectively analyzed tumor tissue for these genetic variants in the GBG studies PADMA (NCT03355157), AMICA (NCT03555877), and DESIREE (NCT02387099).

Methods

- A total of 152 metastatic breast cancer (mBC) patients were analyzed by NGS using a 25-gene customized Archer VariantPlex Solid Tumor Panel, with variants classified via MH Guide software (a proprietary clinical decision support software by Molecular Health GmbH, Heidelberg).



- Pathogenic variants were analyzed using R- and SAS-based workflows to characterize their bioinformatic features and prognostic implications.

Results

All patients had HR+/HER2- mBC, median age was 65 years (range, 31-85), with most patients having G2 disease, at least two metastatic locations, and 32.9% were diagnosed with mBC at primary diagnosis (**Table 1**). Samples were obtained from pretherapeutic biopsies (n=29/152), surgical breast specimen (39/152), or metastatic lesions (74/152). 97/152 samples (63.8%) harbored pathogenic variants and 76/152 (50.0%) harbored at least one actionable (*BRCA1*, *BRCA2*, *PIK3CA*, *AKT*, *PTEN, ESR1, ERBB2* or *PALB2)* pathogenic variant (**Table 2**), predominantly in the *PIK3CA* (47%), *TP53* (25%), followed by *NF1* (14%) and *BRCA* (10%) genes (**Figure 1**). Co-occurrence was strongest for *BRCA1–PALB2* (p=0.001; OR=57.37); *TP53–NF1* also co-occurred, while *ARID1A–PIK3CA*, *ESR1–PIK3CA*, and *NF1–PIK3CA* were mutually exclusive (**Figure 2**). In a study-stratified Cox proportional hazards model, *PIK3CA* pathogenic variants were associated with longer PFS (HR: 0.64, 95%CI: 0.42-0.99, p: 0.05) and a favorable OS trend (HR: 0.63, 95%CI: 0.36-1.11, p: 0.11) (**Figures 3A and 3B**). PI3K pathway alterations (*PIK3CA*/*PTEN*/*AKT1*) were associated with longer PFS (HR: 0.59, 95%CI: 0.39-0.89, p=0.01) and OS (HR: 0.59, 95%CI: 0.35-1.01, p=0.05) (**Figures 4A and 4B**). RTK–RAS pathway alterations (*NF1*/*ERBB2*/*ERBB3*/*KRAS*/*FGFR3*) predicted shorter PFS (HR:1.79, 95%CI: 1.09-2.93, p=0.02), while no significant difference in OS was observed (**Figures 5A and 5B**). No study-level heterogeneity was detected.

Table 1. Tumor characteristics

Parameter value		Overall	AMICA	DESIREE	PADMA
Tumor grading, metastasis	G1	1	0 (0.0)	0 (0.0)	1 (4.8)
	G2	22	1 (33.3)	6 (75.0)	15 (71.4)
	G3	9	2 (66.7)	2 (25.0)	5 (23.8)
	missing	120	18	43	59
Metastasis status at primary diagnosis	M0	94	12 (57.1)	37 (75.5)	45 (56.3)
	M1	56	9 (42.9)	12 (24.5)	35 (43.8)
	missing	2	0	2	0
Number of metastatic locations	1 location	37	6 (28.6)	11 (21.6)	20 (25.0)
	2 locations	55	11 (52.4)	17 (33.3)	27 (33.8)
	≥ 2 locations	60	4 (19.0)	23 (45.1)	33 (41.3)
Treatment setting at primary diagnosis	adjuvant	76	10 (66.7)	28 (54.9)	38 (47.5)
	neo-adjuvant	15	0 (0.0)	8 (15.7)	7 (8.8)
	advanced/ metastatic BC	50	0 (0.0)	15 (29.4)	35 (43.8)
	both adjuvant and neo-adjuvant	5	5 (33.3)	0 (0.0)	0 (0.0)
	missing	6	6	0	0

Table 2. CONSORT data

Study	Total	Pathogenic variants (%)	Actionable variants (%)
Padma	80	46 (57.5)	39 (48.8)
Amica	21	15 (71.4)	10 (47.6)
Desiree	51	36 (70.6)	27 (52.9)
Total	152	97 (63.8)	76 (50.0)
all values represent number of patients			

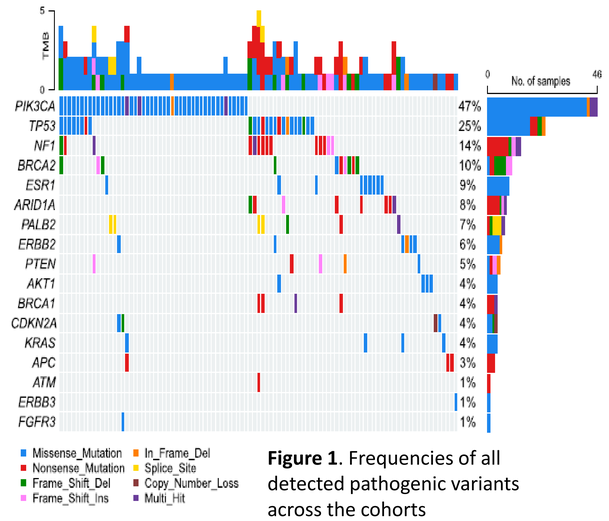


Figure 1. Frequencies of all detected pathogenic variants across the cohorts

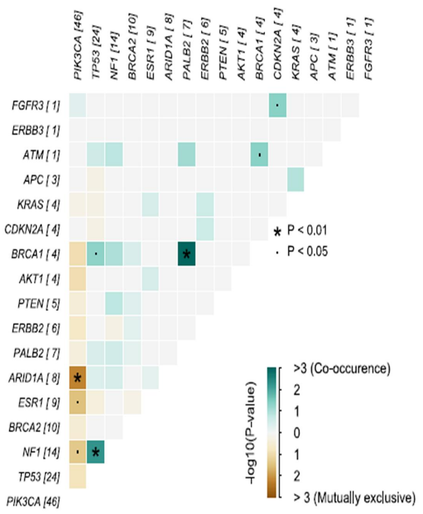


Figure 2. Co-occurrence and mutual exclusivity

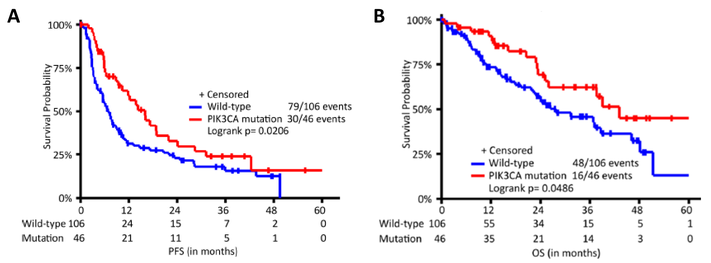


Figure 3. Prognostic impact of *PIK3CA* pathogenic variants on (A) PFS and (B) OS

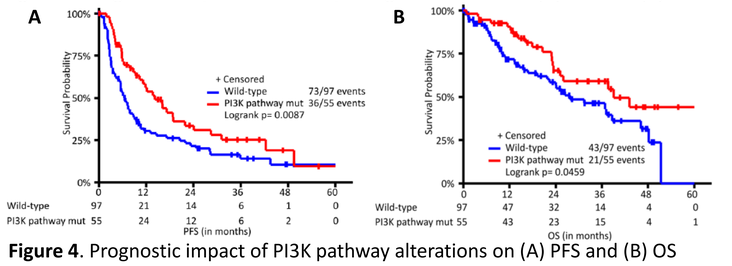


Figure 4. Prognostic impact of PI3K pathway alterations on (A) PFS and (B) OS

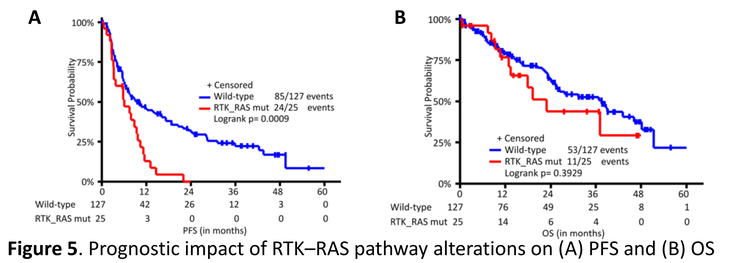


Figure 5. Prognostic impact of RTK–RAS pathway alterations on (A) PFS and (B) OS

Conclusions

- Overall, 63.8% of the samples harbored pathogenic variants. In 50% of the samples, at least one targetable variant in the *BRCA1*, *BRCA2*, *PIK3CA*, *AKT*, *PTEN, ESR1, ERBB2* or *PALB2* gene was identified. Numbers could be even higher, especially for *ESR1*, since 44.7% of samples were obtained from primary tumor, thereof many untreated.
- In this subset, patients harboring a PIK3 pathway alteration had a better and such with RTK/RAS pathway alteration had a worse prognosis.
- We therefore strongly recommend to start molecular testing already prior to initiating first line therapy to select the adequate targeted therapy (PIK3 inhibition or PARP-inhibitor for now) and know options for second line treatment ahead of time.

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