



# Tumor infiltrating lymphocytes as a prognostic factor in early breast cancer

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## Introduction and Aim of the Study

Stromal tumor infiltrating lymphocytes (sTILs) are considered to have prognostic and predictive impact for patients with early breast cancer.

## Patients and Methods

- Prospective, multicenter cohort of 1,270 breast cancer patients (PiA, Prognostic Assessment in Routine application, NCT 01592825)
- Stromal TILs were evaluated following recommendations of the International TILs Working Group 2014<sup>1</sup>
- Stromal TILs were quantified stepwise (per 10% increment) and by assigning to low (<10%), intermediate (10-60%), high TILs (>60%) group

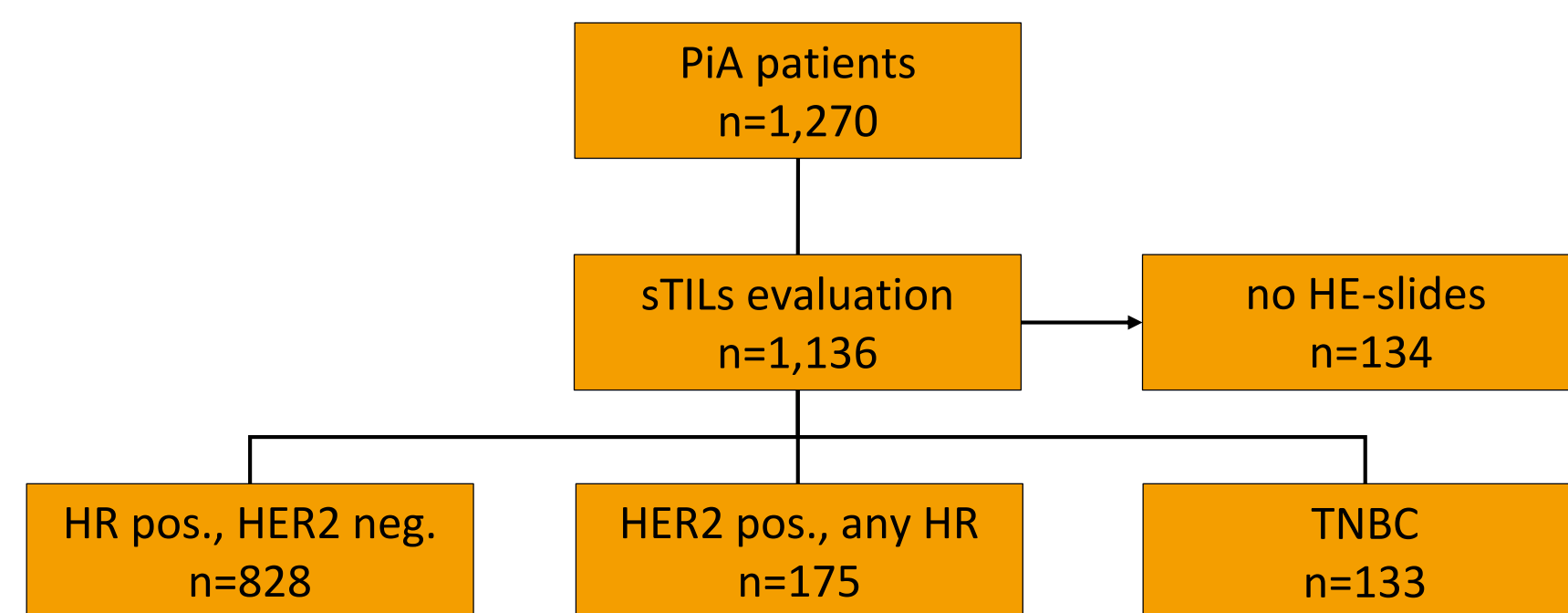


Figure 1: Consort diagram for stromal TILs evaluation

Table 1: Selected patients and tumors characteristics

	HR pos., HER2 neg. n=828 (100%)	HER2 pos., any HR n=175 (100%)	TNBC n=133 (100%)
<b>Age</b>			
< 35 yrs	13 (1.6%)	5 (2.9%)	11 (7.2%)
35 - 50 yrs	176 (21.3%)	53 (30.3%)	45 (19.6%)
50 - 75 yrs	502 (60.6%)	93 (53.1%)	74 (48.7%)
> 75 yrs	137 (16.5%)	24 (13.7%)	22 (14.5%)
<b>Tumor size</b>			
< 2 cm	474 (57.2%)	72 (41.1%)	46 (30.3%)
2 - 5 cm	309 (37.3%)	85 (48.6%)	84 (55.3%)
> 5 cm	45 (5.4%)	18 (10.3%)	22 (14.5%)
<b>Nodal status</b>			
Negative	529 (63.9%)	102 (58.3%)	77 (50.7%)
Positive	299 (36.1%)	73 (41.7%)	75 (49.3%)
<b>Grading</b>			
G1	149 (18.0%)	7 (4.0%)	1 (0.7%)
G2	560 (67.6%)	96 (54.9%)	60 (39.5%)
G3	119 (14.4%)	72 (41.1%)	91 (59.9%)

## Primary and Secondary Objectives

Primary objective was the proportion of stromal TILs dependent on steroid hormone receptor status (HR) and HER2 status of the tumor. Secondary objective was the association of TILs with recurrence free interval (RFI) and overall survival (OS).

## Results

- In HR positive and HER2 negative group: Few tumors (1.5%) have more than 60% TILs
- In HER2 positive and TN tumor: Higher proportions of TILs (9.7% and 18.8%, resp.) were observed

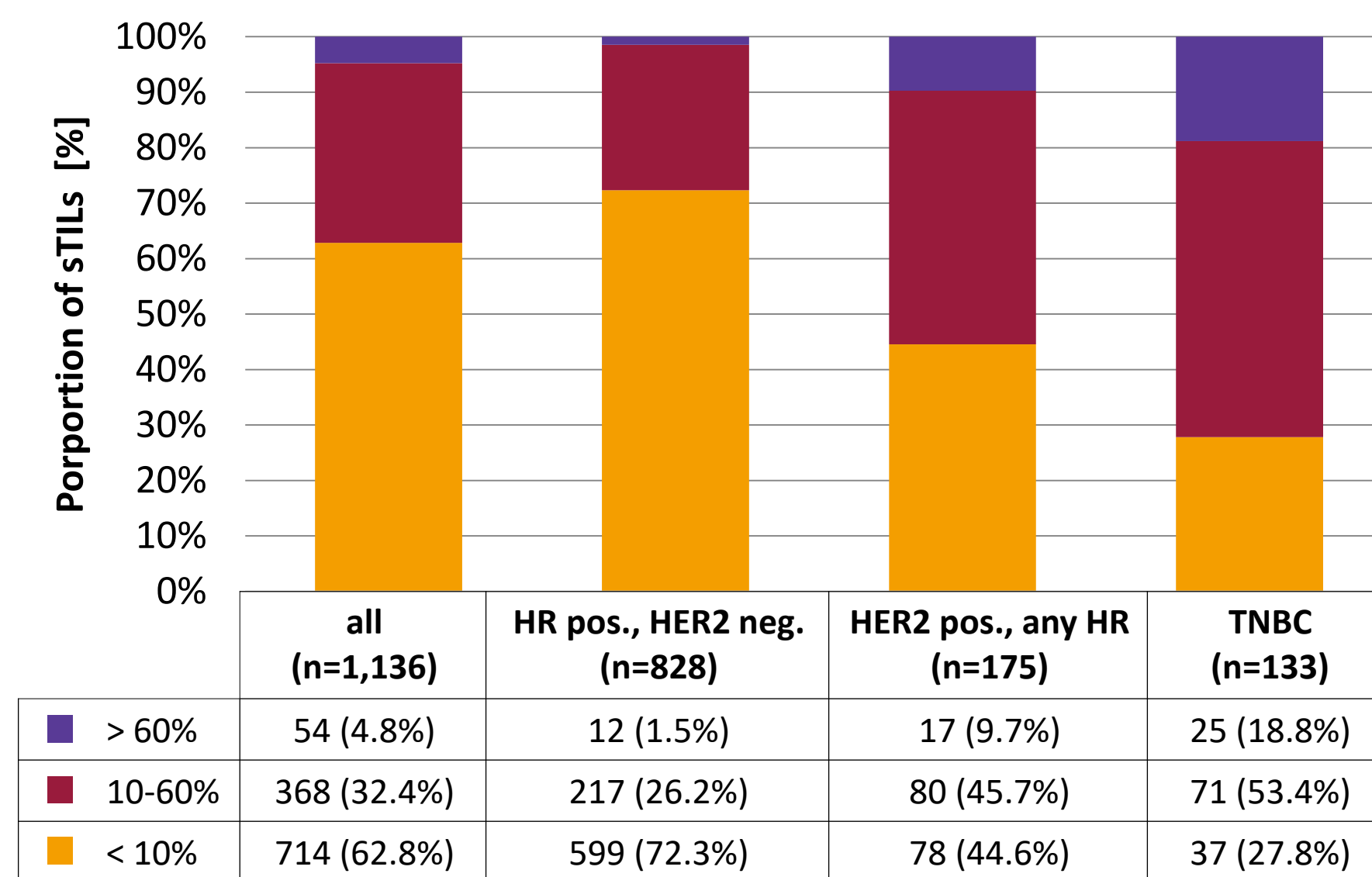


Figure 2: Proportion of stromal TILs

## Stromal TILs and association to survival

- No impact of stromal TILs on RFI and OS in patients with HR positive and HER2 negative tumors
- A proportion of more than 60% TILs led to a better RFI and OS in patients with HER2 positive BC and in TNBC
- A 10% increment of TILs increases RFI and OS in the HER2 positive groups, TNBC groups and the entire cohort

## Best cut-off for proportion of stromal TILs (maximum likelihood)

- HER2 positive: Cut-off **20%**
  - RFI: 2.467, 95% CI 0.903-6.735, p=0.078
  - OS: 4.565, 95% CI 1.583-13.159, p=0.005
- TNBC: Cut-off **5%**
  - RFI: 1.440, 95% CI 0.627-3.308, p=0.390
  - OS: 2.035, 95% CI 0.906-4.571, p=0.085

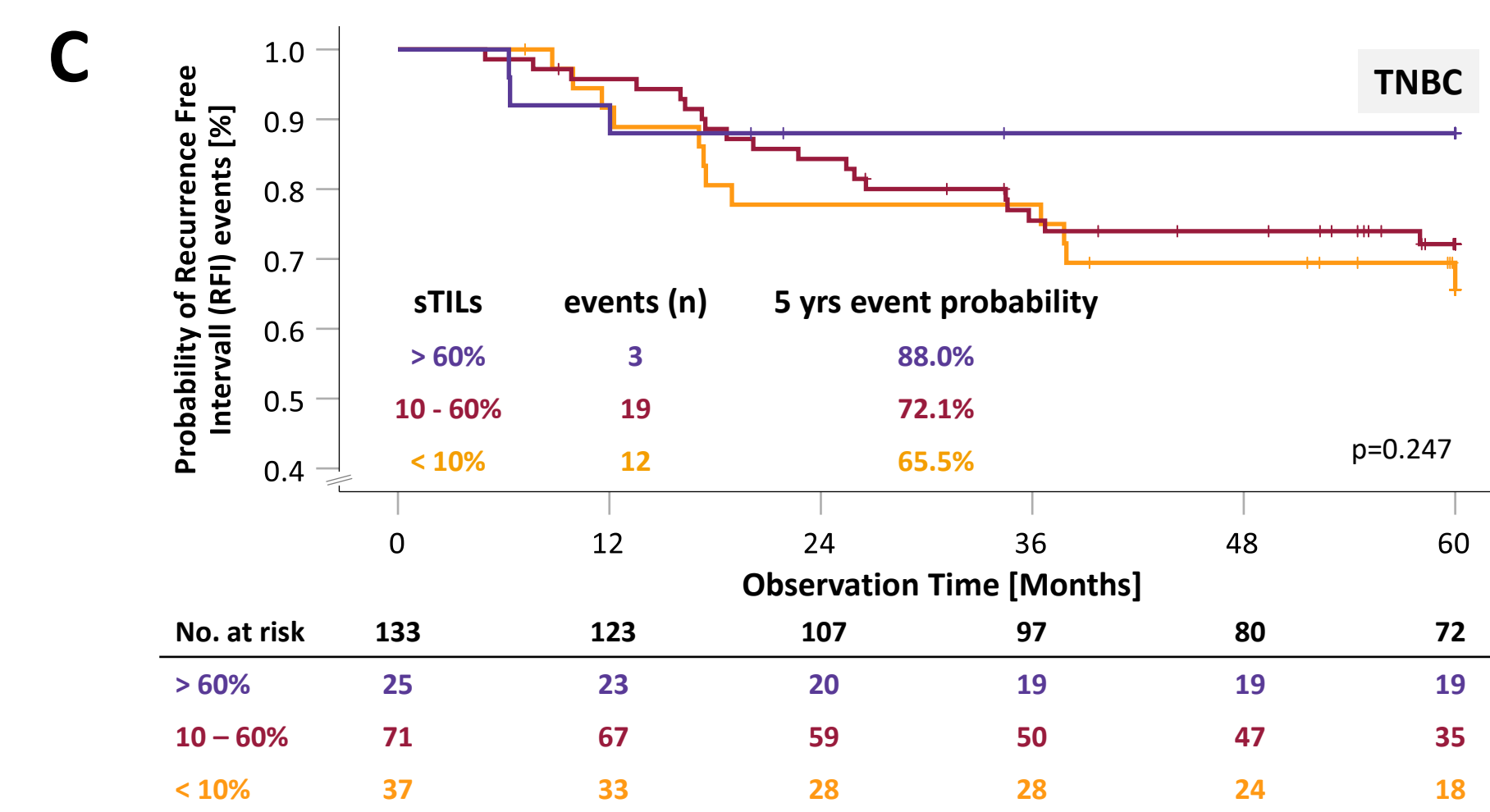
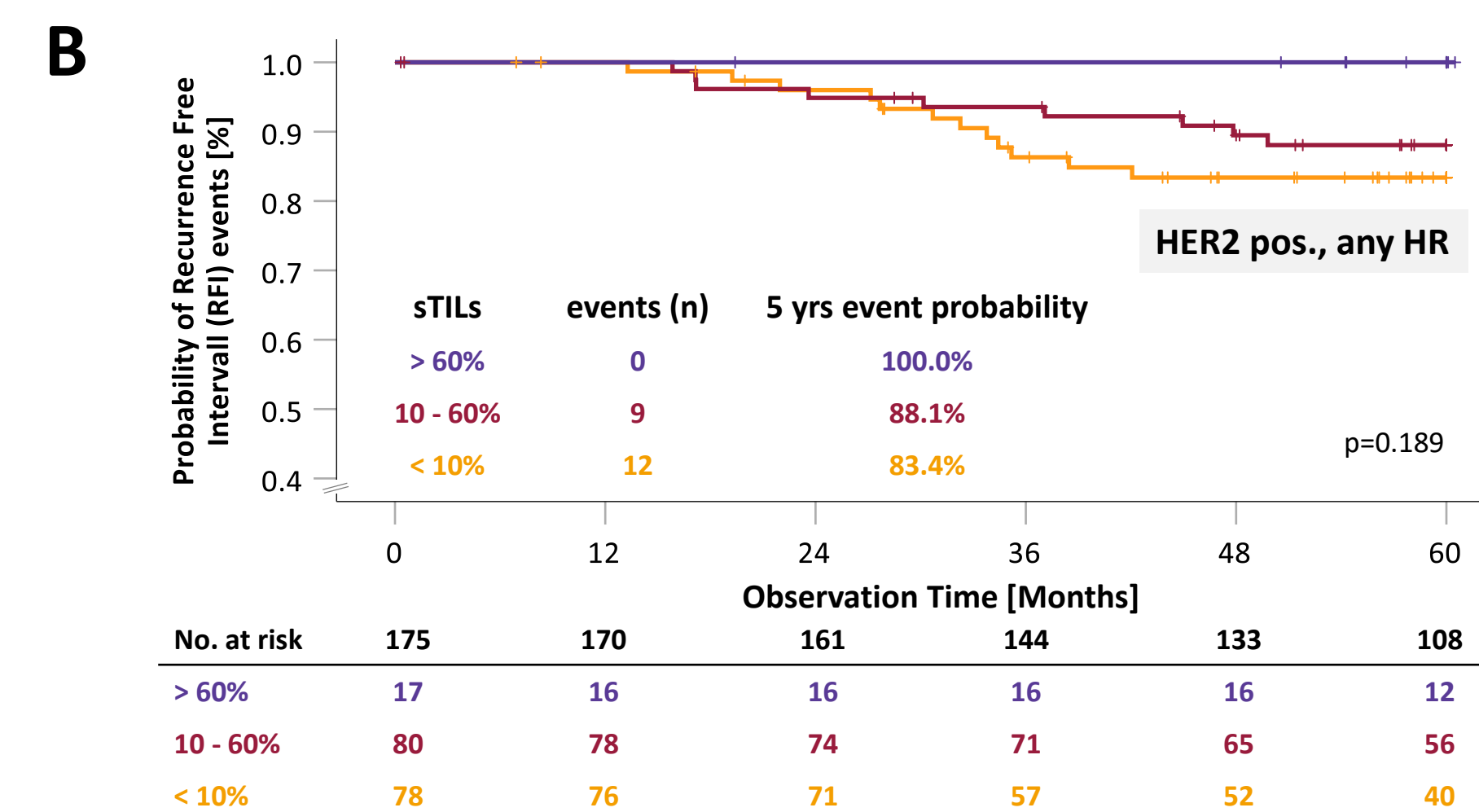
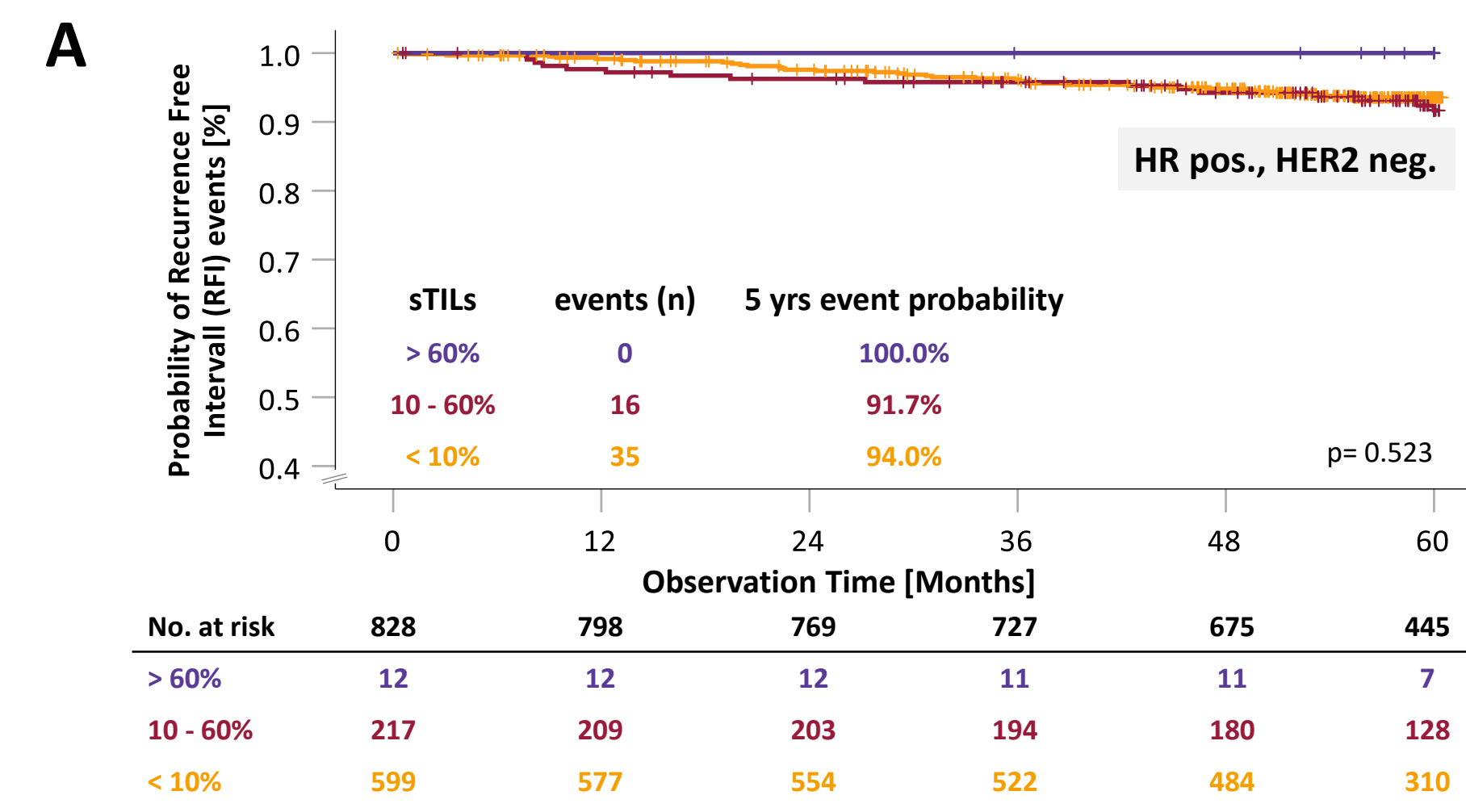


Figure 3: Survival estimates for HR positive and HER2 negative (A), HER2 positive any HR (B), TNBC (C)

Table 2: Multivariate analysis for 10% increment of RFI and OS

Parameters	sample size	Multivariate analysis RFI			Multivariate analysis OS		
		HR	95% CI	p value	HR	95% CI	p value
	n=1,136						
<b>Tumour size at time of diagnosis</b>							
< 2cm	589	1			1		
≥ 2 cm	547	2.154	1.331-3.485	0.002	2.421	1.565-3.745	0.000
<b>Nodal status at time of diagnosis</b>							
negative	698	1			1		
positive	438	2.074	1.374-3.132	0.001	2.014	1.390-2.918	0.000
<b>Grading</b>							
G1	147	1			1		
G2	711	4.671	1.131-19.296	0.033	1.584	0.719-3.492	0.254
G3	268	5.911	1.379-25.338	0.017	2.649	1.150-6.099	0.022
<b>Hormone receptor status</b>							
HR positive	943	1			1		
HR negative	193	3.351	2.146-5.235	0.000	1.882	1.232-2.873	0.003
<b>HER2-Status</b>							
HER2 negative	961	1			1		
HER2 positive	175	1.132	0.963-1.847	0.621	1.159	0.752-1.785	0.505
<b>TILs</b>							
per 10% increment	1,136	0.895	0.795-1.007	0.066	0.889	0.794-0.997	0.044

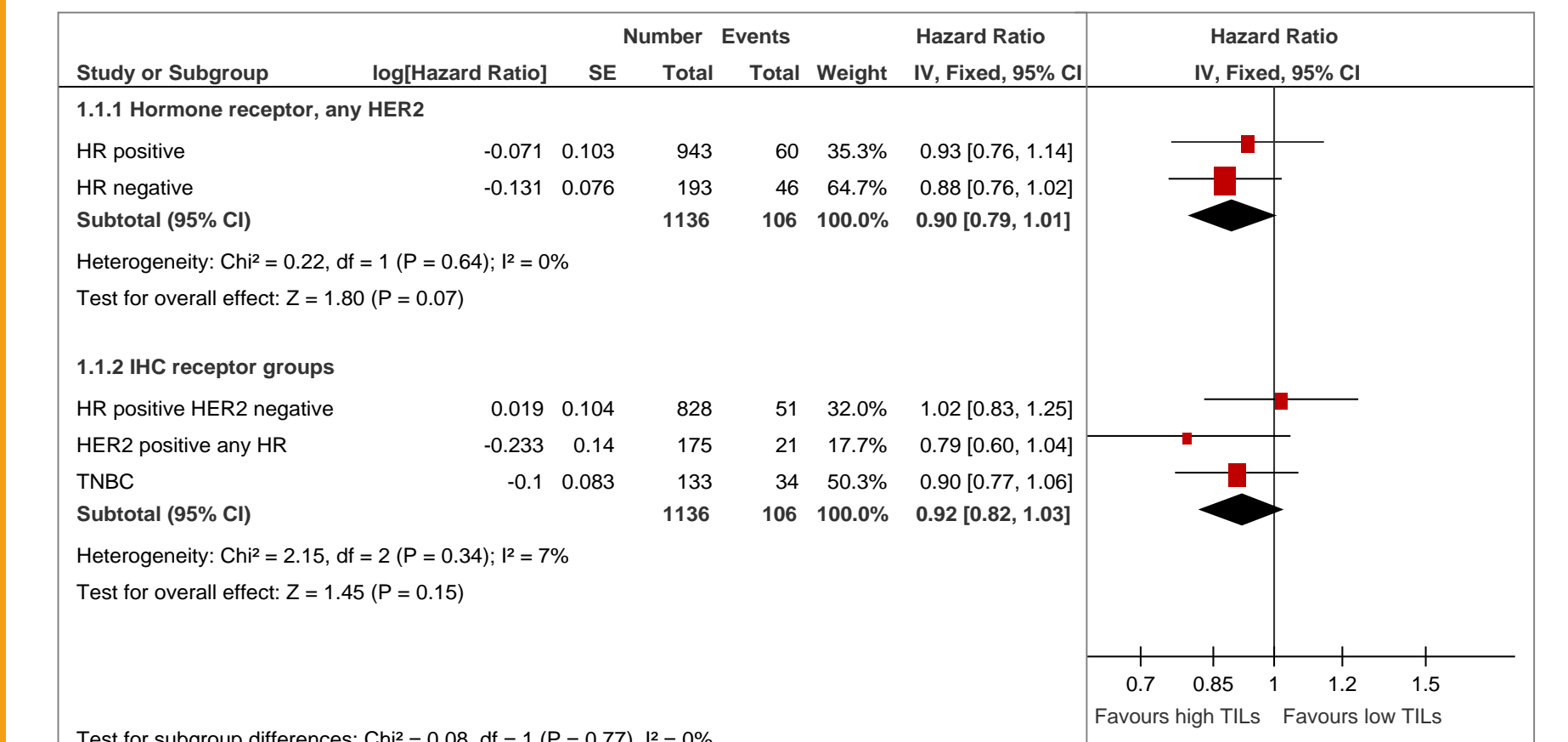


Figure 4: Forest plot for different IHC receptor groups

## Conclusion

Using data from our multicenter, consecutive enrolled cohort, TILs were ascertained as a rather strong though not significant prognostic factor for patients with HER2 positive and TN tumors. For clinical use we suggest to use 20% as the cut-off for HER2 positive tumors and 5% for TN tumors

## References

- (1) Salgado R et al., The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: recommendations by an International TILs Working Group 2014. Ann Oncol. 2015 Feb;26(2):259-71. doi: 10.1093/annonc/mdu450

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