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

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P129

Background

TROP-2 is involved in regulating cancer growth and invasion in different tumour types. It is also a potent therapeutic target, being addressed by antibody drug conjugates (ADC)[1,2]. However, the impact of TROP-2 expression and localization on breast cancer (BC) prognosis is yet unclear. This study aims at its evaluation in high-risk, node-positive BC of the German adjuvant intergroup node-positive (GAIN) cohort[3].

Patients and Methods

Tissue microarrays (TMAs) were generated from Formalin-fixed paraffin-embedded pre-therapeutic surgical resection tissue (*n* = 1358, Figure 1) from the prospective adjuvant phase III GAIN-1 trial comparing two dose-dense regimens (epirubicin (E), paclitaxel (taxol; T), cyclophosphamide (C)) vs. EC-TX (capecitabine (X)) with or without Ibandronate). Immunohistochemical staining was performed with human TROP-2 antibody SP295 (Figure 2). Membranous and cytoplasmic expression of TROP-2 in invasive tumour cells was assessed as to proportion (in 5 % steps) and staining intensity in 4 categories. For membranous (m)TROP-2, a product score (IRS) of grouped percentage and staining intensity was generated. Cutoff Finder web application[4] was used for identification of the best cutoff point according to disease-free survival (DFS) and overall survival (OS). For *n* = 996 patients, data on hormone receptor (HR), HER2 and Ki-67 status were available. The association of mTROP-2 and cytoplasmic (c)TROP-2 expression with molecular intrinsic subgroups, TNM stages, age, proliferation and HR status were evaluated (Table 1). Correlation with DFS and OS was evaluated with Kaplan Meier curves, log rank tests and Cox regression.

Figure 1: CONSORT diagram.

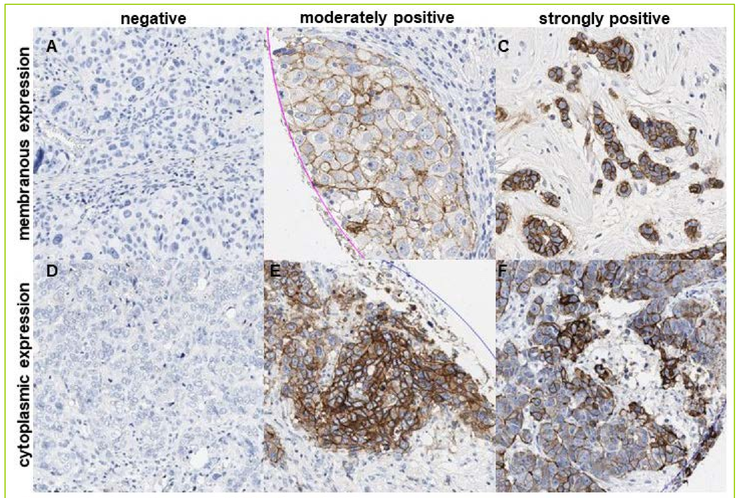

Figure 2: Staining patterns for TROP-2 antibody SP295.

References

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Results

For 1186 TMA spots valid TROP-2 evaluation was available (Figure 1). The Cutoff Finder identified 70 % as best cutoff for cTROP-2 expression. cTROP-2 ≤ 70 % was significantly associated with prognostic factors including better grading and HR positivity, while cTROP-2 > 70 % was significantly associated with HER2 positivity (Table 1). DFS and OS in GAIN cohort and significant association with molecular subgroups are presented in Figure 3. In multivariate Cox regression analysis, cTROP-2 ≤ 70 % was associated with improved DFS in luminal/HER2- (hazard ratio (hr) 1.773 [95 % CI 1.182 – 2.660], *p* = 0.006) and luminal A-like tumours (hr 1.767 [95 % CI 1.127 – 2.770], *p* = 0.013). Interestingly, higher mTROP-2 expression (IRS > 3) was associated with better DFS and OS in HER2+/ HR any and HER2+/ HR+ patients (uni-/ multivariate (DFS HER+/ HR any (hr 0.561 [95 % CI 0.365 – 0.862], *p* = 0.008), DFS HER2+/ HR+ (hr 0.491 [95 % CI 0.290 – 0.832], *p* = 0.008), OS HER2+/ HR any (hr 0.496 [95 % CI 0.274 – 0.897], *p* = 0.020), OS HER2+/ HR+ (hr 0.396 [95 % CI 0.193 – 0.812], *p* =0.012)).

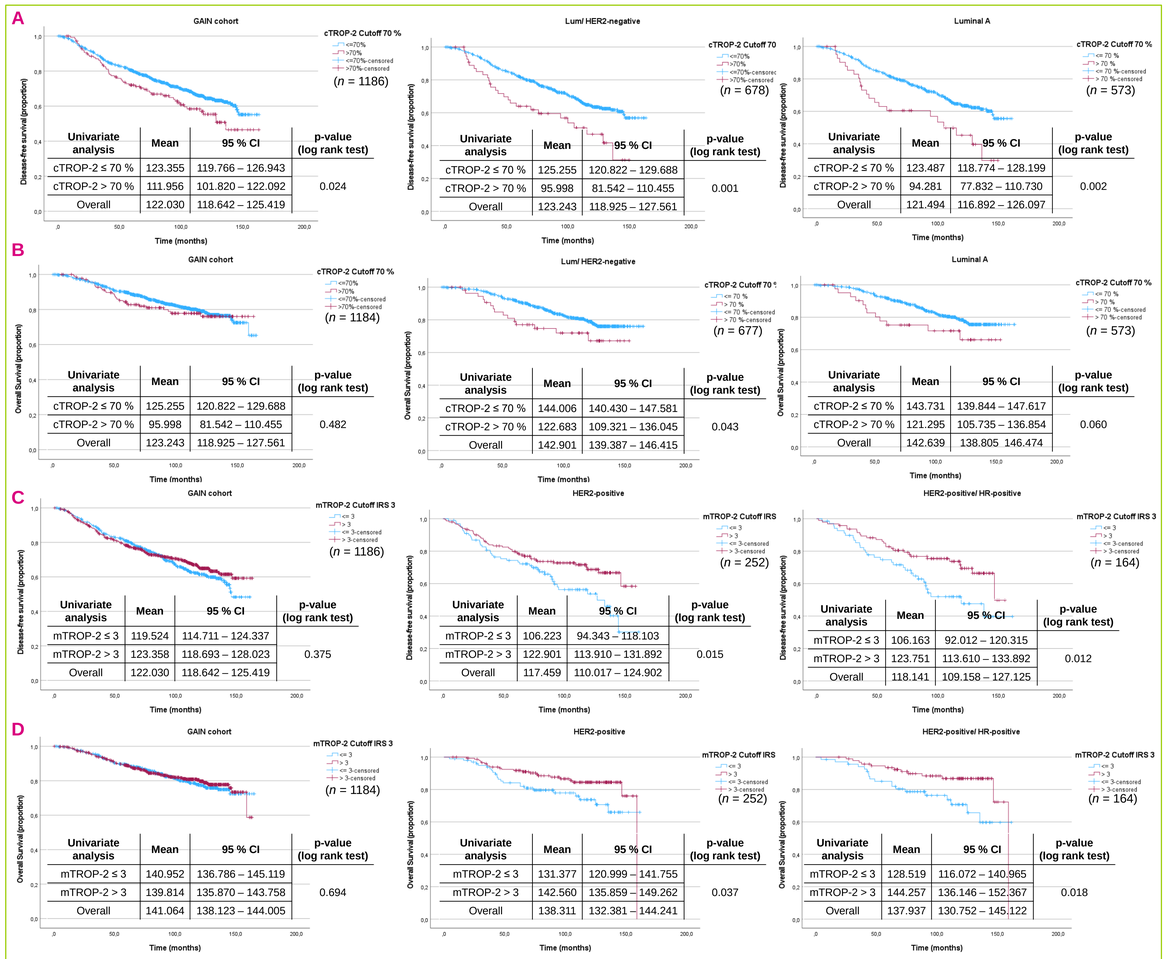

Figure 3: Survival curves. A) disease-free survival in subgroups for cTROP-2. B) overall survival in subgroups for cTROP-2. C) disease-free survival in subgroups for mTROP-2. B) overall survival in subgroups for mTROP-2.

Conclusions

TROP-2 is commonly expressed in breast cancer with its cellular localization differentially affecting survival. Cytoplasmic expression ≤ 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. These findings might be interesting for future risk assessments and need to be validated prospectively.

Table 1: Baseline characteristics *n* (%), *p*-value from Fisher's exact or [1] Pearson Chi²-test

Parameter	All (*n* = 1186)	cTROP-2 <= 70 %	cTROP-2 > 70 %	*p*-value
Hormone receptor status (HR)				**< 0.001**
negative	287 (24.2)	234 (81.5)	53 (18.5)	
positive	899 (75.8)	810 (90.1)	89 (9.9)	
HER2 status				**< 0.001**
negative	855 (77.2)	770 (90.1)	85 (9.9)	
positive	252 (22.8)	204 (81)	48 (19)	
missing	79			
Molecular subgroup				**< 0.001**
Lum/HER2-	678 (61.2)	622 (91.7)	56 (8.3)	
HER2+	252 (22.8)	204 (81)	48 (19)	
TNBC	177 (16)	148 (83.6)	29 (16.4)	
missing	79			
Grading				**< 0.001**
G1-2	601 (50.7)	554 (92.2)	47 (7.8)	
G3	584 (49.3)	489 (83.7)	95 (16.3)	
missing	1			
pT				1
T1-2	1040 (88)	915 (88)	125 (12)	
T3-4	142 (12)	125 (88)	17 (12)	
missing	4			
pN				0.716
N1	488 (41.1)	432 (88.5)	56 (11.5)	
N2-3	698 (58.9)	612 (87.7)	86 (12.3)	
Ki67				**0.008**
≤ 25 %	912 (87.9)	812 (89)	100 (11)	
> 25 %	125 (12.1)	100 (80)	25 (20)	
missing	149			
Histological tumor type				**0.046** [1]
NST	924 (78)	802 (86.8)	122 (13.2)	
ILC	131 (11)	122 (93.1)	9 (6.9)	
Other	131 (11)	120 (91.6)	11 (8.4)	
Therapy				0.592
ETC	599 (50.5)	524 (87.5)	75 (12.5)	
EC-TX	587 (49.5)	520 (88.6)	67 (11.4)	
Ibandronate				**0.048**
No	410 (34.6)	350 (85.4)	60 (14.6)	
Yes	776 (65.4)	694 (89.4)	82 (10.6)	
TIL				**0.003** [1]
No TILs	354 (31)	319 (90.1)	35 (9.9)	
1-10 %	464 (40.6)	421 (90.7)	43 (9.3)	
11-25 %	241 (21.1)	196 (81.3)	45 (18.7)	
26-50 %	56 (4.9)	47 (83.9)	9 (16.1)	
51-60 %	21 (1.8)	17 (81)	4 (19)	
> 61 %	6 (0.5)	6 (100)	0 (0)	
missing	44			
PDL1+ immune cells				**0.005** [1]
< 1 %	1051 (93.3)	932 (88.7)	119 (11.3)	
1 - 5 %	38 (3.4)	31 (81.6)	7 (18.4)	
6 - 10 %	21 (1.9)	14 (66.7)	7 (18.4)	
11 - 24 %	14 (1.2)	10 (71.4)	4 (28.6)	
25 - 50 %	3 (0.3)	3 (100)	0 (0)	
missing	59			
PDL1+ tumor cells				**0.021** [1]
< 1 %	1109 (98.4)	977 (88.1)	132 (11.9)	
1 - 5 %	14 (1.2)	11 (78.6)	3 (24.4)	
11 - 24 %	3 (0.3)	2 (66.7)	1 (33.3)	
25 - 50 %	1 (0.1)	0 (0)	1 (100)	
missing	59			

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