SFSPM Novembre 2017

Valeur prédictive et pronostique de l'infiltrat immunitaire dans les cancers du sein traités par chimiothérapie néoadjuvante

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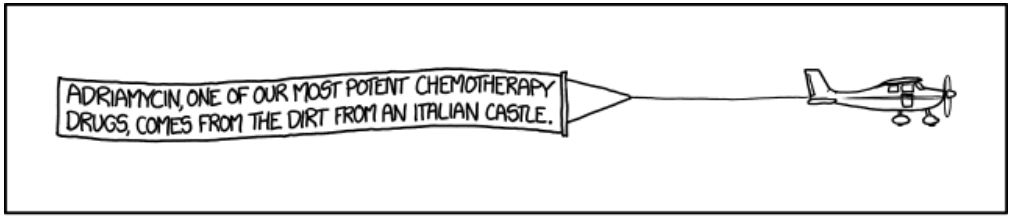


MY HOBBY:
BREAKING INTO AIRPLANE HANGARS AND REPLACING THE ADS ON THEIR GIANT BANNERS WITH COOL FACTS

Tumor infiltration in the neoadjuvant setting

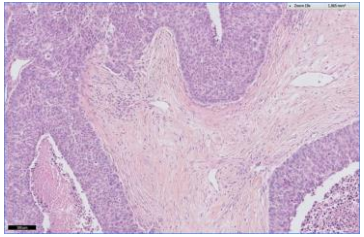
- Role of tumor-infiltrating lymphocytes (TILs)
  - High levels of TILs at diagnosis : better response to NAC
  - Better prognosis (triple negative breast cancers (TNBC) and *HER2*-positive BC)

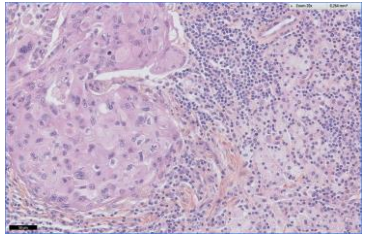
- TILs following neoadjuvant chemotherapy (NAC) ?

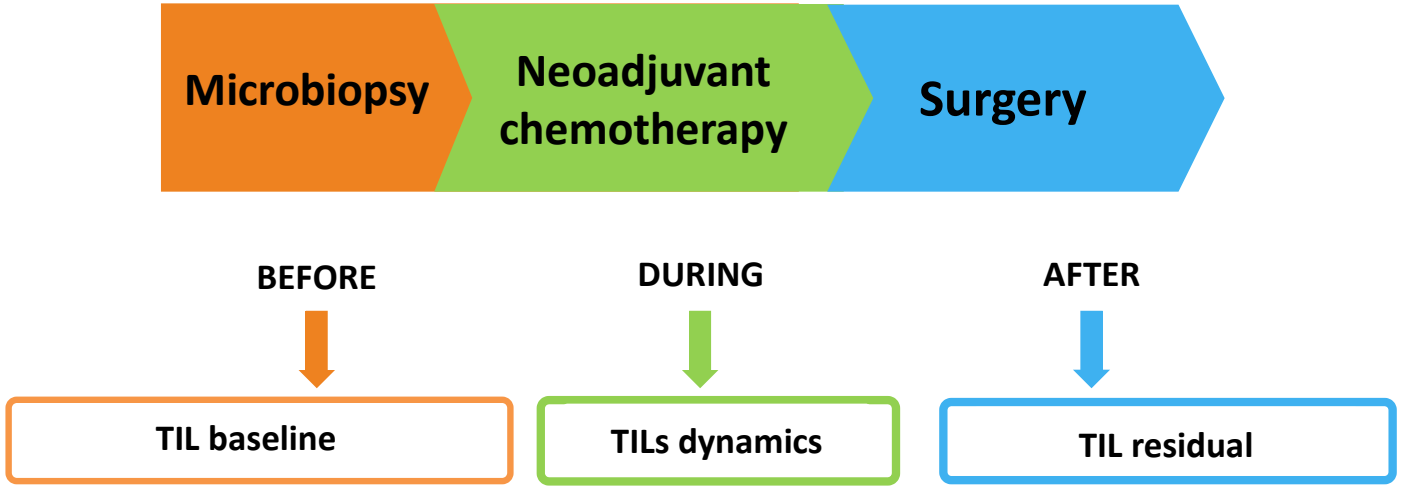
	Myashita	Dieci	Loi	Hamy
BC subtype	TNBC	TNBC	TNBC	*HER2*-pos
Numbers	n=131	n=278	n=111	n=175
Pairs pre & post	**n=78**	**n=19**	**n=39**	**n=175**
Analysis in pCR patients	No	No	No	**Yes**

Tumor infiltration and response to treatment in breast cancer

NEOREP cohort
Institut Curie
2002-2011
n=718







Identify patterns of immune infiltration related to response to treatment and prognosis

Patients characteristics

NEOREP cohort

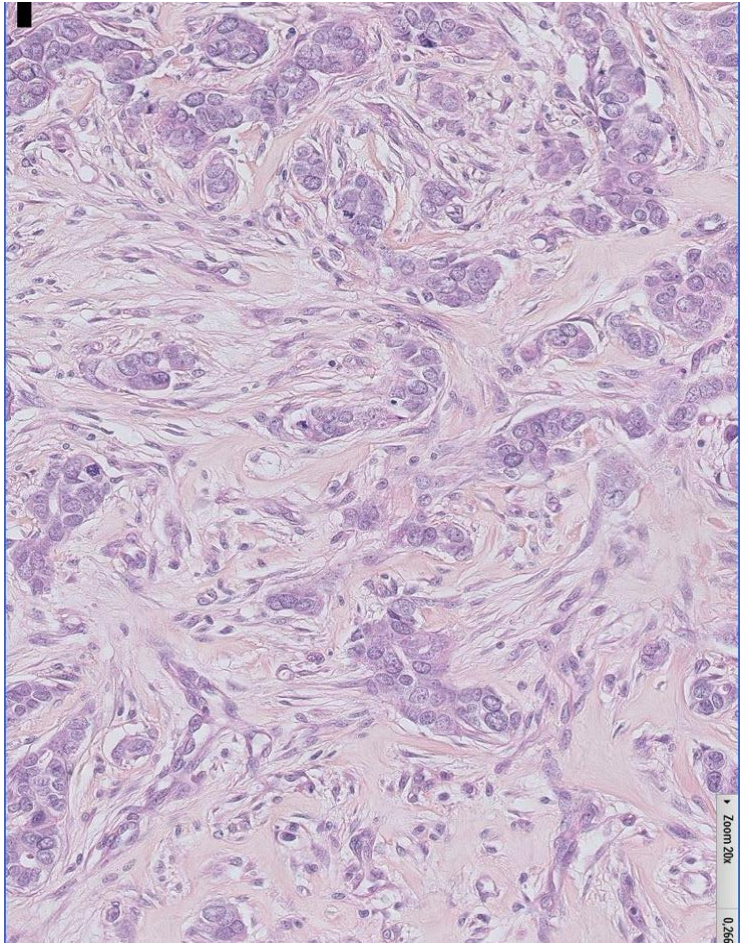
n=718
Mean age : 48 y.o

TNBC 44%
Luminal 31%
HER2 24%

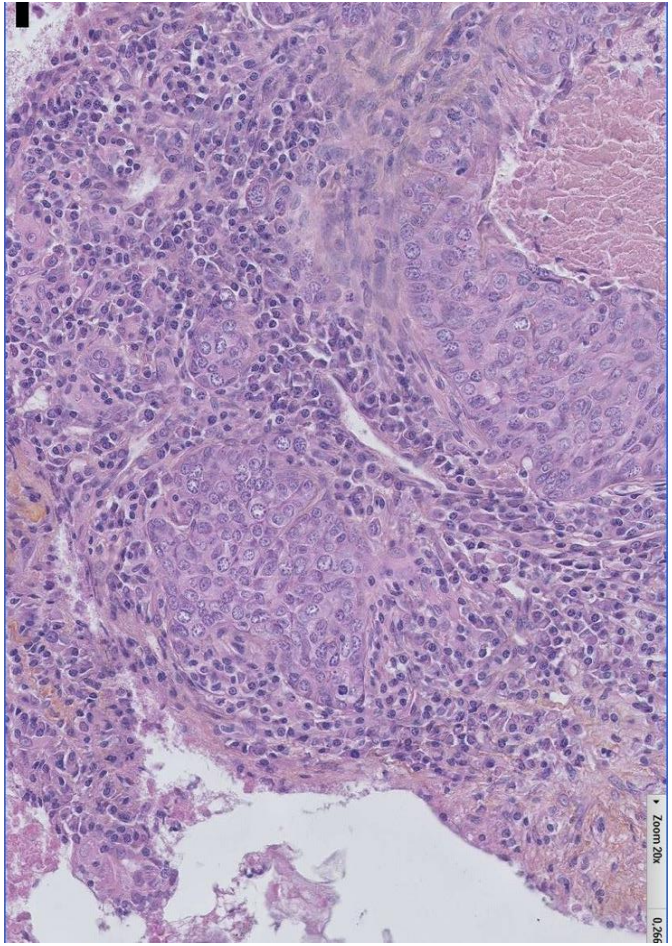
Median tumor size: 45mm

Anthra – taxanes (80.4%)

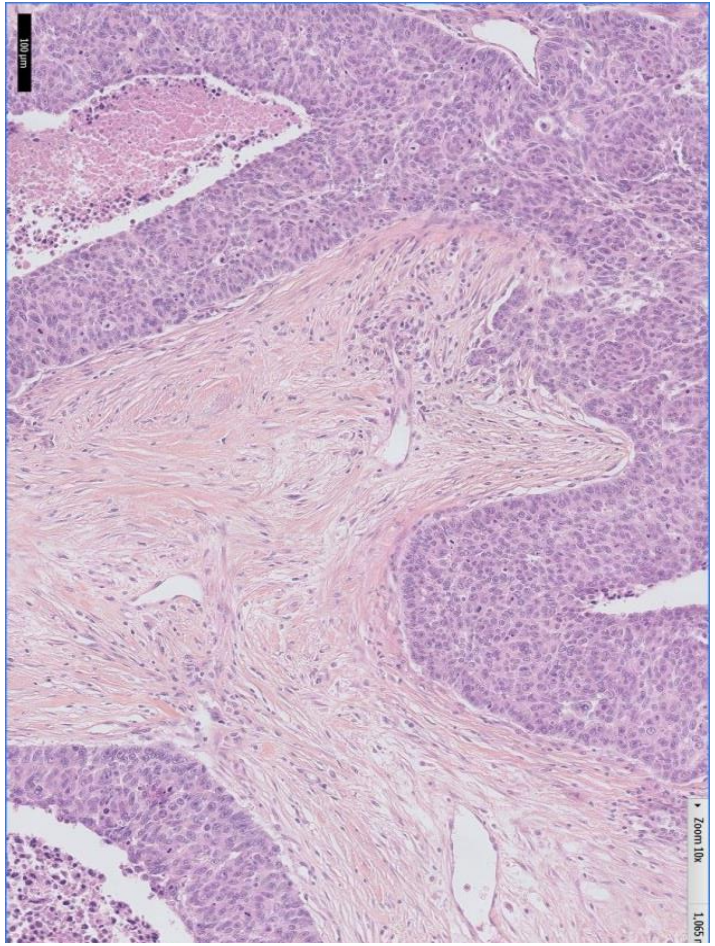
		N=718
BMI class	BMI<19	41 (5.7)
	BMI: 19 to 25	414 (57.7)
	BMI: 25 to 30	166 (23.2)
	BMI>30	96 (13.4)
Tumor size		45.0 (20.5)
Tumor size	T1	47 (6.5)
	T2	482 (67.1)
	T3	189 (26.3)
Clinical node status	N0	282 (39.3)
	N1-N2-N3	435 (60.7)
BC subtype	Luminal	223 (31.1)
	TNBC	320 (44.6)
	HER2	175 (24.4)
Histology	Ductal carcinoma NST	661 (92.6)
	Other	53 (7.4)
Grade	Grade I-II	211 (30.1)
	Grade III	491 (69.9)
NAC regimen	Anthracyclines based regimens	61 (8.5)
	Anthracyclines-taxanes regimens	577 (80.4)
	Others	80 (11.1)



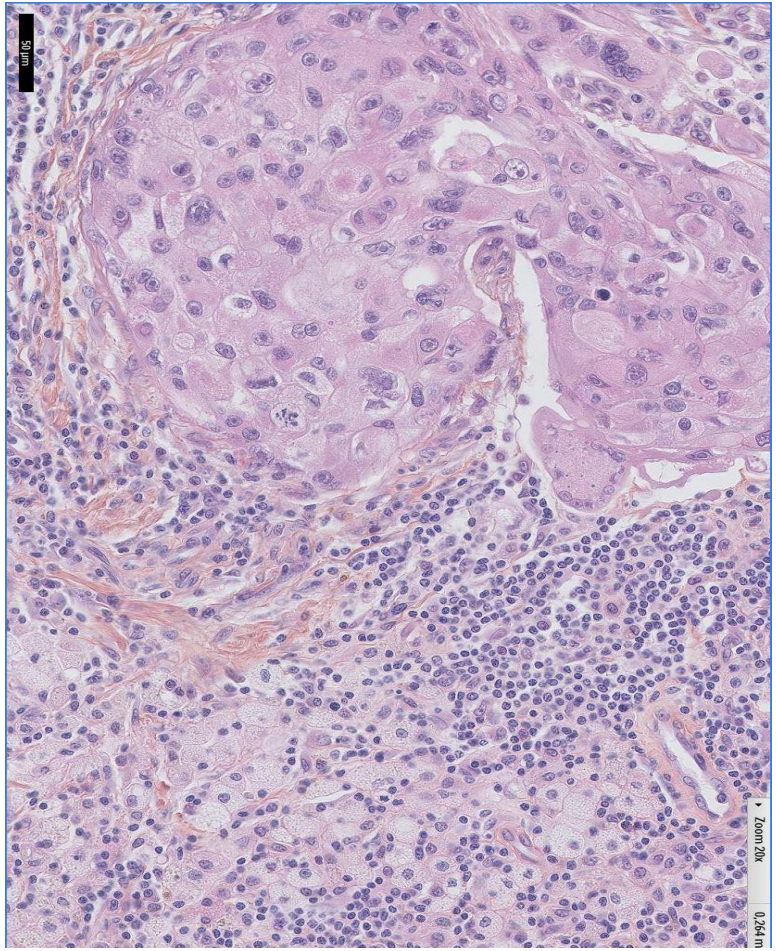
Microbiopsy before NAC TIL=2%



Microbiopsy before NAC TIL>60%



Surgical Specimen after NAC TIL=2%

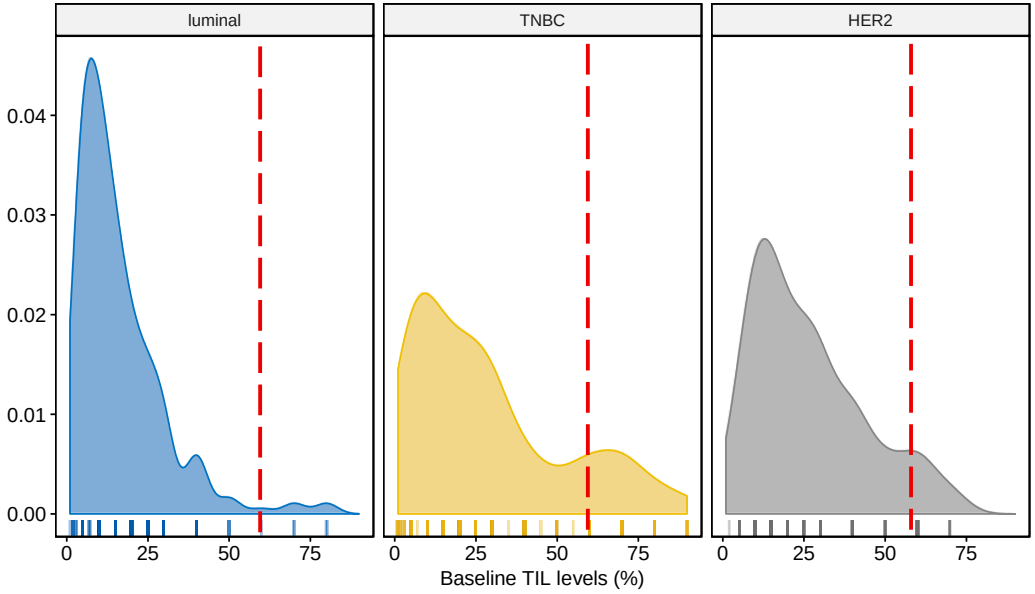


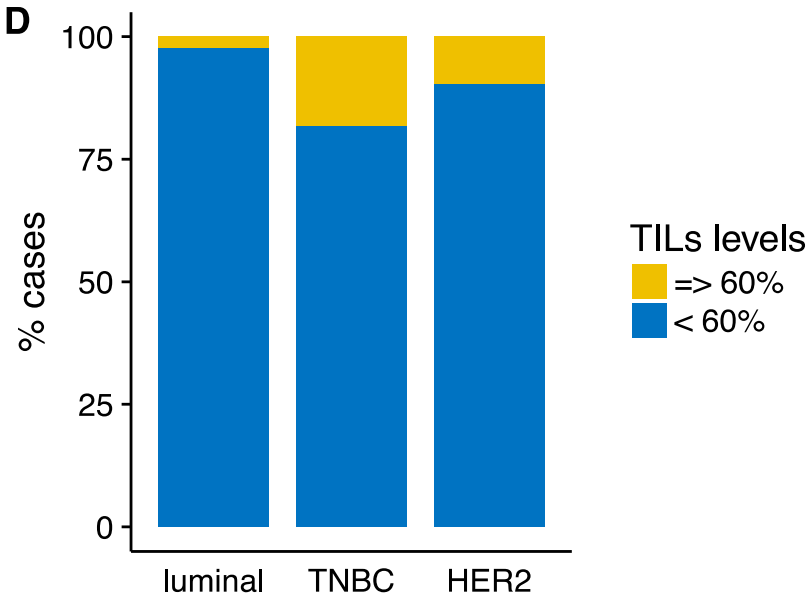
Surgical Specimen after NAC TIL>60%

Lymphocyte PBC before neoadjuvant chemotherapy is a *rare* entity

Lymphocyte predominant breast cancer

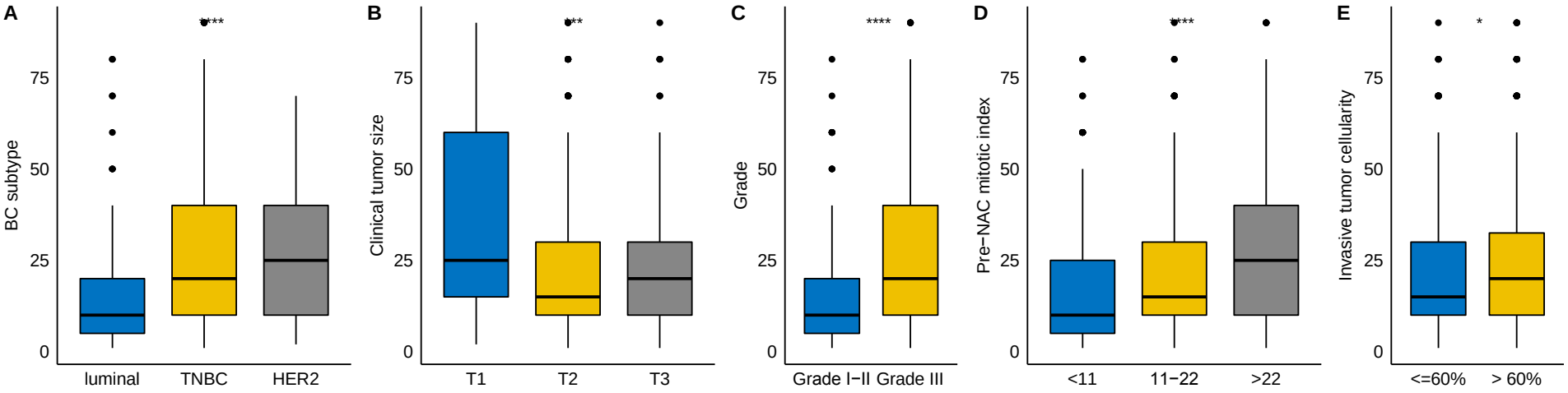
Cut-off stromal TILs : ≥ 50 or 60%





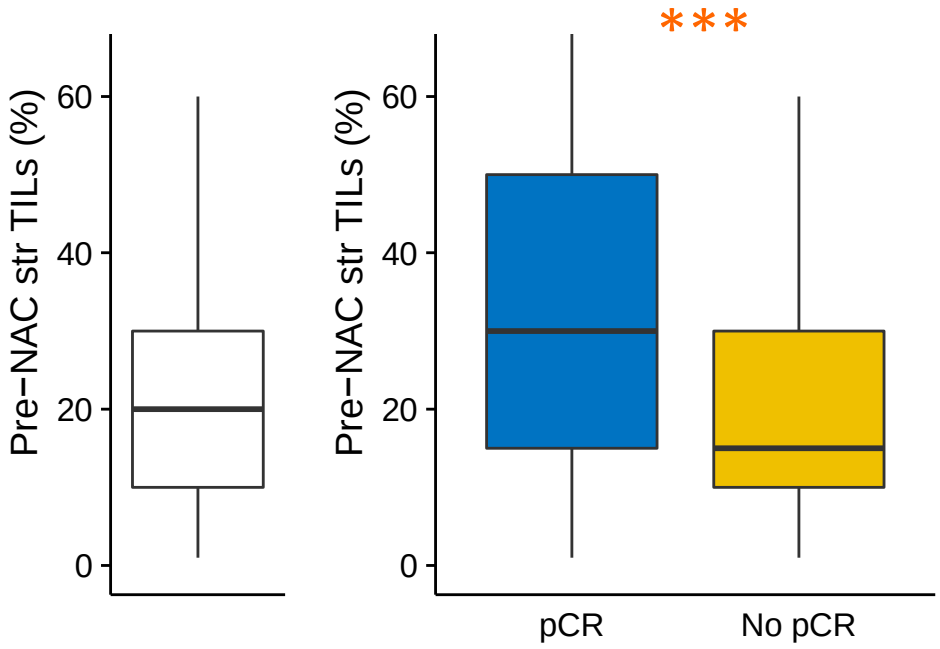
Luminal	**2%**
TN	**18%**
***HER2*-positive**	**10%**

Baseline TILs vary by BC subtype
Baseline TILs are associated with agressive tumor characteristics



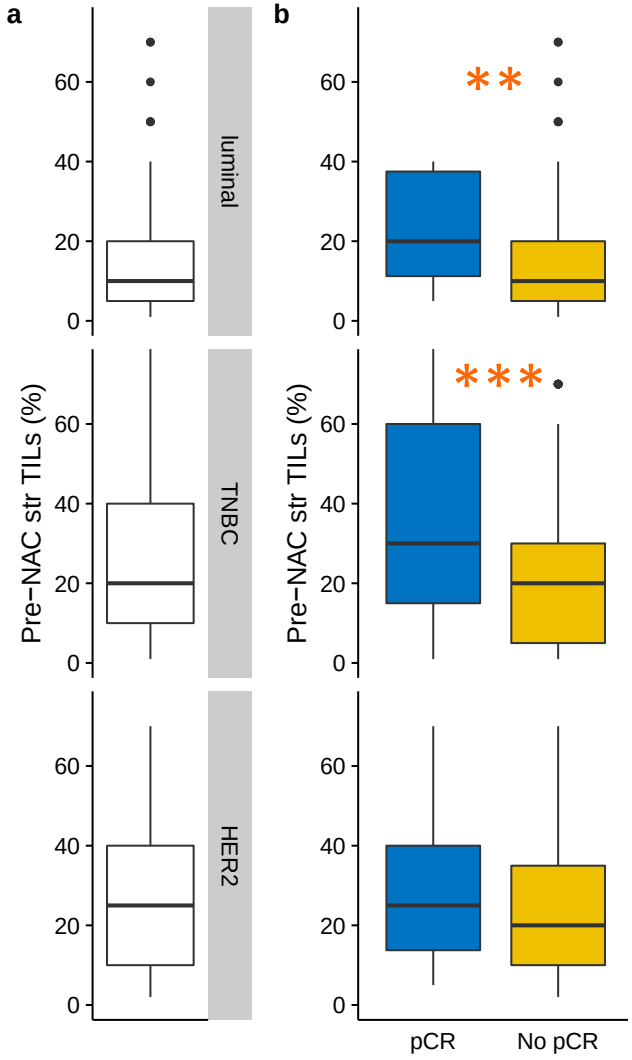
Response to treatment

Baseline TIL levels* are associated with pCR

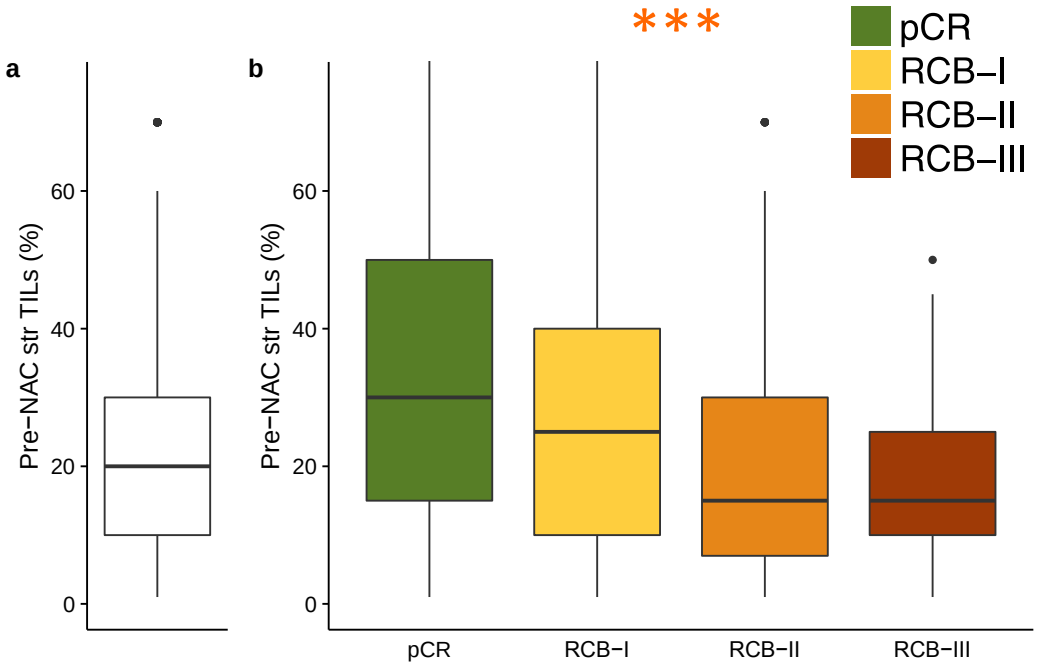


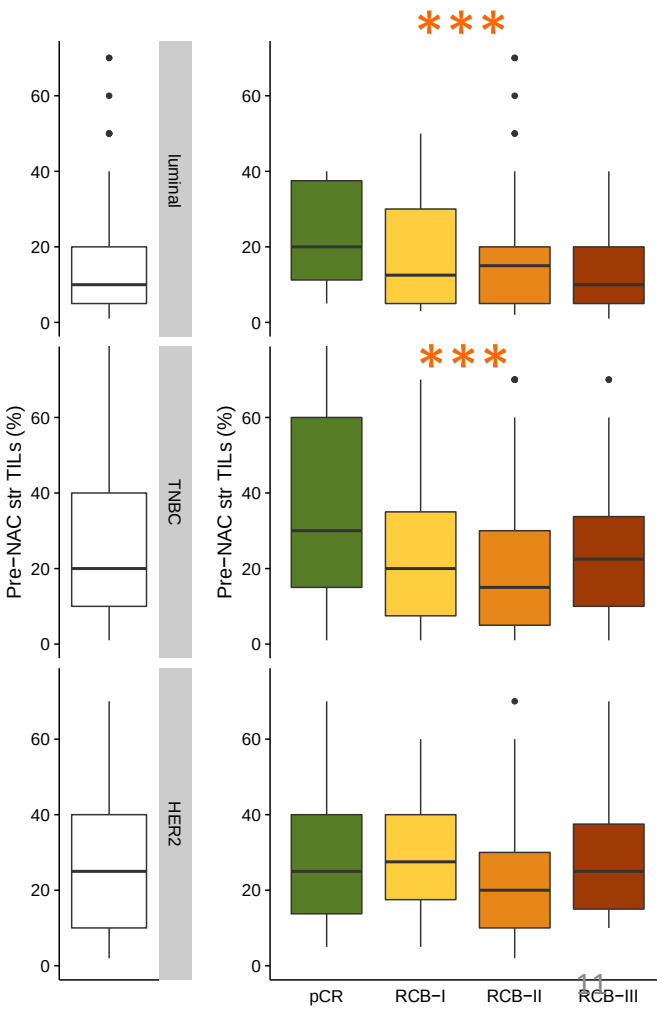
Luminal and **TNBC** and **NOT** in **HER2+** BC

Significant interaction by BC subtype (p=0.04)



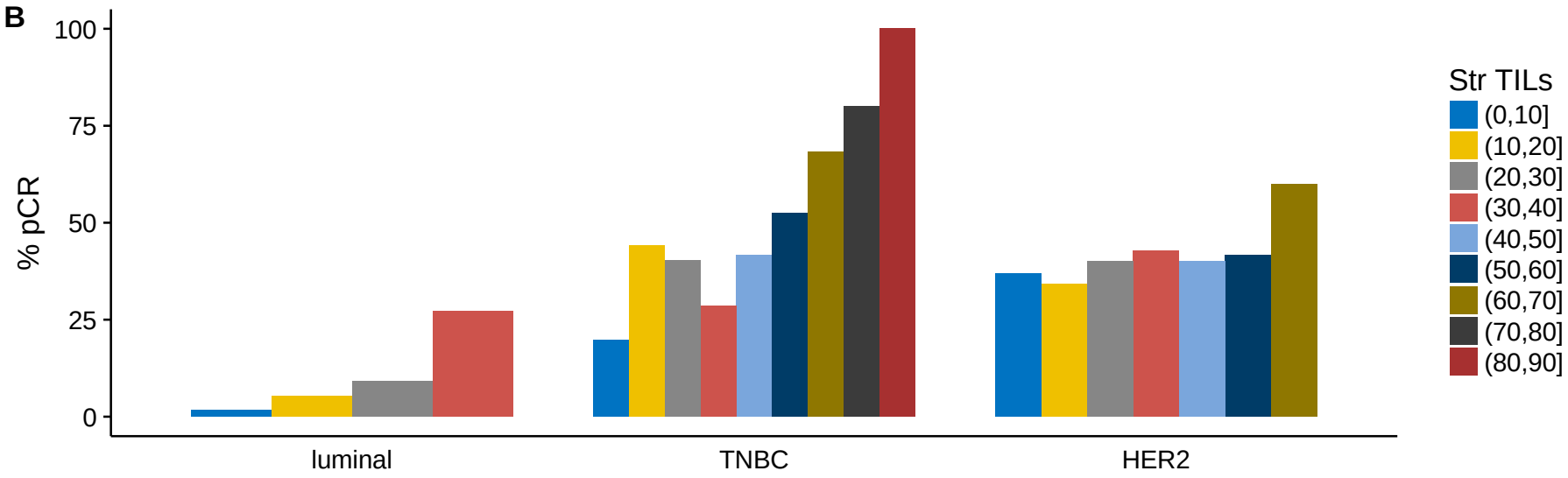
Baseline TIL levels* are associated with RCB





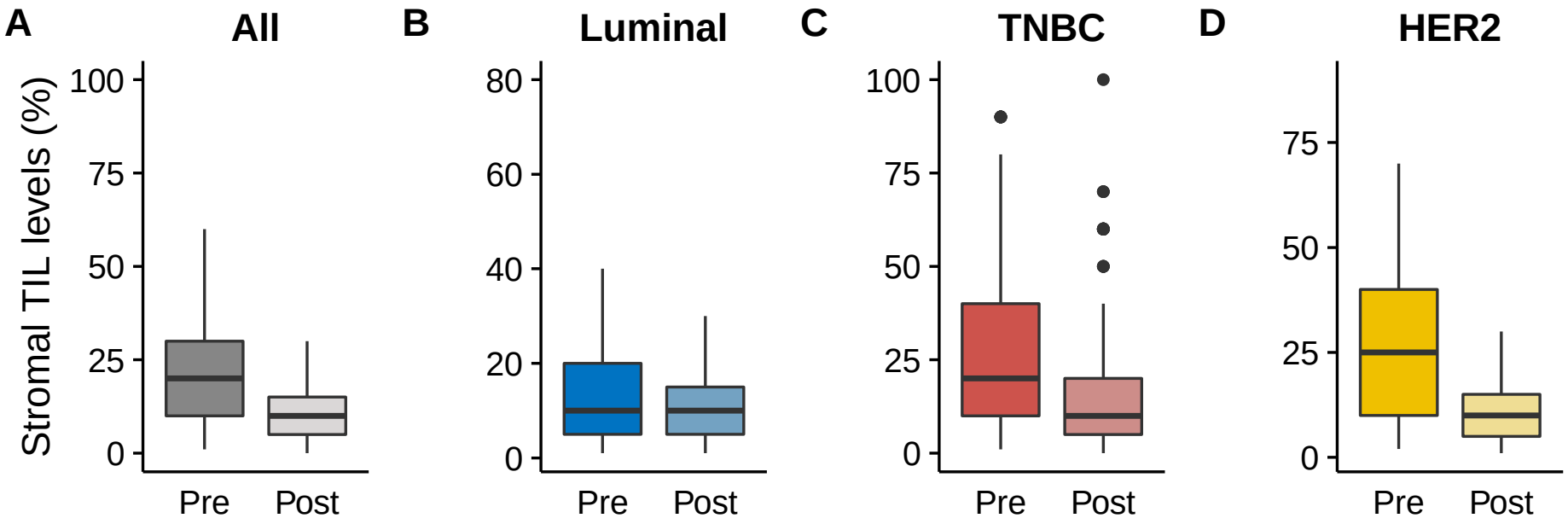
In **luminal** and **TNBC, NOT** in **HER2+** BC

Baseline TILs levels are associated with pCR in luminal and TNBC not in HER2-positive BC

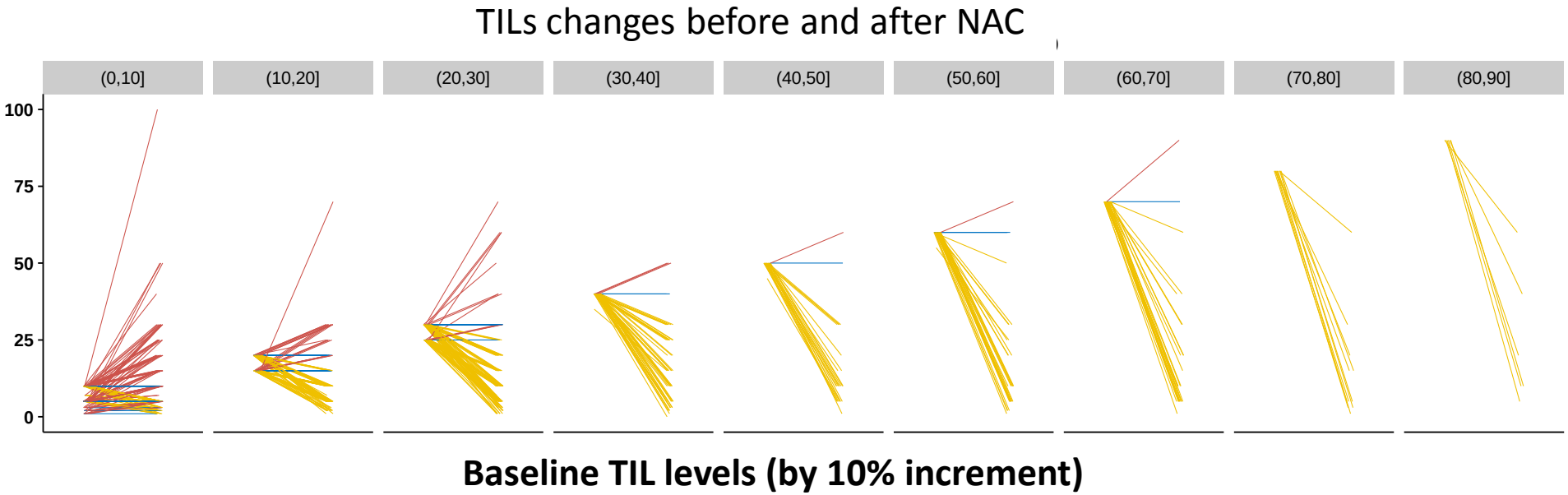


TILs dynamic

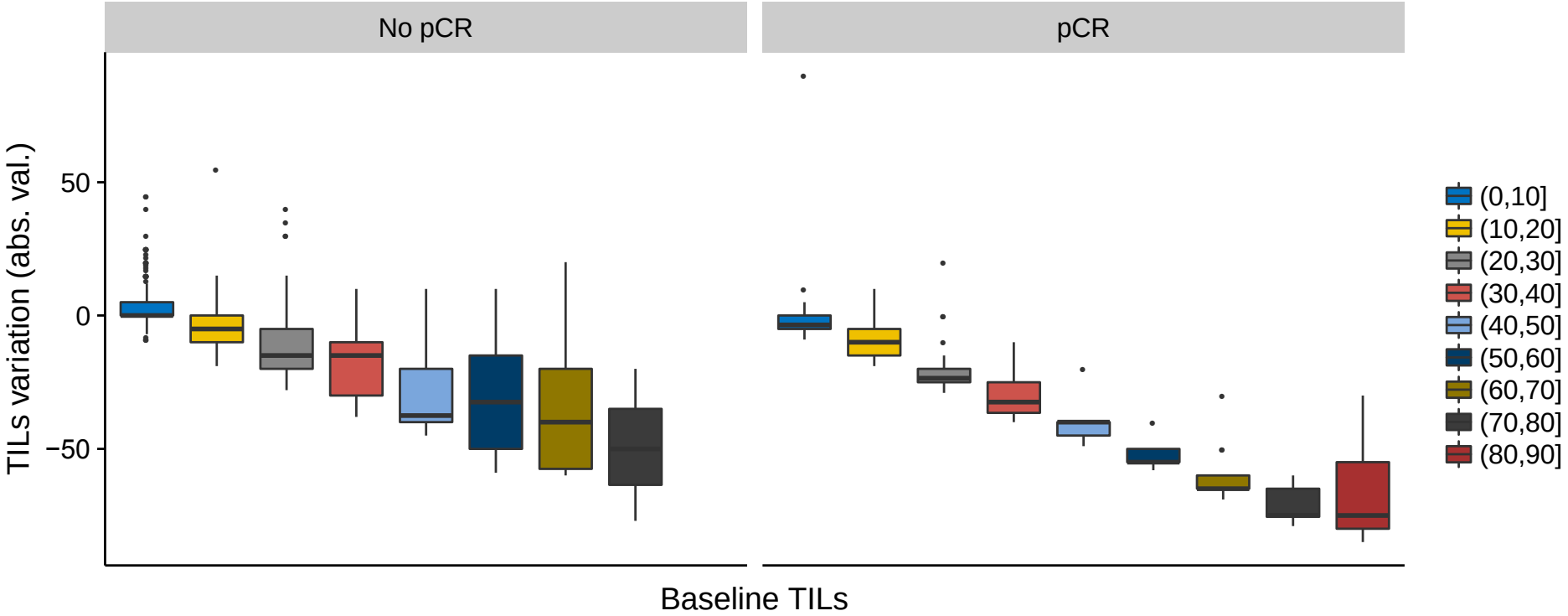
TILs levels decrease after neoadjuvant chemotherapy



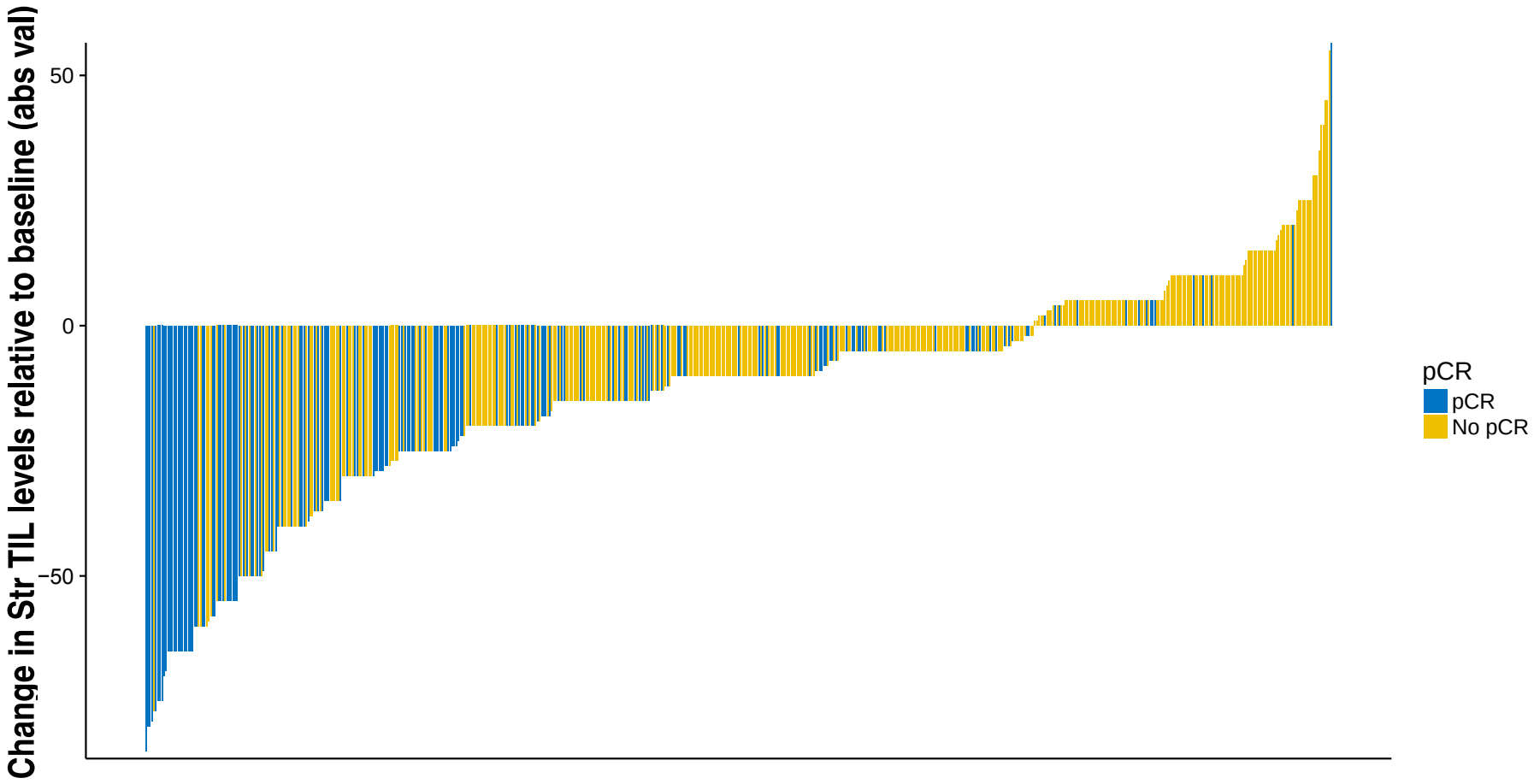
TILs dynamics is strongly correlated with baseline TILs levels …



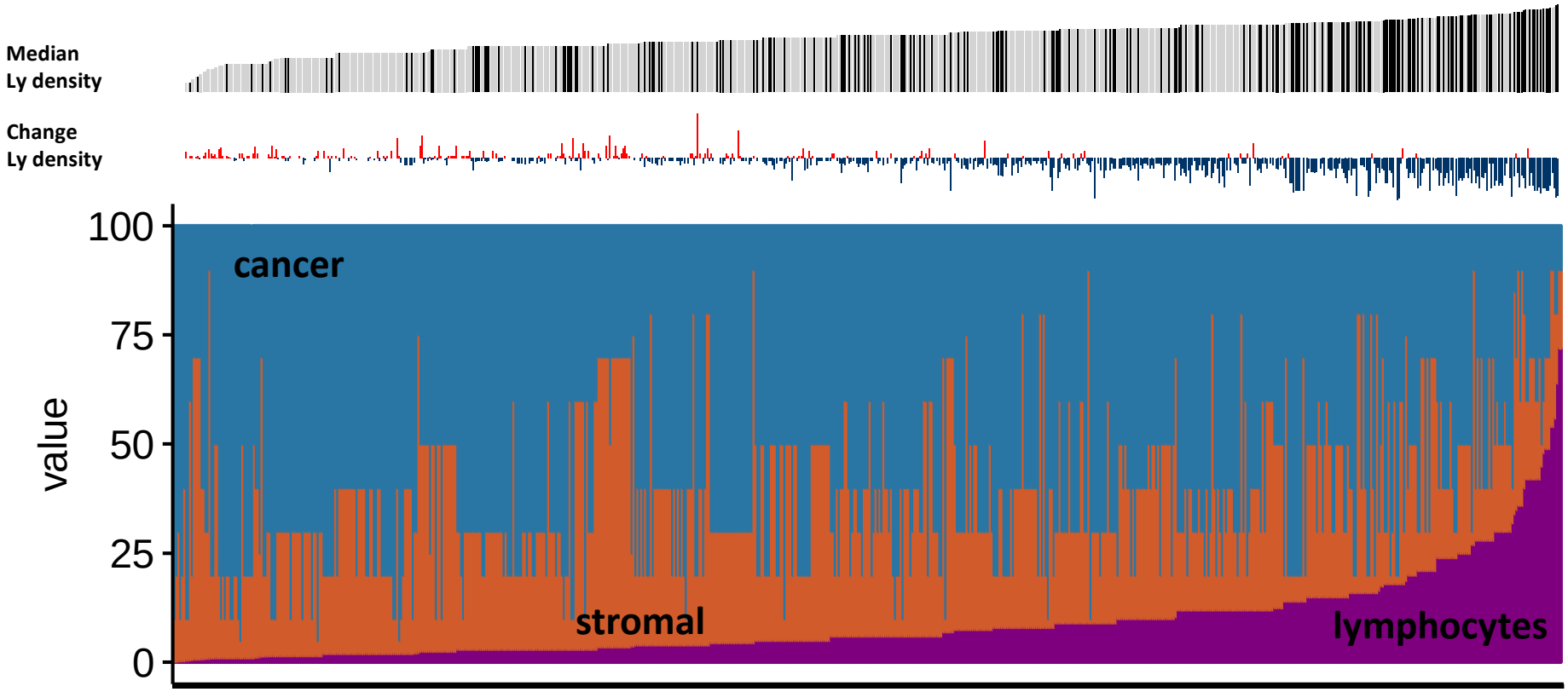
… irrespective of response to treatment



A ***high decrease*** in stromal TIL levels is associated with pCR

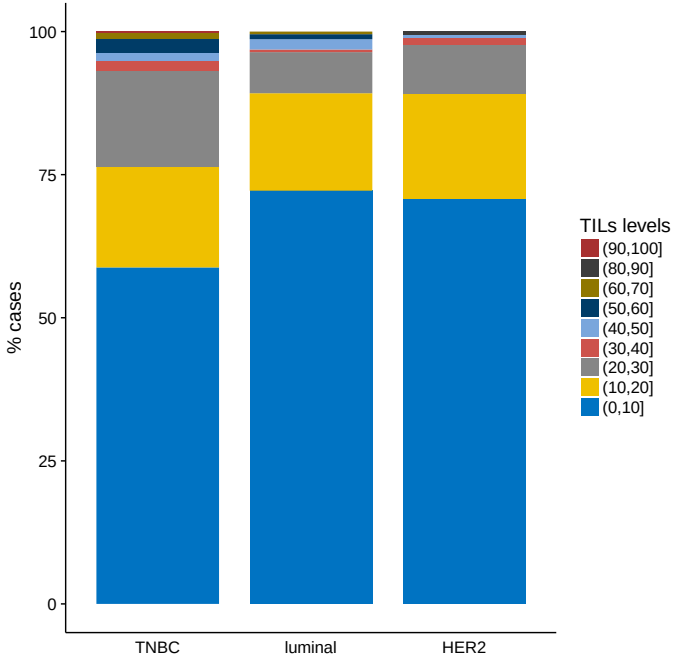


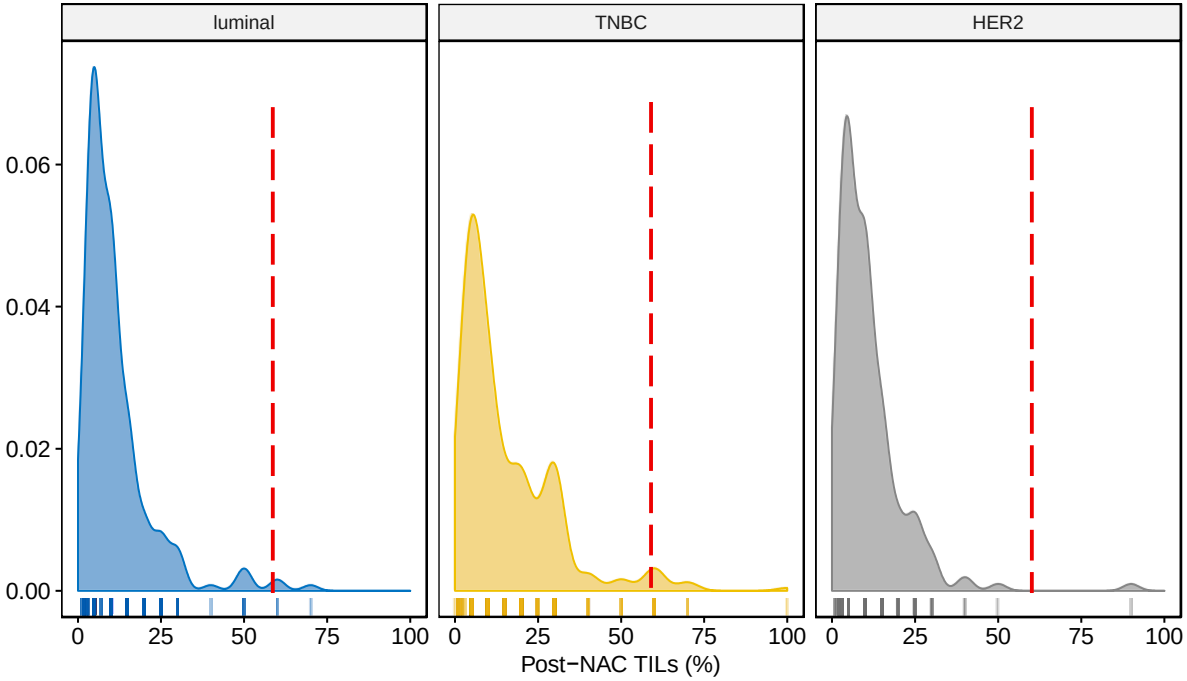
High baseline TILs and high decrease of lymphocytes after NAC are associated with pCR



Post-NAC stromal TILs

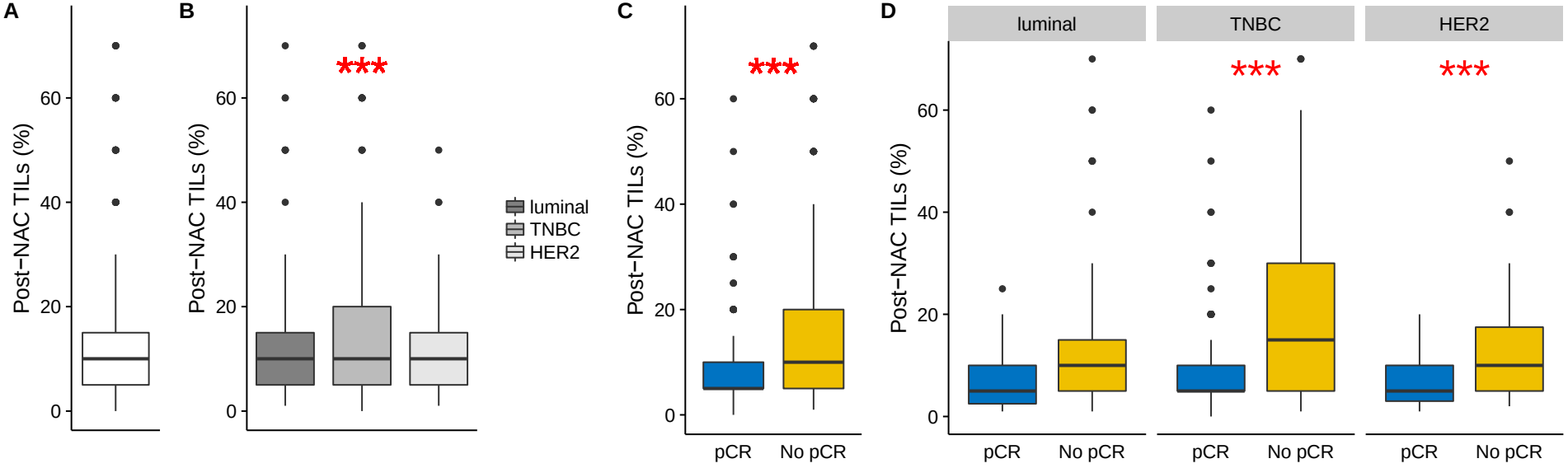
Lymphocyte-predominant breast Cancer is even *rarer* after NAC than before



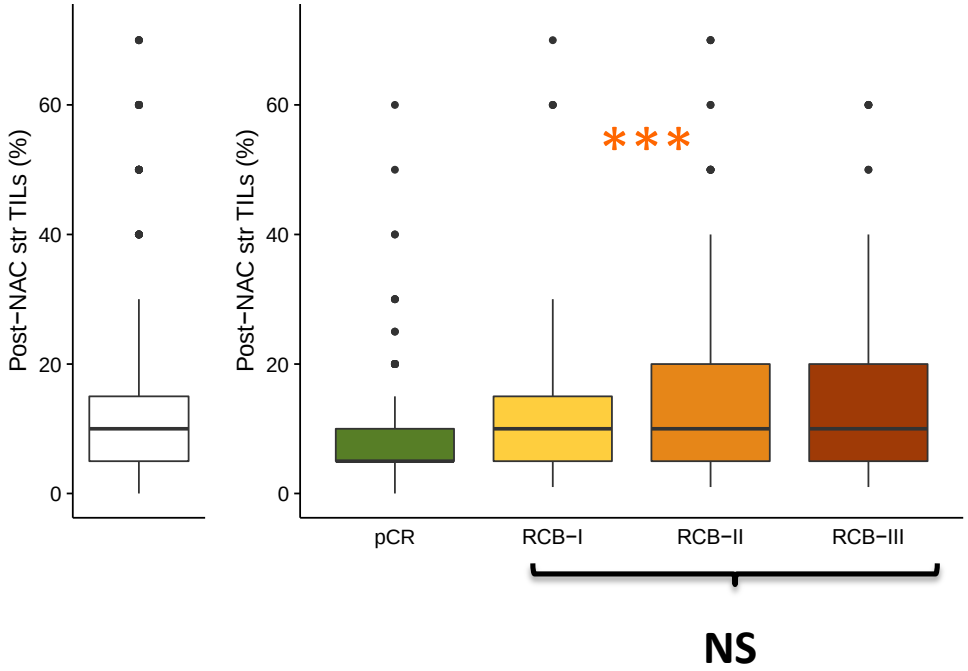


Luminal	**1%**
TN	**4%**
***HER2*-positive**	**1%**

Post-NAC TILs are *higher* in tumors with *residual disease* than in pCR specimens



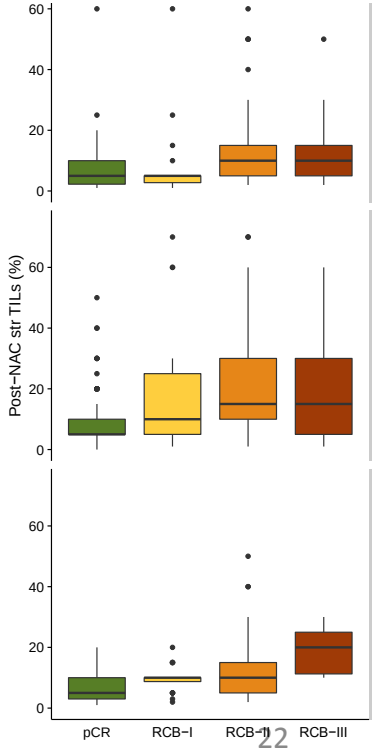
Higher post-NAC TIL levels are associated with increasing RCB only in *HER2*-positive BC



luminal

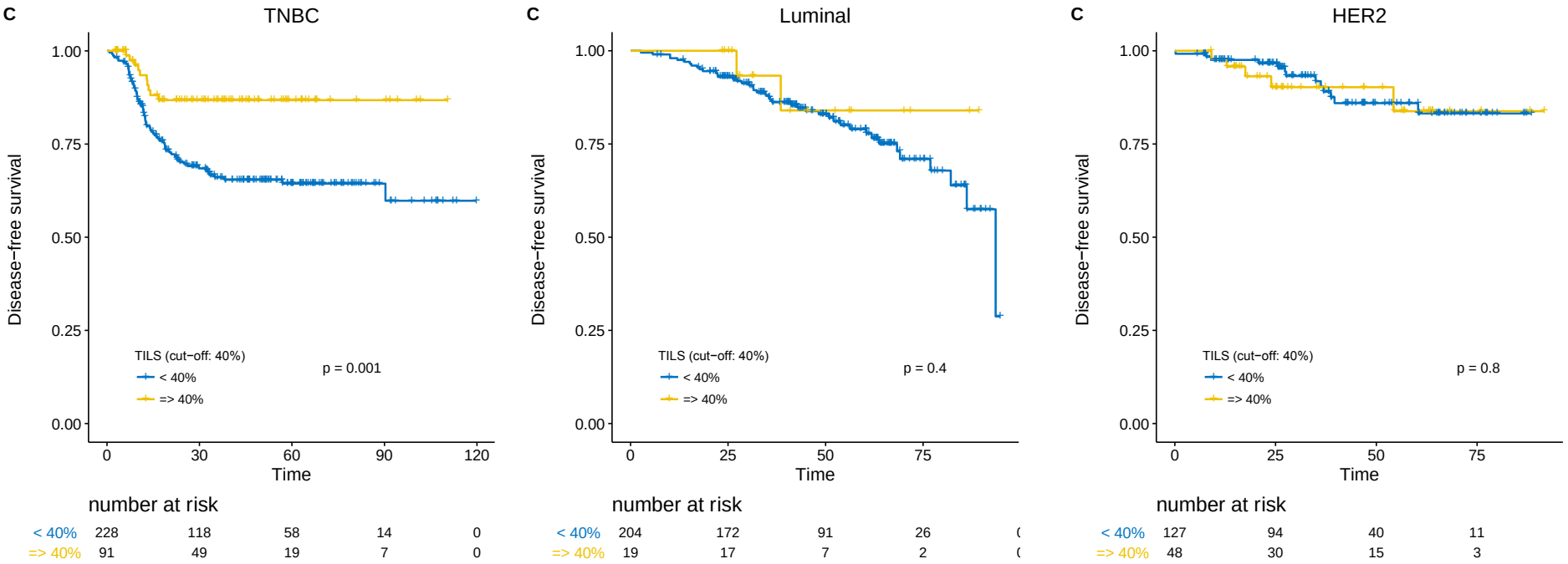
TNBC

HER2

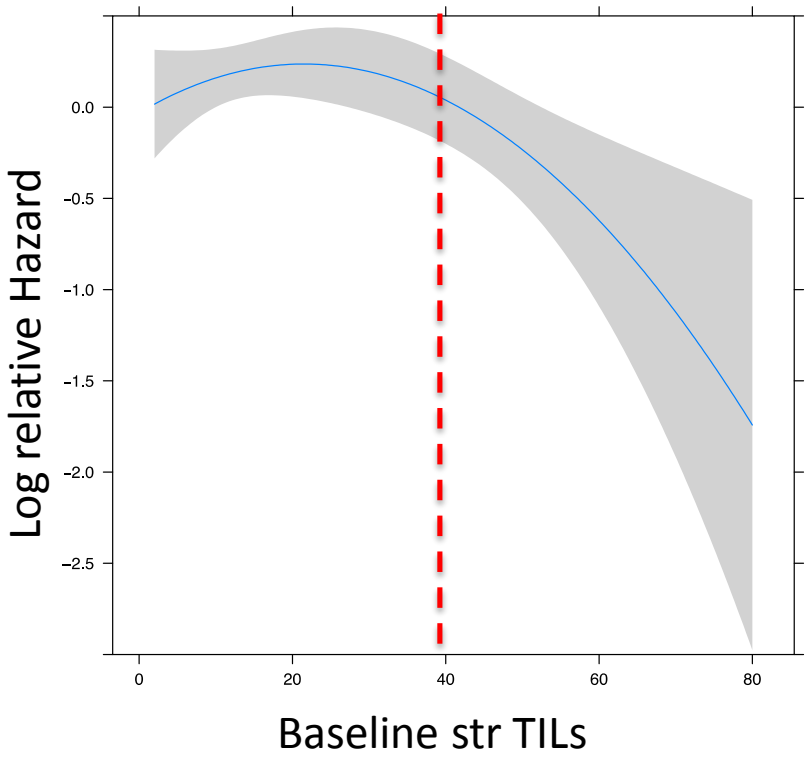


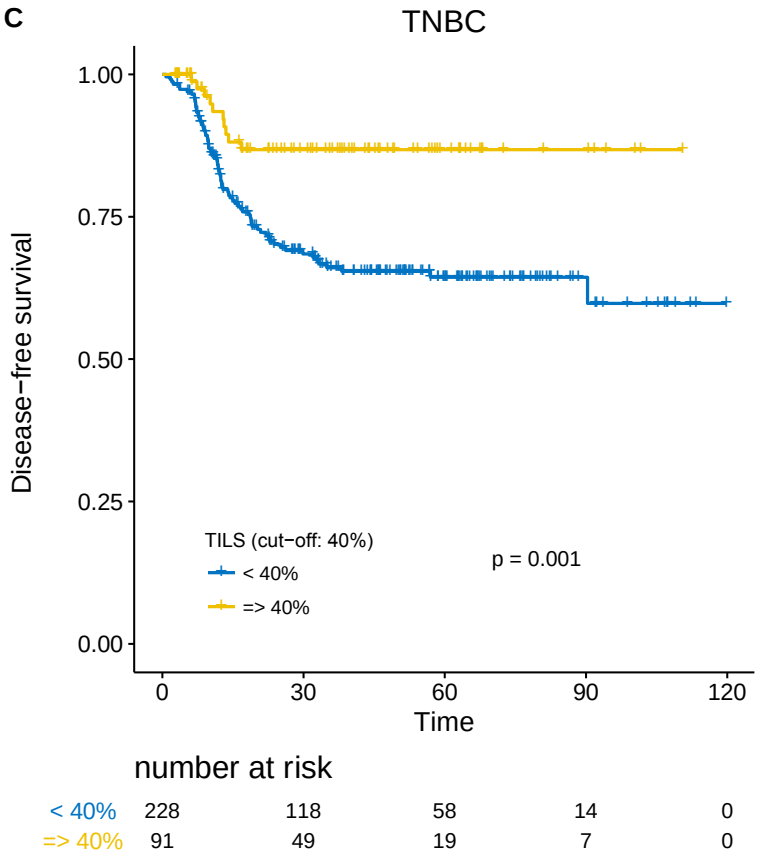
($P_{interaction}$=0.04)

Impact on prognosis

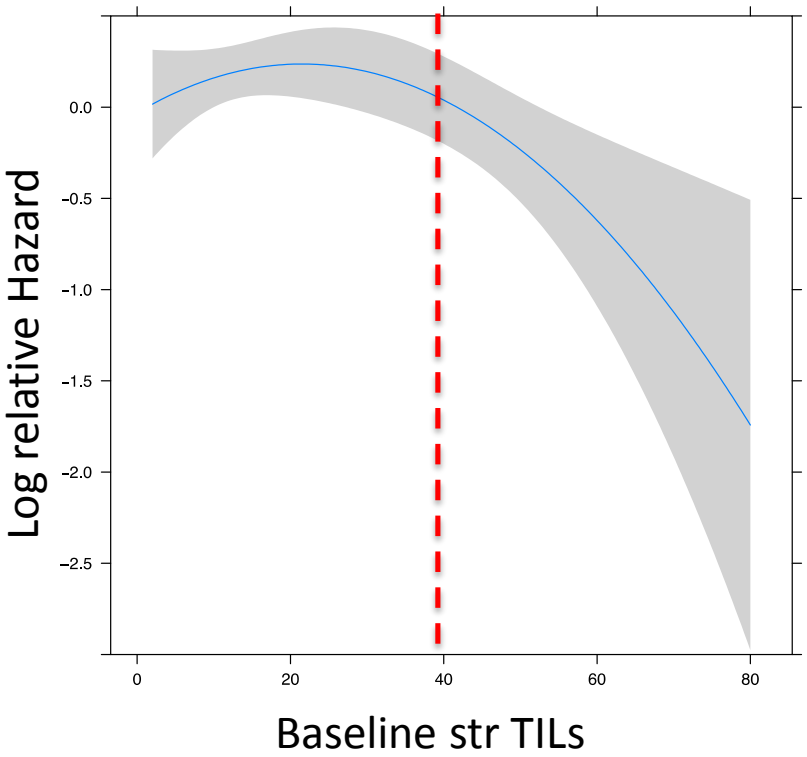

C
TNBC
Disease−free survival
1.00
0.75
0.50
0.25
0.00
TILS (cut−off: 40%)
< 40%
=> 40%
p = 0.001
0
30
60
90
120
Time
number at risk
< 40% 228 118 58 14 0
=> 40% 91 49 19 7 0
C
Luminal
Disease−free survival
1.00
0.75
0.50
0.25
0.00
TILS (cut−off: 40%)
< 40%
=> 40%
p = 0.4
0
25
50
75
Time
number at risk
< 40% 204 172 91 26
=> 40% 19 17 7 2
C
HER2
Disease−free survival
1.00
0.75
0.50
0.25
0.00
TILS (cut−off: 40%)
< 40%
=> 40%
p = 0.8
0
25
50
75
Time
number at risk
< 40% 127 94 40 11
=> 40% 48 30 15 3

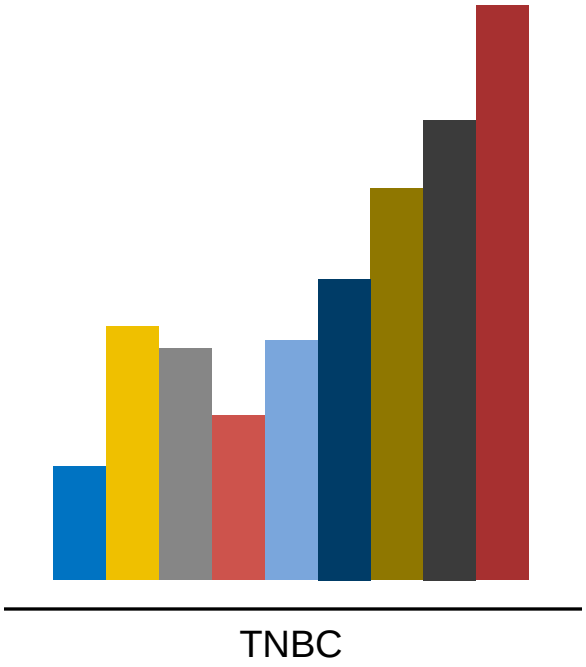
Baseline stromal TIL levels are associated with *DFS* in TNBC





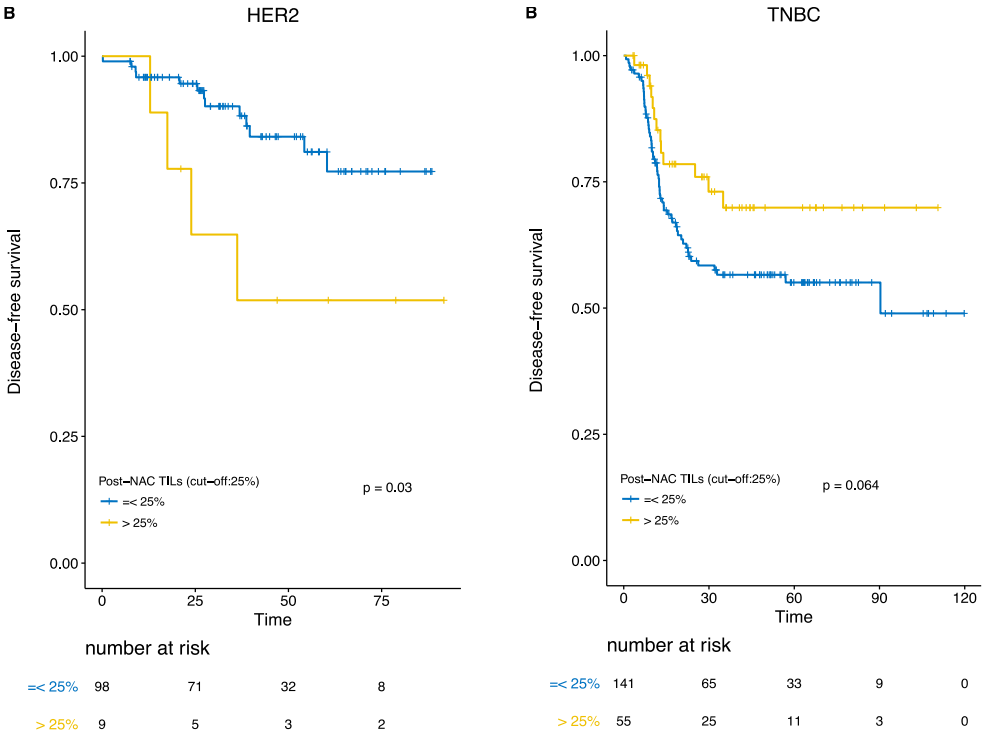
Baseline stromal TIL levels are associated with *DFS* in TNBC





Post-NAC TILs are *NOT* associated with DFS, but this effect differs by BC subtype

- ***Significant interaction*** with BC subtype
- Effect of post-NAC TILs on DFS **different in TNBC / *HER2*-positive** ($P_{interaction}$ = 0.04)
- Effect linear : cut-off unknown ?



Adverse impact of high post-NAC TILs in RD in HER2-positive BC, but trend to protective effect in TNBC

Take home messages

- Confirmation association pre-NAC TILs – pCR
- Dynamics : The highest baseline TILs are, the highest their level decrease
- High TILs decrease correlates with pCR
- Different prognostic value pre and post-NAC = > Complex interactions BC subtype and TILs
- TILs subsetting is pivotal to understand mechanisms of resistance to treatment
- Assessment pre NAC & post NAC should become routine practice

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U932 Immunity and Cancer

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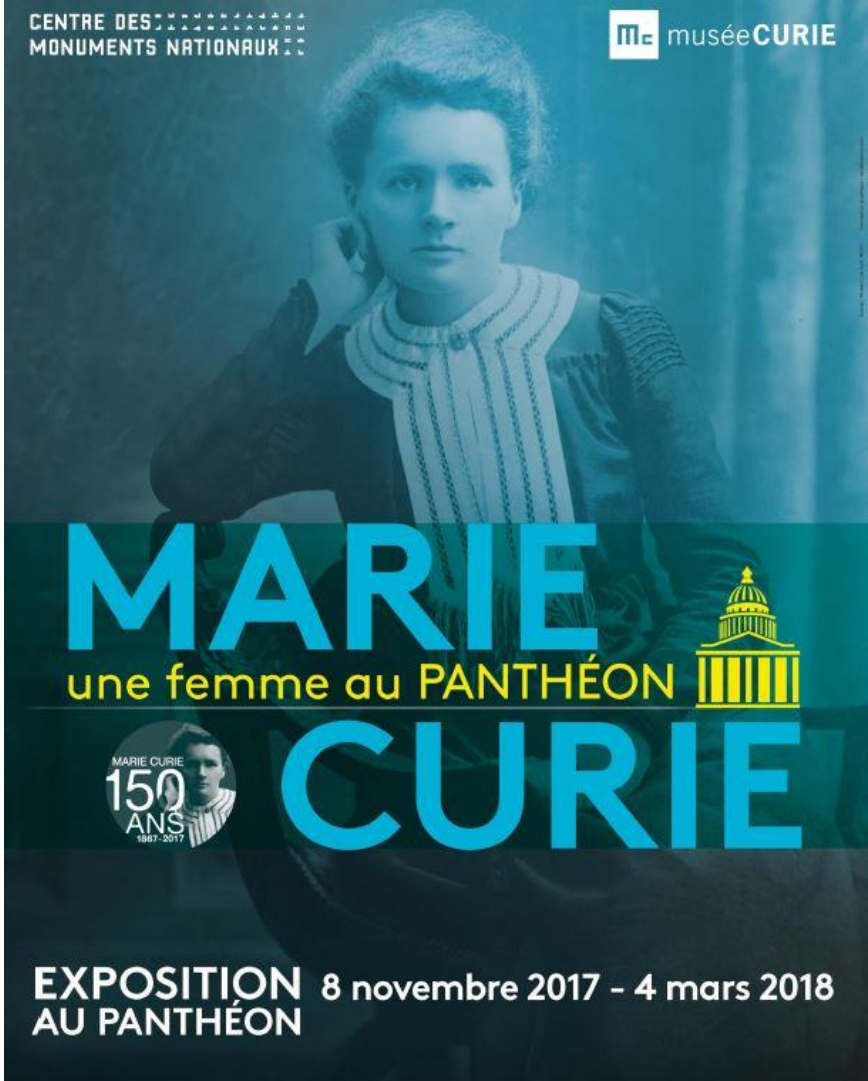

Multivariate analysis pCR

		Univariate			Multivariate		
name	levels	OR	95%CI	pval	OR	95%CI	p
Age	<45 y.o	1					
	45-55 y.o	0.97	[0.66 - 1.42]	0.877			
	>55 y.o	1.4	[0.93 - 2.11]	0.101			
Menopausal status	postmenopausal	1					
	premenopausal	0.8	[0.57 - 1.12]	0.193			
BMI class	BMI: 19 to 25	1					
	BMI<19	0.56	[0.24 - 1.19]	0.156			
	BMI: 25 to 30	0.76	[0.5 - 1.14]	0.186			
	BMI>30	0.9	[0.55 - 1.47]	0.69			
Tumor size (2 cl)	T1-T2	1					
	T3	0.8	[0.54 - 1.16]	0.245			
Clinical nodal status	N0	1					
	N1-N2-N3	0.9	[0.65 - 1.26]	0.546			
ER status	ER negative	1					
	ER positive	0.2	[0.13 - 0.29]	<0.001			
PR status	PR negative	1					
	PR positive	0.13	[0.08 - 0.22]	<0.001			
HER2 status	HER2 negative	1					
	HER2 positive	1.94	[1.35 - 2.78]	<0.001			
BC subtype	TNBC	1			1		
	luminal	0.08	[0.04 - 0.15]	<0.001	0.09	[0.04 - 0.18]	<0.001
	HER2	1.02	[0.7 - 1.48]	0.927	1.01	[0.68 - 1.5]	0.958
Histology	ductal	1					
	other	0.82	[0.41 - 1.52]	0.543			
Grade	Grade I-II	1					
	Grade III	2.71	[1.8 - 4.16]	<0.001			
ki67	ki67<20	1					
	ki67>=20	2.56	[1.05 - 7.23]	0.051			
NAC regimen	Anthracyclines based regimens	1					
	Anthracyclines-taxanes regimens	0.98	[0.55 - 1.8]	0.936			
	Others	1.32	[0.64 - 2.76]	0.456			
Pre-NAC mitotic index 3	Mitotic index <= 10	1					
	Mitotic index 11-22	1.38	[0.86 - 2.25]	0.187			
	Mitotic index >22	2.05	[1.34 - 3.19]	0.001			
Pre-NAC tumor cellularity	Pre-NAC tumor cellularity (inv.) <= 60%	1					
	Pre-NAC tumor cellularity (inv.) > 60%	0.94	[0.68 - 1.31]	0.733			
IS component (pre NAC)	No pre-NAC in situ component	1					
	Pre-NAC in situ component	0.83	[0.51 - 1.3]	0.417			
Str TIL levels (continuous)		1.03	[1.02 - 1.04]	<0.001	1.03	[1.02 - 1.03]	<0.001

Whole population

- **Baseline** TILs (continuous or cut-off 40%)
- BC subtype

Multivariate analysis DFS

		TNBC						
		Univariate				Multiivariate		
TNBC	Class	HR	CI	p	p	HR	CI	p
Pre-NAC parameters								
Age, years	<45	1			0.78			
	45-55	1.02	[0.63 - 1.67]	0.93				
	>55	0.84	[0.48 - 1.49]	0.55				
Menopause status	Post	1			0.47			
	Pre	1.18	[0.75 - 1.86]	0.47				
BMI class	BMI < 25	1			0.25			
	BMI>= 25	1.29	[0.83 - 1.98]	0.26				
Tumor size	T1-T2	1			**<0.01**			
	T3	1.66	[1.18 - 2.34]	<0.01				
Clinical node status	N0	1			0.15			
	N1-N2-N3	1.38	[0.89 - 2.15]	0.15				
Histology	Ductal carcinoma NST	1			0.44			
	Other	1.34	[0.64 - 2.77]	0.44				
Grade	Grade I-II	1			0.6			
	Grade III	1.19	[0.61 - 2.31]	0.6				
Ki 67	<20%	1			0.52			
	≥20%	1.32	[0.56 - 3.14]	0.52				
Pre-NAC mitotic index	<11	1			0.37			
	11-22	1.68	[0.67 - 4.22]	0.27				
	>22	1.81	[0.78 - 4.2]	0.17				
Pre-NAC inv. tumor cellularity	≤60%	1			0.19			
	> 60%	0.74	[0.47 - 1.17]	0.19				
Pre-NAC str TILs (cut-off 40%)	< 40%	1			**<0.01**	1	-	-
	≥ 40%	0.35	[0.18 - 0.67]	<0.01		0.39	[0.18 - 0.86]	0.02
Post-NAC parameters								
pCR	No pCR	1			**<0.01**			
	pCR	0.22	[0.12 - 0.41]	<0.01				
RCB index	pCR	1			**<0.01**			
	RCB-I	1.39	[0.39 - 4.92]	0.61		1	-	-
	RCB-II	3.52	[1.84 - 6.73]	<0.01		1.67	[0.21 - 12.99]	0.626
	RCB-III	11.27	[5.7 - 22.26]	<0.01		6.18	[0.79 - 48.09]	0.082
Post-NAC Str TILS (cut-off 25%)	str TILs ≤ 25%							
	str TILs > 25%							
Post-NAC Mitotic index	≤ 10	1			**<0.01**	1	-	-
	11-22	2.38	[0.81 - 6.97]	0.11		2.01	[0.68 - 5.9]	0.207
	>22	4.89	[2.46 - 9.71]	<0.01		4.92	[2.41 - 10.05]	<0.001
Post-NAC inv. tumor cellularity	≤30%	1			0.07			
	> 30%	1.61	[0.96 - 2.7]	0.07				
Post-NAC Str TILS (continuous)		0.99	[0.98-1.01]		0.79			

TNBC

- **Baseline** TILs
- RCB
- Post-NAC mitotic index

Multivariate analysis DFS

		HER2						
		Univariate				Multiivariate		
TNBC	Class	HR	CI	p	p	HR	CI	p
Pre-NAC parameters								
Age, years	<45	1			0.33			
	45-55	1.29	[0.48 - 3.43]	0.62				
	>55	0.42	[0.09 - 1.97]	0.27				
Menopause status	Post	1			0.38			
	Pre	1.58	[0.56 - 4.44]	0.38				
BMI class	BMI < 25	1			**<0.01**	1	-	-
	BMI>= 25	3.37	[1.33 - 8.57]	0.01		4.83	[1.75 - 13.36]	0.002
Tumor size	T1-T2	1			0.15			
	T3	1.96	[0.78 - 4.98]	0.15				
Clinical node status	N0	1			0.57			
	N1-N2-N3	1.35	[0.48 - 3.8]	0.57				
ER status	Negative	1			0.81			
	Positive	1.12	[0.44 - 2.85]	0.81				
PR status	Negative	1			0.74			
	Positive	0.84	[0.29 - 2.41]	0.74				
Grade	Grade I-II	1			**0.01**	1	-	-
	Grade III	0.32	[0.13 - 0.81]	0.02		0.18	[0.06 - 0.54]	0.002
Pre-NAC mitotic index	<11	1			0.63			
	11-22	0.72	[0.25 - 2.06]	0.54				
	>22	0.56	[0.16 - 1.92]	0.36				
Pre-NAC inv. tumor cellularity	≤60%	1			0.7			
	> 60%	0.83	[0.33 - 2.1]	0.7				
Pre-NAC str TILs (continuous)					0.61			
Pre-NAC str TILs (cut-off 40%)	< 40%	1			0.8			
	≥ 40%	1.14	[0.41 - 3.21]	0.8				
Post-NAC parameters								
pCR	No pCR	1			**<0.01**			
	pCR	0.09	[0.01 - 0.7]	0.02				
RCB index	pCR	1			**<0.01**			
	RCB-I	3.29	[0.21 - 52.63]	0.4				
	RCB-II	11.01	[1.43 - 84.72]	0.02				
	RCB-III	19.99	[2.23 - 178.86]	<0.01				
Post-NAC Str TILS (cut-off 25%)	str TILs ≤ 25%	1			**<0.01**	1	-	-
	str TILs > 25%	5.05	[1.66 - 15.36]	<0.01		9.61	[2.51 - 36.8]	0.001
Post-NAC Mitotic index	≤ 10	1			0.03			
	11-22	1.6	[0.2 - 12.66]	0.66				
	>22	3.52	[1.31 - 9.47]	0.01				
Post-NAC inv. tumor cellularity	≤30%	1			0.13			
	> 30%	2.07	[0.8 - 5.38]	0.13				
Post-NAC Str TILS (continuous)		1			**<0.01**			

HER2

- **Post-NAC** TILs
- Grade
- BMI