Effect of pertuzumab plus neoadjuvant trastuzumab-based chemotherapy in early-stage HER2-positive breast cancer according to BluePrint molecularly defined breast cancer subtypes

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Background

- The addition of pertuzumab to neoadjuvant trastuzumab-based chemotherapy significantly improves pCR rates in HER2-positive breast cancer, but effects on long-term survival are modest[1-5]
- BluePrint (BP) is an 80-gene molecular subtyping test that classifies breast tumors as basal-, luminal- or HER2-subtype. A small proportion of tumors exhibits two functionally activated BluePrint pathways and are referred as dual subtypes.
- Results from an APHINITY sub-analysis suggest that pertuzumab benefit is largely restricted to patients with single-activated HER2-type tumors[7]

Goal

To evaluate BluePrint subtype as biomarker for response to trastuzumab-based neoadjuvant chemotherapy with or without pertuzumab.

Methods

- Stage II-III HER2-positive breast cancer treated with trastuzumab-based chemotherapy between January 2013 - January 2016
- Pertuzumab was only available in hospitals participating in the TRAIN2 study (NCT01996267 – BOOG 2012-03)[8]
- Data was collected from the nationwide Netherlands Cancer Registry
- Blueprint molecular subtypes were successfully determined using pre-treatment biopsies for 822 patients of whom 404 received pertuzumab and 398 matched controls did not receive pertuzumab
- Pathological complete response (pCR) and overall survival (OS) were analyzed by treatment arm and BluePrint subtypes using logistic and Cox regression
- Kaplan-Meier curves are shown for illustration purposes

Results

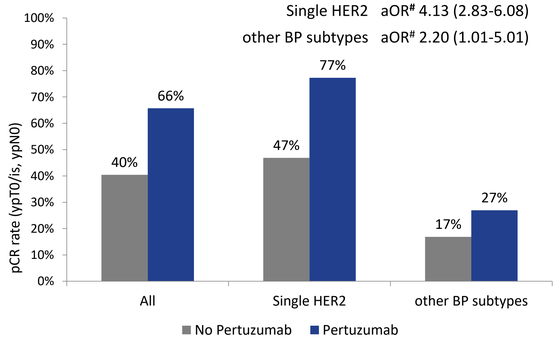
- BluePrint read out: 85.4% HER2-type, 12.8% Luminal-type and 1.8% Basal-type
- BluePrint dual subtypes: 13% reclassified, mostly to Luminal-HER2 (10.6%)
- PCR is higher in patients treated with Pertuzumab (40% vs. 66%). Absolute pCR rate and increase with Pertuzumab were higher in single HER2 subtype (47% vs. 77%) than in the other BP subtypes combined (17% vs. 27%)
- Overall survival is higher in patients treated with Pertuzumab (adjusted hazard ratio [aHR] 0.41, 95% CI 0.24 – 0.71). Increase in OS was higher in patients with single HER2 subtype (aHR 0.31, 95% CI 0.16 - 0.60) than in the other BP subtypes (aHR 0.64, 95% CI 0.24 – 1.73)
- However, tests for interaction between pertuzumab and BluePrint subtypes are not significant (data not shown)

Baseline & treatment characteristics

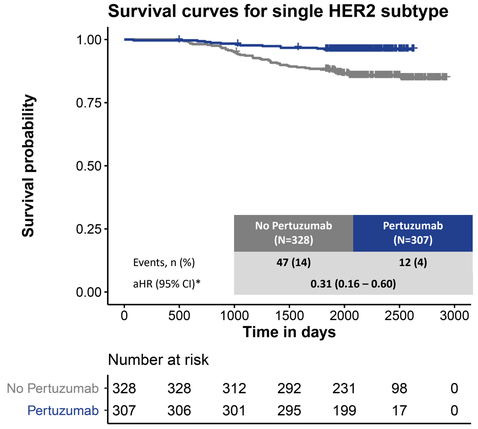
	No Pertuzumab (n=424)		Pertuzumab (n=398)		
	n	%	n	%	p-value
Age, mean (SD)	50.6	(12.5)	49.3	(9.85)	0.19
HR-status					0.67
negative	158	37.3%	154	38.7%	
positive	266	62.7%	242	60.8%	
Clinical T-stage					0.65
cT1-2	289	68.2%	278	69.8%	
cT3-4	135	31.8%	120	30.2%	
Clinical N-stage					0.03
cN0	128	30.2%	150	37.7%	
cN+	293	69.1%	245	61.6%	
Grade					0.001
grade 1-2	158	37.3%	197	49.5%	
grade 3	262	61.8%	201	50.5%	
Chemotherapy					<0.001
no anthracyclines	156	36.8%	189	47.6%	
anthracyclines	268	63.2%	209	52.2%	
Surgery					<0.001
BCS	196	46.2%	229	57.5%	
mastectomy	228	53.8%	169	42.5%	

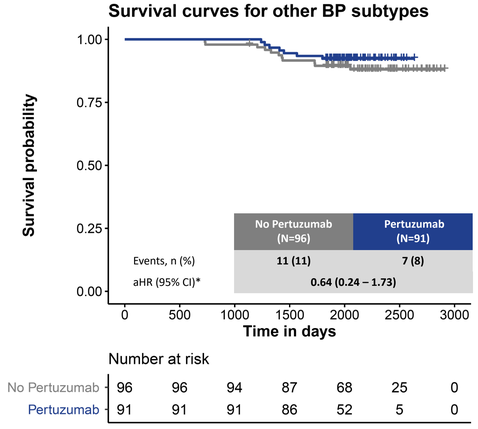
HR, hormone receptor; NA, neoadjuvant; BCS, breast-conserving surgery; P-values are based on Wilcoxon rank sum test and Fisher's exact test for categorical variables; some percentages do not count to 100% due to missing values

pCR rates without and with pertuzumab



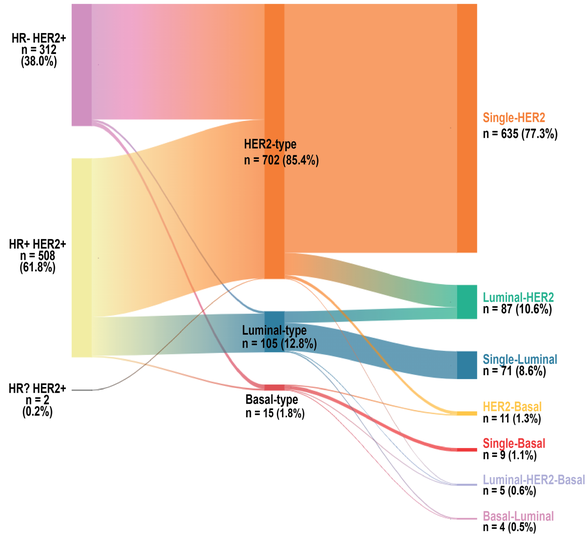
Kaplan-Meier curves





*aHR + #aOR,; adjusted for age, hormone receptor status, cT, cN, grade & anthracyclines (yes/no)

BluePrint & BluePrint dual subtypes



Conclusion

The benefit of adding pertuzumab to (neo)adjuvant trastuzumab-based chemotherapy is highest in patients with a molecularly defined single-activated HER2-subtype. In the other subtypes combined, pCR rates and survival are worse with less pronounced benefit of pertuzumab. Patients with single HER2 subtype identified by BluePrint could be optimal candidates for chemotherapy de-escalation.

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