Desmocollin 2 as a Predictive Marker for the Development of Distant Metastasis in Breast Cancer

Elena Laakmann[1], Leticia Oliveira-Ferrer[2], Marion van Mackelenbergh[3], Johann Kornowski[1], Tanja Fehm[4], Michael Untch[5], Paul Jank[6], Carsten Denkert[7], Peter Fasching[8], Christine Stürken[9], Maren Darsow[10], Thomas Karn[11], Georg Kunz[12], Aurelia Noske[13], Frederik Marmé[14], Christian Schem[15], Elmar Stickeler[16], Vanessa Schaser[17], Volkmar Müller[2], Sibylle Loibl[17,18]

[1]Klinik und Poliklinik für Gynäkologie, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany; [2]Zentrum für Operative Medizin, Klinik und Poliklinik für Gynäkologie, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany; [3]Klinik für Gynäkologie und Geburtshilfe, Universitätsklinikum Schleswig-Holstein, Kiel, Germany; [4]Klinik für Frauenheilkunde und Geburtshilfe, Universitätsklinikum Düsseldorf, Düsseldorf, Germany; [5]Helios Kliniken Berlin-Buch, Berlin, Germany; [6]Klinik für Gynäkologie mit Brustzentrum, Charité Universitätsmedizin Berlin, Berlin, Germany; [7]Institut für Pathologie Philipps-Universität Marburg, Marburg, Germany; [8]Frauenklinik, Universitätsklinikum Erlangen, Erlangen, Germany; [9]MSH Medical School Hamburg – University of Applied Sciences and Medical University, Hamburg, Germany; [10]Brustzentrum am Luisenkrankenhaus Düsseldorf, Düsseldorf, Germany; [11]Department of Gynecology and Obstetrics, University of Frankfurt, Frankfurt am Main, Germany; [12]Dortmund St. Johannes Hospital, Brustzentrum, Dortmund, Germany; [13]Institute of Pathology, School of Medicine and Health, TUM Munich, Munich, Germany; Pathology Medica Enge, Zurich, Switzerland; [14]Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany, [15]Mammazentrum Hamburg am Krankenhaus Jerusalem, Hamburg, Germany, [16]Klinik für Gynäkologie und Geburtsmedizin, Uniklinik Aachen, RWTH Aachen, Aachen, Germany, [17]GBG Forschungs GmbH, Neu-Isenburg, Germany; [18]Goethe University Frankfurt, Frankfurt, Germany

78P

Background

- The development of distant metastases is the most critical determinant of breast cancer (BC) survival (1).
- Circulating tumor cell (CTC) clusters exhibit markedly increased metastatic potential compared to single CTCs, with desmosomal proteins such as Desmocollin 2 (DSC2) playing a key role in cluster formation and stability.
- Our group analyzed DSC2 at mRNA and protein level using microarray data, western blot analysis and immunohistochemistry and showed that DSC2 expression is higher in aggressive BC subtypes (HER2-positive, TNBC) and is associated with shorter disease-free and overall survival (OS), as well as increased brain and lung metastases (2).
- In the present analysis we aim to corroborate our previous findings on DSC2 on tumor tissue in a large cohort of GeparQuinto (G5) and GeparSixto (G6) studies.

Patients and Methods

- A total of 3,160 patients were included in the GeparQuinto and GeparSixto studies.
- Tissue from 733 BC patients was evaluable using a validated protocol and IRS scoring (2).
- DSC2 expression was divided into 3 groups (high, moderate, negative) based on the tertiles, Figure 1.
- The median follow up was 60.4 months (IQR 46.1-77).
- Primary endpoint was the development of central nervous system (CNS) metastases as first metastatic site. The time to development of first CNS metastasis was defined as time (in months) from randomization to the occurrence of CNS metastasis as first site of metastatic, with extracranial metastases, contralateral BC, secondary malignancy and death prior to developing CNS metastasis as competing events. Cumulative incidence functions were used for a graphical display and Gray's test was used for group comparison. Univariate and multivariate Fine and Gray models were used to estimate subdistribution hazard ratios (HR) with 95%-confidence interval (CI) for the development of CNS. All univariate as well as multivariate models and group comparisons were stratified by study (G5 vs. G6) to account for potential differences between trials.
- Secondary endpoints included non-CNS metastases, distant disease-free survival (DDFS) and OS. DDFS and OS are defined as time (in months) from randomization until occurrence of distant recurrence or death, whichever comes first or until death, respectively. Survival curves were graphically displayed using Kaplan-Meier curves and group comparison was based on log-rank test stratified by study cohort (G5 vs. G6).

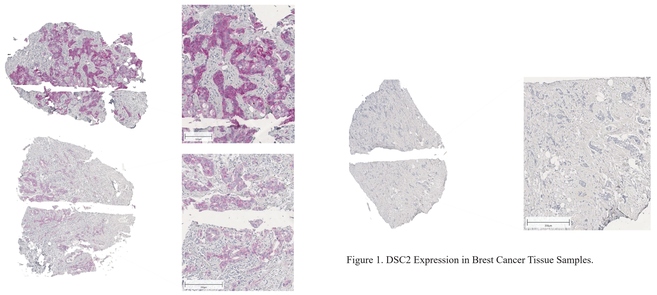

Figure 1. DSC2 Expression in Brest Cancer Tissue Samples.

Results

Patients' characteristics

- In total 104 (of 733) patients (14.2%) developed a metastatic disease: n=26, 3.6% CNS metastases, n=78, 10.6% non-CNS metastases as the first site of distant metastasis. 629 (85.8%) patients showed no distant relapse.
- In the subgroup of patients with CNS metastases as the first metastatic site the median age at diagnosis of CNS metastases was 46.5 years (range 27-70). 7.7% (n=2) of tumors were Luminal A-like, no tumors had a Luminal B subtype, 23.1% (n=6) were HER2-positive, and 69.2% (n=18) were TNBC.
- In the subgroup with non-CNS metastases as the first site of distant metastasis, the median age at diagnosis of distant metastases was 48.0 years (range 26-73). Luminal A-like 14.1% (n=11), luminal B-like 9.0% (n=7), HER2-positive 26.9% (n=21) and TNBC 50.0% (n=39).
- In the subset of patients with CNS metastases, 23.1% (n=6) had previously achieved a pCR (defined as ypT0 ypN0). In the subset of patients with non-CNS metastases, 14.1% (n=11) had achieved pCR. Both sets are based on patients with no event and still at risk until the landmark (defined as 12 months for G5 and 18 weeks for G6).

Association of DSC2 with clinical, histopathological and molecular data

- 733 biopsies (G5 n=499 and G6 n=234) were categorized into three groups (tertiles) based on the DSC2 expression: negative (IRS=0; n=273, 37.2%), moderate (0<IRS≤3; n=221, 30.2%), and high with strong DSC2 expression (IRS>3; n=239, 32.6%).
- The DSC2 expression was significantly associated with aggressive subtypes with higher rates of triple-negative BC (TNBC) in higher DSC2 expression levels
  - high DSC2 level in 81.5% (n=194) of TNBC vs. 9.7% (n=23) of HER2+ vs. 6.7% (n=16) luminal B vs. 2.1% (n=5) in luminal A; moderate DSC2 level in 55.7% (n=123) of TNBC vs. 22.6% (n=50) of HER2+ vs. 9.5% (n=21) luminal B vs. 12.2% (n=27) in luminal A; negative DSC2 level 22.7% (n=62) of TNBC vs. 30% (n=82) of HER2+ vs. 13.9% (n=38) luminal B vs. 33.3% (n=91) in luminal A; p<0.001
- Also, higher DSC2 levels were significantly associated with higher baseline Ki67>20%
  - for high DSC2 97.1% (n=168); moderate DSC2 86.7% (n=117); negative DSC2 66.1% (n=84)) and pCR rates (high DSC2 45.2% (n=108); moderate DSC2 45.7% (n=101); negative DSC2 28.2% (n=77); both p<0.001

No association of DSC2 expression with the development of CNS metastases

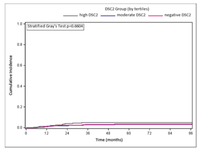

Figure 2. DSC2 expression and development of CNS metastases

The 5-year cumulative incidence for CNS metastases:
- 3.1% (95% CI: 1.5%-5.8%) in the negative DSC2 group
- 3.5% (95% CI: 1.5%-6.8%) in the moderate DSC2 group
- 4.9% (95% CI: 2.6%-8.3%) in the high DSC2 group

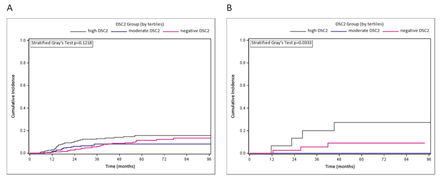

Figure 3. DSC2 expression and development of non-CNS metastases A overall B in luminal B subgroup

Association of DSC2 expression with the development of non-CNS metastases

The 5-year cumulative incidence for non-CNS metastases:
- 11.3% (95% CI: 7.6%-15.9%) in the negative DSC2 group
- 8.1% (95%CI:4.9%-12.3%) in the moderate DSC2 group
- 15.7% (95% CI: 11.0%-21.1%) in the high DSC2 group

For the luminal B subgroup, development of non-CNS metastases
- 3 of 38 among patients with negative DSC2 expression
- 0 of 21 in the moderate group
- 4 of 16 in the high DSC2 group

Association of DSC2 expression with DDFS and OS

- The difference between the DSC2 levels was significant for DDFS and OS, Figure 4 & 5
  - High DSC2 expression was linked to worse DDFS (high vs. negative DSC2: HR 1.66, 95% CI 1.11-2.48; log-rank p=0.010) and OS (high vs. negative DSC2 HR 2.41, 95% CI 1.44-4.02; log-rank p=0.005) in univariate analysis, despite higher pCR rates.
- These associations were also indicated in multivariate analysis considering known prognostic factors like grading, nodal involvement and subtype.

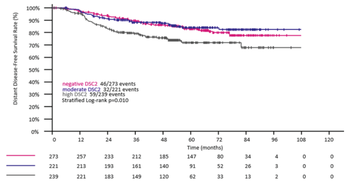

Figure 4. Kaplan-Maier curve for DSC2 expression and DDFS

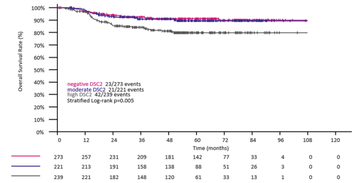

Figure 5. Kaplan-Maier curve for DSC2 expression and OS

Table 1. Multivariate Cox frailty model for DDFS with predefined covariates as fixed effects and 'study' as random effect

		DDFS		OS	
Parameter	Category	HR (95% CI)	p-value*	HR (95%CI)	p-value*
Age, years		1.05 (.895, 1.23)	0.561	1.03 (.844, 1.26)	0.764
DSC2 group (by tertiles)	negative DSC2		0.025		0.050
	moderate DSC2	.859 (.528, 1.40)	0.539	1.04 (.546, 1.97)	0.912
	high DSC2	1.54 (.980, 2.42)	0.061	1.83 (1.01, 3.29)	0.045
clinical Tumor stage	cT1-2				
	cT3-4	1.73 (1.17, 2.55)	0.006	2.33 (1.44, 3.74)	<.001
clinical Nodal stage	cN0				
	cN+	1.92 (1.32, 2.78)	<.001	1.87 (1.16, 3.02)	0.010
Grading	G1-2				
	G3	.807 (.552, 1.18)	0.268	.875 (.536, 1.43)	0.594
Subtype	Luminal A (grade 1-2) or B (grade 3)		0.833		0.939
	HER2+	.974 (.474, 2.00)	0.943	.971 (.329, 2.87)	0.958
	TNBC	.822 (.330, 2.04)	0.672	1.09 (.308, 3.88)	0.891
Hormone receptor status	both ER and PgR negative				
	ER and/or PgR positive	.437 (.212, .901)	0.025	.352 (.126, .985)	0.047

Conclusions

- Our results suggest that DSC2 indicates biological aggressiveness rather than metastatic sites. The strong association with Ki67 also suggests a possible functional relationship with proliferation.
- DSC2 could potentially serve as a prognostic biomarker for risk stratification in BC.
- We could not confirm a significant association between high DSC levels in primary BC and the development of CNS metastases. This may be partly explained by our focus on CNS involvement as the first site of distant metastasis—although CNS metastases more commonly occur later in the disease course—as well as by the limited sample size within specific BC subtypes.
- We urgently need reliable biomarkers—beyond BC subtype—that can accurately predict the development of CNS metastases.

References

1. Largillier et al. Prognostic factors in 1,038 women with metastatic breast cancer. Ann Oncol. 2008 Dec;19(12):2012-9. doi: 10.1093/annonc/mdn424
2. Reimer et al. The role of the desmosomal protein desmocollin 2 in tumour progression in triple negative breast cancer patients. Cancer Cell Int. 2023 Mar 16;23(1):47. doi: 10.1186/s12935-023-02896-9

Presented at: ESMO Breast Cancer 2026

GeparQuinto is financially supported by GlaxoSmithKline, Novartis, Roche, and Sanofi Aventis.
GeparSixto is financially supported by Cephalon, GlaxoSmithKline, and Roche.
The presenting author declares no conflicts of interest related to the presented analysis.