Neoadjuvant chemotherapy in inflammatory breast cancer:
A meta-analysis of 10 trials of the AGO-B Study Group and German Breast Group (GBG)

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249P

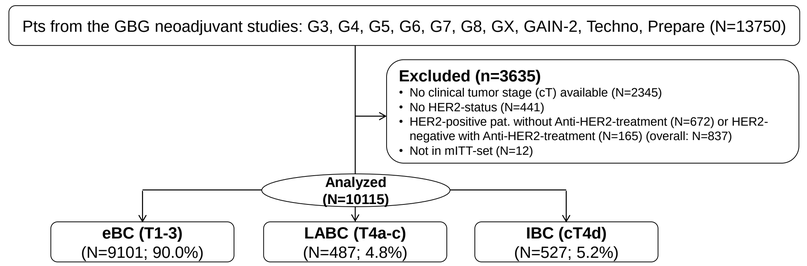
Background

Inflammatory breast cancer (IBC) is a rare clinic-pathologic entity associated with poor clinical outcome.[1] Currently, no approved IBC-specific systemic treatment recommendations are available. We investigated clinical, pathological, and prognostic features associated with IBC in a meta-analysis of 10 neoadjuvant trials conducted by GBG.

Patients and Methods

We performed a post-hoc analysis of patients (pts) from the G3-G8, GX, GAIN-2, TECHNO, and PREPARE trials, aiming to compare early breast cancer (eBC, cT1-3) with locally advanced breast cancer (LABC, cT4a-c) and IBC (cT4d) concerning clinic-pathological features and prognostic behavior after adjusting for selected clinical factors (Figure 1).

Figure 1: Study design



Results

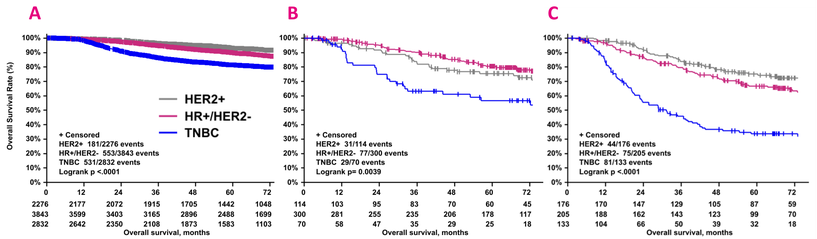
Out of 10.115 pts included 9.101 pts (90.0%) had eBC, 487 (4.8%) LABC and 527 (5.2%) IBC. Pts with LABC and IBC were older and had a higher body mass index compared to eBC pts. IBC pts presented more often with nodal involvement, hormone receptor negative or human epidermal growth factor receptor 2 positive (HER2+) disease. Pathological complete response (pCR) rates (ypT0/is ypN0) were significantly lower in LABC and IBC pts compared to eBC pts (eBC 33.6% vs LABC 17.2%, p<0.001 vs IBC 24.5%, p=0.010; Table 1). Multivariate cox frailty models revealed LABC and IBC compared to eBC as independent risk factors for recurrence and death (disease-free survival; LABC hazard ratio [HR] 1.59, 95% CI 1.23-2.06; IBC HR 2.45, 95% CI 1.99-3.02; overall survival [OS]: LABC HR 1.97, 95% CI 1.43-2.70; IBC HR 3.05, 95% CI 2.37-3.93, all p<0.001) by considering established prognostic factors like nodal involvement, BC subtype or grading (Table 2). Triple negative (TN) IBC pts had strikingly poor prognosis (median OS 31.3 months; 2-years OS 55.4%) compared to pts with TN eBC or LABC, respectively, (2-years OS; eBC 91.0%, LABC 74.8%) or HER2+ and luminal IBC (2-years OS; HER2+ 92.1%, luminal 87.2%; Figure 2).
Survival differences were consistently observed in all trials and sustained with longer FU. No treatment showed specific benefit for pts with IBC (data not shown).

Table 1: Patients' characteristics stratified by cT-stage

Parameter	Category	eBC (cT1-3) N=9101 N (valid %)	LABC (cT4a-c) N=487 N (valid %)	IBC (cT4d) N=527 N (valid %)	Overall N=10115 N (valid %)	p-value strat. (eBC vs LABC)*	p-value strat. (eBC vs IBC)*
Age, years	Median (Range)	48.0 (20.0, 80.0)	54.0 (27.0, 80.0)	54.0 (22.0, 77.0)	49.0 (20.0, 80.0)	<.001	<.001
BMI, kg/m²	Median (Range)	24.7 (14.2, 58.0)	25.4 (15.4, 44.1)	27.7 (16.9, 54.4)	24.9 (14.2, 58.0)	0.014	<.001
Clinical nodal status	Negative	4864 (57.3)	155 (33.0)	98 (20.2)	5117 (54.2)	<.001	<.001
	Positive	3625 (42.7)	315 (67.0)	388 (79.8)	4328 (45.8)		
Estrogen receptor	Negative	3972 (44.3)	140 (28.9)	249 (48.3)	4361 (43.8)	<.001	0.007
	Positive	4985 (55.7)	345 (71.1)	267 (51.7)	5597 (56.2)		
Progesteron receptor	Negative	4757 (53.1)	185 (38.1)	310 (60.1)	5252 (52.8)	<.001	<.001
	Positive	4196 (46.9)	300 (61.9)	206 (39.9)	4702 (47.2)		
HER2-status	Negative	6825 (75.0)	373 (76.6)	351 (66.6)	7549 (74.6)	0.907	<.001
	Positive	2276 (25.0)	114 (23.4)	176 (33.4)	2566 (25.4)		
Molecular subtype	HER2 +	2276 (25.4)	114 (23.5)	176 (34.1)	2566 (25.8)	<.001	<.001
	HR +, HER2 -	3848 (42.9)	301 (62.1)	207 (40.1)	4356 (43.7)		
	TNBC	2837 (31.7)	70 (14.4)	133 (25.8)	3040 (30.5)		
pCR (ypT0/is ypN0)	No pCR	6039 (66.4)	403 (82.8)	398 (75.5)	6840 (67.6)	<.001	0.010
	pCR	3062 (33.6)	84 (17.2)	129 (24.5)	3275 (32.4)		

*van-Elteren-test for continuous variables and Cochrane-Mantel-Haenszel-Test for categorical variables, stratified by study.

Figure 2: KM-curve for OS* between subtypes in patients with eBC (A), LABC (B) and IBC (C)



*analysis without consideration of study-specific differences. A comparison with meta-analytic methods of the OS estimates revealed no significant heterogeneity between studies and no great differences to the pooled OS estimates.

Table 2. Multivariate Cox frailty model for DFS (A) and OS (B) with predefined covariates as fixed effects and the parameter 'study' as random effect

A

Parameter	Category	HR	95% CI	P-value
cT-stage	eBC (cT1-3)			<.001
	LABC (cT4a-c)	1.59	(1.23, 2.06)	<.001
	IBC (cT4d)	2.45	(1.99, 3.02)	<.001
Age, years	<40			
	≥40	.882	(.767, 1.01)	.079
Clinical nodal status	Node neg.			
	Node pos.	1.69	(1.51, 1.89)	<.001
Molecular subtype	HER2 +			<.001
	HR +, HER2 -	1.05	(.907, 1.21)	.527
	TNBC	1.64	(1.42, 1.89)	<.001
Histological tumor type	Ductal			.554
	Lobular	.909	(.703, 1.17)	.463
	other	1.07	(.895, 1.28)	.452
LPBC (sTILs < vs ≥60)	no LPBC			
	LPBC	.639	(.537, .759)	<.001
Tumor grading	G1/G2			
	G3	1.13	(1.01, 1.27)	.040
pCR (ypT0/is ypN0)	No pCR			
	pCR	.433	(.380, .495)	<.001

B

Parameter	Category	HR	95% CI	P-value
cT-stage	eBC (cT1-3)			<.001
	LABC (cT4a-c)	1.97	(1.43, 2.70)	<.001
	IBC (cT4d)	3.05	(2.37, 3.93)	<.001
Age, years	<40			
	≥40	1.01	(.827, 1.24)	.898
Clinical nodal status	Node neg.			
	Node pos.	2.02	(1.73, 2.37)	<.001
Molecular subtype	HER2 +			<.001
	HR +, HER2 -	1.32	(1.07, 1.64)	.010
	TNBC	2.36	(1.92, 2.91)	<.001
Histological tumor type	Ductal			.667
	Lobular	.961	(.684, 1.35)	.821
	other	1.11	(.872, 1.42)	.394
LPBC (sTILs < vs ≥60)	no LPBC			
	LPBC	.703	(.558, .885)	.003
Tumor grading	G1/G2			
	G3	1.23	(1.05, 1.45)	.011
pCR (ypT0/is ypN0)	No pCR			
	pCR	.296	(.241, .363)	<.001

Conclusions

Pts with IBC, especially TN IBC have a disproportional high risk of recurrence and death. Therefore, IBC pts should be offered trial participation in innovative neoadjuvant and postneoadjuvant trials given the limited prognosis with standard treatments.

References

1 Hance KW et al.; Trends in inflammatory breast carcinoma incidence and survival: the surveillance, epidemiology, and end results program at the National Cancer Institute. J Natl Cancer Inst. 2005;97(13):966–75.

Presented at: ESMO-Congress-2024, 13 - 17 Sep 2024. Barcelona, Spain.

The funding for the 10 neoadjuvant GBG trials included in this study was provided by the following sponsors: G3 (Amgen, Roche, Sanofi-Aventis), G4 (Roche Germany), G5 (Celgene Germany, Roche Germany), G6 (GlaxoSmithKline), G7 (Roche, Celgene), G8 (Teva, Amgen, Vifor, Roche), GX (Amgen, Celgene), GAIN-2 (Roche, Amgen, Celgene), TECHNO (Roche), and PREPARE (Amgen, Bristol-Myers Squibb Germany).