Molecular plasticity of luminal breast cancer and response to CDK 4/6 inhibition – the biomarker program of the PENELOPE-B trial investigating post-neoadjuvant Palbociclib

PD-02-04

Carsten Denkert[1], Frederik Marmé[2], Miguel Martin[3,4], Michael Untch[5], Hervé Bonnefoi[6], Sung-Bae Kim[7], Harry Bear[8], Agnieszka Witkiewicz[9], Seock-Ah Im[10], Angela DeMichele[11], Laura Van't Veer[12], Nicole McCarthy[13], Thorsten Stiewe[14], Karen A. Gelmon[15], José A. García-Sáenz[4,16], Catherine M. Kelly[17], Toralf Reimer[18], Erik Knudsen[9], Nicholas Turner[19], Federico Rojo[20], Peter A. Fasching[21], Julia Teply-Szymanski[1], Yuan Liu[22], Masakazu Toi[23], Hope S. Rugo[24], Michael Gnant[25], Andreas Makris[26], Bärbel Felder[27], Karsten Weber[27], Sibylle Loibl[27]

1 Institute of Pathology, Philipps-Universität Marburg and University Hospital Marburg, Marburg, Germany; 2 Universitätsfrauenklinik Mannheim, Mannheim, Germany; 3 Instituto de Investigacion Sanitaria Gregorio Marañon, CIBERONC, Universidad Complutense, Madrid, Spain; 4 Spanish Breast Cancer Group, GEICAM, Madrid, Spain; 5 Helios Kliniken Berlin-Buch, Berlin, Germany, AGO B Study Group, Germany; 6 Institut Bergonié and Université de Bordeaux, Bordeaux, France; 7 Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; 8 Division of Surgical Oncology, Massey Cancer Center, Virginia Commonwealth University, VCU Health, Richmond, VA, United States of America; 9 Roswell Park Comprehensive Cancer Center, Buffalo NY, United States of America; 10 Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea; 11 Penn Medicine Abramson Cancer Center, Philadelphia PA, United States of America; 12 University of California, San Francisco CA, United States of America; 13 Breast Cancer Trials Australia and New Zealand and University of Queensland, Brisbane, Australia; 14 Genomics Core Facility, Philipps University Marburg, Marburg, Germany; 15 BC Cancer, Vancouver, British Columbia, Canada; 16 Service de Oncología Médica, Hospital Clínico San Carlos, Madrid, Spain; 17 Breast Group, Cancer Trials Ireland, Dublin, Ireland; 18 Department of Obstetrics and Gynecology, University of Rostock, Rostock, Germany; 19 The Institute of Cancer Research: Royal Cancer Hospital, London, Great Britain; 20 Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain; 21 University Hospital Erlangen, Department of Gynecology and Obstetrics, Comprehensive Cancer Center Erlangen-EMN, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany; 22 Pfizer Inc., San Diego, CA, United States of America; 23 Breast Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan; 24 University of California San Francisco Comprehensive Cancer Center, San Francisco, CA, United States of America; 25 Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria; 26 Institute of Cancer Research, London, UK; 27 German Breast Group, Neu-Isenburg, Germany

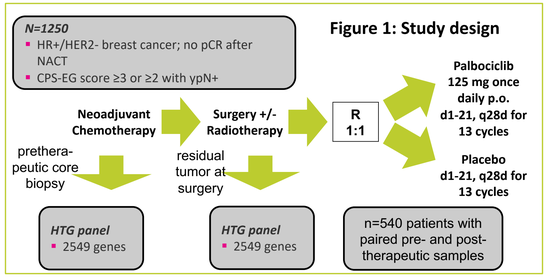
Background

Molecular plasticity of breast cancer can contribute to the development of therapy-resistant disease. In this investigation, we studied changes in molecular signatures between pretherapeutic (pre-Tx) and post-therapeutic (post-NACT) tumor samples from patients included in the PENELOPE-B (NCT01864746) trial (**Figure 1**). After completion of NACT, PENELOPE-B patients were randomized to palbociclib versus placebo in addition to standard endocrine therapy. The PENELOPE-B study did not show a significant benefit from palbociclib in women with HR+, HER2- primary breast cancer without a pathological complete response after taxane-containing neoadjuvant chemotherapy (NACT) and at high-risk of relapse (CPS-EG score ≥3 or 2 and ypN+)[1]. However, the first translational investigations showed that some patients with a luminal-B tumor subtype, based on absolute intrinsic molecular subtyping (AIMS)[2] subtyping after NACT, had a numerical benefit from post-NACT palbociclib. We have therefore extended the analysis and included a cohort of paired pre-Tx and post-NACT samples.

Methods

We investigated gene expression in pre-Tx (n=540) tumor tissue samples using the HTG EdgeSeq Oncology Biomarker Panel including 2549 genes (HTG Molecular Diagnostics Inc.); for the same patients the same panel on post-NACT residual tumor samples were available. Based on 91 genes of this panel, the AIMS subtype was calculated. In addition, we performed exploratory biomarker analyses to identify genes with prognostic and predictive relevance.

Figure 1: Study design



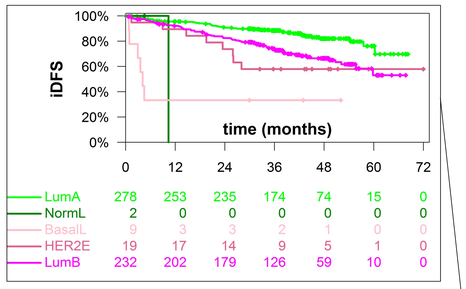


Figure 2A: Prognostic role of AIMS subtypes determined in pre-therapeutic core biopsies

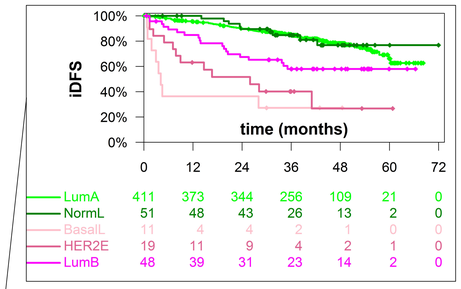


Figure 2B: Prognostic role of AIMS subtypes determined in post-therapeutic residual tumor samples

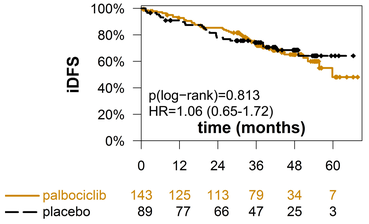


Figure 4A: LumB pre-therapeutic – no differences between therapy arms

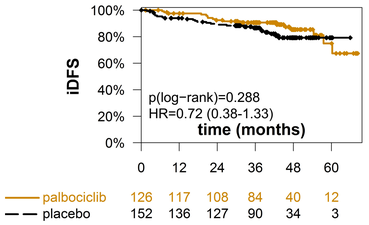


Figure 4B: LumA pre-therapeutic – no differences between therapy arms

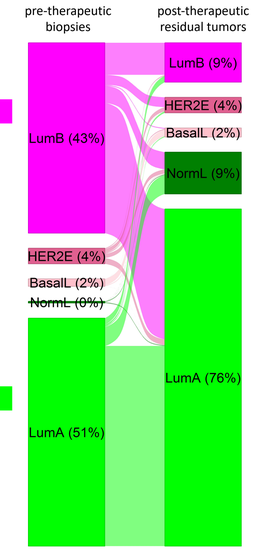


Figure 3: Molecular plasticity – changes in AIMS subtypes in pre-and post-therapy samples

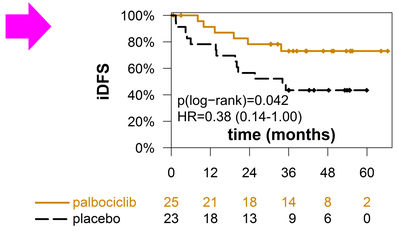


Figure 5A: LumB post-Tx: small group of patients with significant differences between therapy arms

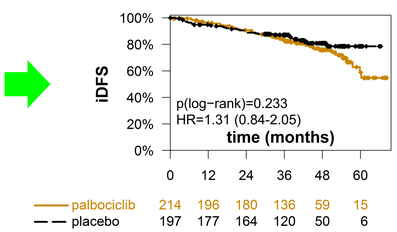


Figure 5B: LumA post-therapeutic – no differences between therapy arms

Table 1: Pre-therapeutic and post-therapeutic AIMS subtypes (LumB/BasalL/HER2E vs LumA/NormL) are independent prognostic parameters for iDFS

model	AIMS subtype		
	HR (95% CI)	HR (95% CI)	p
Bivariable n=540	pre-therapeutic	1.86 (1.26-2.73)	0.002
	post-therapeutic	2.83 (1.90-4.20)	<0.001
multivariable* n=532	pre-therapeutic	1.90 (1.26-2.86)	0.002
	post-therapeutic	2.66 (1.68-4.20)	<0.001

*covariables: age, region, cT, ypT, ypN, Ki-67, grade, and risk status

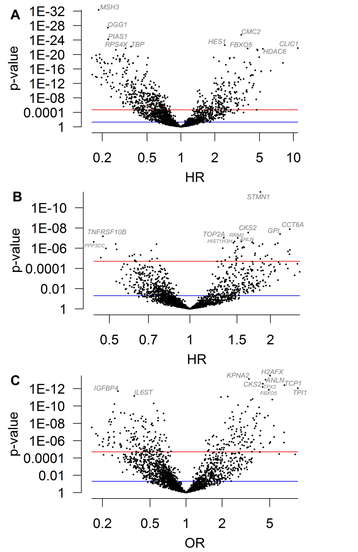


Figure 6: Differential gene expression (n=540). A: pre-therapeutic genes for iDFS, B: post-therapeutic genes for iDFS, C: Subtype switch: pre-therapeutic genes for prediction of post-therapeutic AIMS subtype (LumB/BasalL/HER2E vs LumA/NormL). Blue line: significance level p=0.05; red line: significance after Bonferroni correction.

Results

AIMS subtypes were prognostic in pre-therapeutic biopsies (**Figure 2A**) and post-therapeutic tumors (**Figure 2B**). The prevalence of AIMS subtypes, in particular LumA vs LumB, changed from pre-Tx to post-NACT tumors (**Figure 3**). In the pre-Tx samples, 278 (51%) and 232 (43%) of tumors had LumA and LumB subtypes, respectively, as expected from a high-risk cohort. However, in the post-NACT samples, LumA tumors were predominant (n=411, 76%) over LumB (n=48, 9%). 159 (29%) and 8 (1%) tumors switched their subtype from LumB to LumA and LumA to LumB, respectively.

We compared the groups of low proliferating (LumA and NormL) and high proliferating subtypes (LumB, BasalL and HER2E). In bivariable Cox regression analysis, the grouped pre-Tx and post-NACT AIMS subtypes were independent prognostic factors for iDFS **(Table 1).** These and further Cox models investigating interaction effects show that patients with tumors changing from high (pre-Tx) to low proliferation (post-NACT) had a worse iDFS risk compared to stable low proliferating tumors, but an improved iDFS risk compared to stable high proliferating tumors.

A benefit from palbociclib was observed in post-therapeutic lumB tumors (**Figure 5A**), but not in any of the pre-Tx AIMS subgroups (**Figure 4A,B**) or the post-Tx lumA subtype (**Figure 5B**). Based on the results of the AIMS subtyping, we extended the exploratory analysis to identify genes that might be involved in the prognostic effects as well as genes driving the subtype switch (**Figure 6A,B,C**).

Conclusions

Our findings show that the switch from high-risk molecular subtypes (in particular LumB) to low-risk subtypes (in particular LumA) is common in neoadjuvant therapy of luminal tumors. The adaptation of luminal high-risk tumors to chemotherapy-induced stress is crucial for the clinical outcome and the results suggest that molecular defined tumor subtypes might not be as stable as originally thought.

References

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2. Paquet ER, Hallett MT. Absolute assignment of breast cancer intrinsic molecular subtype. J Natl Cancer Inst. 2014 Dec 4;107(1):357.

Presented at: San Antonio Breast Cancer Symposium, 2021

The trial was financially supported by Pfizer Inc. We thank all patients, participating sites and collaborating study groups: ANZBCTG, ABCSG, BC Cancer, Unicancer, ICORG, JBCRG, Korean BC group, GEICAM, ICR-CTSU