Impact of TROP-2 and its cellular localization on prognosis of breast cancer in the GAIN cohort

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Background

TROP-2, involved in regulating cancer growth and invasion in different tumour types, is a relevant therapeutic target for antibody drug conjugates (ADC)[1,2]. This study evaluates the impact of TROP-2 on breast cancer (BC) prognosis in high-risk, node-positive BC of the German adjuvant intergroup node-positive (GAIN) cohort[3].

Material

Tissue microarrays (TMA) were generated from Formalin fixed paraffin embedded-pre-therapeutic tissue (n=1358, Figure 1).

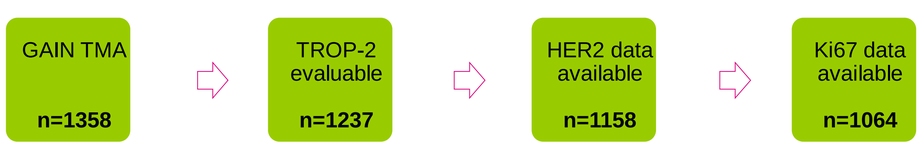


Figure 1: CONSORT diagram.

Method

Membranous (m) and cytoplasmic (c) expression of TROP-2 in invasive tumor cells were assessed with human TROP-2 antibody SP295 with respect to proportion and staining intensity (Figure 2). Cutoff Finder web application was used for identification of the best cutoff according to disease-free survival (DFS) and overall survival (OS)[4]. We evaluated association of mTROP-2 and cTROP-2 expression with DFS, OS and baseline parameters (Table 1).

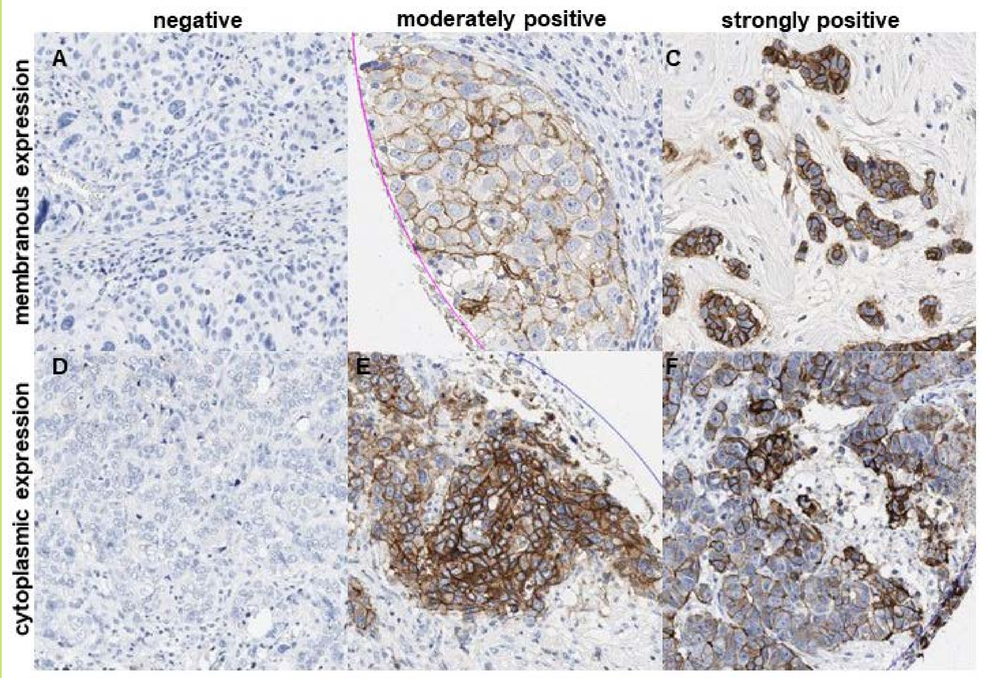


Figure 2: Staining patterns for TROP-2 antibody SP295.

Results

For 1237 TMA spots valid TROP-2 evaluation was available (median follow-up 112 months), Figure 3 for categorized proportion of staining. Cutoff Finder analysis was performed for overall and molecular subgroups identifying 70 % as best cutoff for cTROP-2 and 0.5 % for mTROP-2 for DFS and OS. cTROP-2 > 70 % was significantly associated with worse grading (16 % vs. 7.9 %), negative hormone receptor (17.5 % vs. 10.1 %) and positive HER2 status (18.6 % vs. 9.9 %), each p < 0.001 (Table 1). In multivariate Cox regression analysis, cTROP-2 > 70 % was associated with worse DFS in overall (hazard ratio (hr) 1.389 [95 % CI 1.039-1.856], p = 0.026), luminal/HER2-negative (hr 1.592 [95 % CI 1.070-2.368], p = 0.022) and HER2-negative cohorts (hr 1.614 [95 % CI 1.151-2.263], p = 0.006), Figure 4A-C. mTROP-2 > 0.5 % was associated with improved DFS in overall (hr 0.729 [95 % CI 0.564-0.942], p = 0.016) and HER2-negative cohorts (hr 0.708 [95 % CI 0.534-0.938], p = 0.016) in multivariate analysis, Figure 5A/B.

Figure 3. Pie charts demonstrating categorized proportion of TROP-2 staining, A mTROP-2, B cTROP-2.

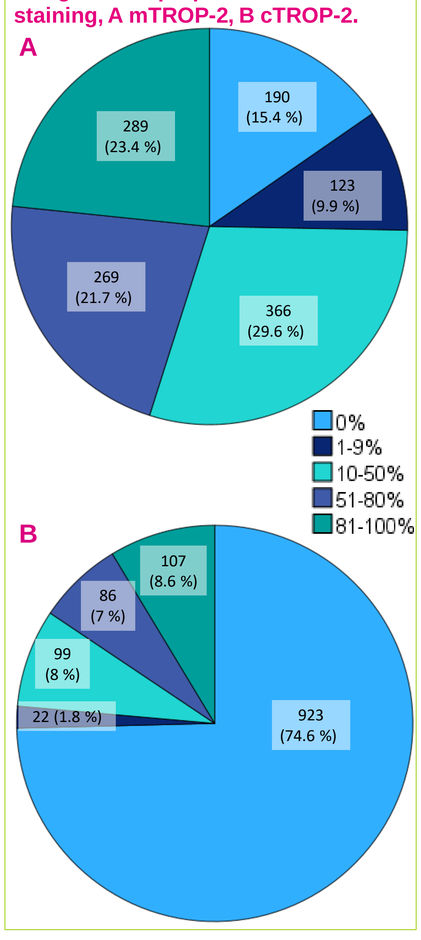


Table 1: Baseline characteristics, A cTROP-2, B mTROP-2 *n* (%), *p*-value = Fisher's exact or [1]Pearson Chi²-test

Parameter A	All (*n* = 1237)	cTROP-2 ≤ 70 %	cTROP-2 > 70 %	*p*-value
Hormone receptor status (HR)				**0.001**
negative	292 (23.6 %)	241 (82.5 %)	51 (17.5 %)	
positive	945 (76.4 %)	850 (89.9 %)	95 (10.1 %)	
HER2 status				**< 0.001**
negative	900 (77.7 %)	811 (90.1 %)	89 (9.9 %)	
positive	258 (22.3 %)	210 (81.4 %)	48 (18.6 %)	
missing	79			
Molecular subgroup				**< 0.001**
Lum/HER2-	719 (62.1 %)	658 (91.5 %)	61 (8.5 %)	
HER2+	258 (22.3 %)	210 (81.4 %)	48 (18.6 %)	
TNBC	181 (15.6 %)	153 (84.5 %)	28 (15.5 %)	
missing	79			
Grading				**< 0.001**
G1-2	636 (51.5 %)	586 (92.1 %)	50 (7.9 %)	
G3	600 (24.2 %)	504 (84 %)	96 (16 %)	
missing	1			
pT				1
T1-2	1087 (88.2 %)	958 (88.1 %)	129 (11.9 %)	
T3-4	146 (11.8 %)	129 (88.4 %)	17 (11.6 %)	
missing	4			
pN				0.655
N1	504 (40.7 %)	442 (87.7 %)	62 (12.3 %)	
N2-3	733 (59.3 %)	649 (88.5 %)	84 (11.5 %)	
Histological tumor type				**0.03[1]**
NST	963 (77.8 %)	837 (86.9 %)	126 (13.1 %)	
ILC	137 (11.1 %)	128 (93.4 %)	9 (6.6 %)	
Other	137 (11.1 %)	126 (92 %)	11 (8 %)	

Parameter B	mTROP-2 ≤ 0.5 %	mTROP-2 > 0.5 %	*p*-value
Hormone receptor status (HR)			0.307
negative	39 (13.4 %)	253 (86.6 %)	
positive	151 (16 %)	794 (84 %)	
HER2 status			0.234
negative	141 (15.7 %)	759 (84.3 %)	
positive	32 (12.4 %)	226 (87.6 %)	
missing			
Molecular subgroup			**0.371[1]**
Lum/HER2-	115 (16 %)	604 (84 %)	
HER2+	32 (12.4 %)	226 (87.6 %)	
TNBC	26 (14.4%)	155 (85.6 %)	
missing			
Grading			0.937
G1-2	97 (15.3 %)	539 (84.7 %)	
G3	93 (15.5 %)	507 (84.5 %)	
missing			
pT			**0.027**
T1-2	158 (14.5 %)	929 (85.5 %)	
T3-4	32 (21.9 %)	114 (78.1 %)	
missing			
pN			0.521
N1	73 (14.5 %)	431 (85.5 %)	
N2-3	117 (16 %)	616 (84 %)	
Histological tumor type			**0.018[1]**
NST	134 (13.9 %)	829 (86.1 %)	
ILC	25 (18.2 %)	112 (81.8 %)	
Other	31 (22.6 %)	106 (77.4 %)	

Figure 4: Kaplan Meier curves and univariate/ multivariate Cox regression analysis for cTROP-2 expression in the overall cohort (A), lum/HER2-negative (B) and HER2-negative (C) subgroups.

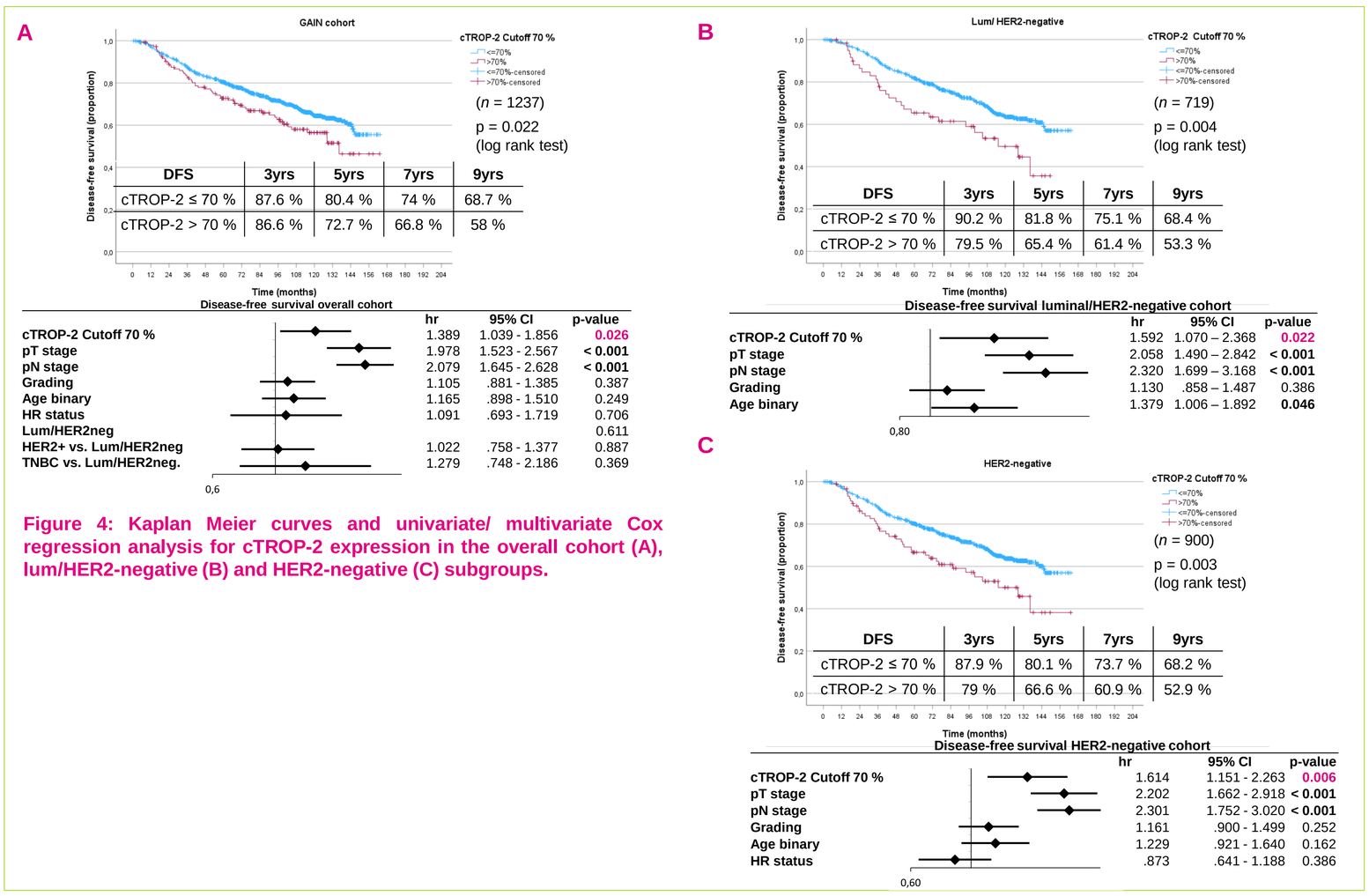
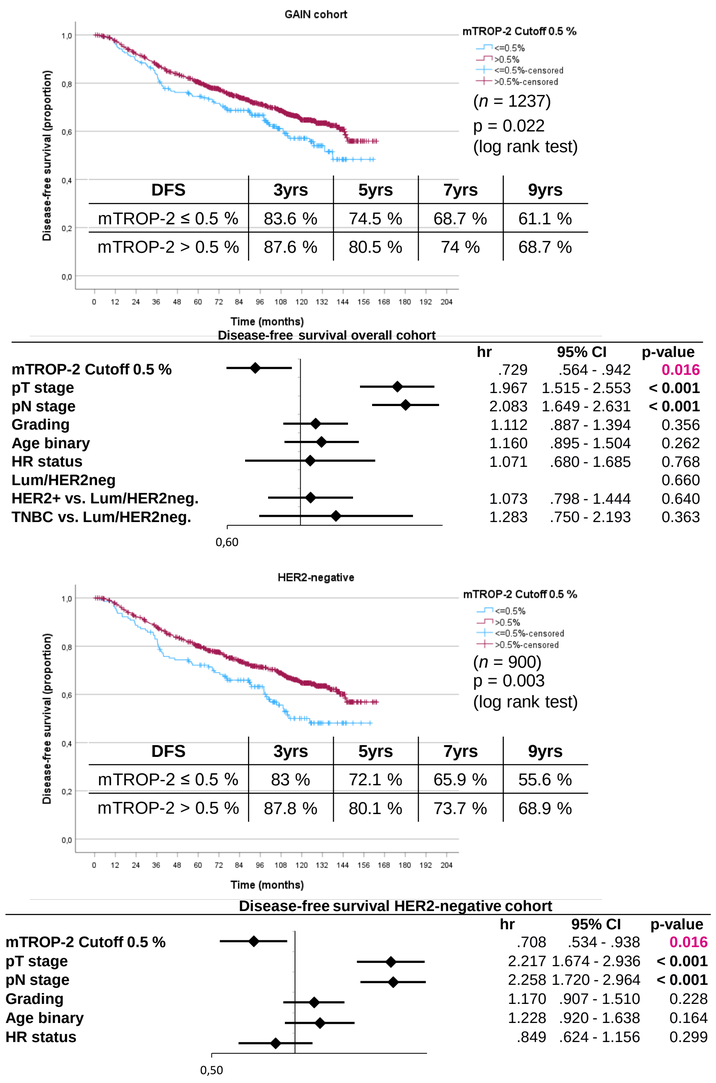


Figure 5: Kaplan Meier curves and univariate/ multivariate Cox regression analysis for mTROP-2 expression in the overall cohort (A) and HER2-negative (B) subgroups.



Conclusion

Cellular localization of TROP2 differentially affects survival in BC. cTROP-2 ≤ 70 % was associated with favorable pathologic features (G1/2, HR+), but also with HER2 negativity in the GAIN cohort. Clinical features (pT, pN) did not correlate with cTROP-2. mTROP-2 was associated with higher pT stage. The results are relevant for biomarker strategies for future therapeutic concepts.

Disclosure Statement

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