TUMOR INFILTRATING LYMPHOCYTES AND CORRELATION WITH PCR IN THE CHER-LOB STUDY.

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Background

Tumor infiltrating lymphocytes (TIL) are emerging as a strong prognostic factor and as a predictive biomarker for response to neoadjuvant therapy in breast cancer, especially for the triple negative and HER2-positive subtypes.[1-5]

Recently, TIL have been proposed to predict for the efficacy of trastuzumab in HER2-positive breast cancer.[6]

Aims

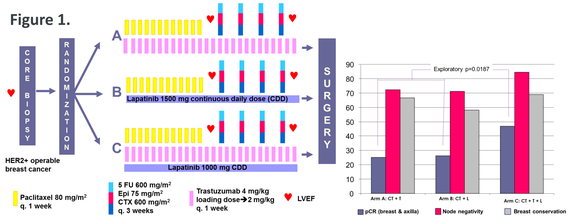
-To **correlate TIL at baseline with pCR** for HER2-positive BC patients treated with neoadjuvant chemotherapy plus anti-HER2 agents.

-To evaluate the **changes in TIL before and after neoadjuvant treatment** for HER2 positive BC patients treated with neoadjuvant chemotherapy plus anti-HER2 agents not achieving a pCR.

Methods

Patients: 121 HER2-positive stage II-IIIA breast cancer patients enrolled in the phase II neoadjuvant CherLOB study who were randomized to anthracyclines/taxane-based chemotherapy plus trastuzumab, lapatinib, or both[7]. Study design and results are reported in **Figure 1**.

Figure 1.



TIL evaluation: Hematoxilin and Eosin stained slides from both pre-treatment biopsies and post-treatment surgical samples were centralized and evaluated for the % of intratumoral (It) and stromal (Str) TIL. Samples were classified as:
- LPBC (lymphocyte-predominant breast cancer) if ItTIL and/or StrTIL ≥60%
- non-LPBC if ItTIL and StrTIL <60%.

Definition of pCR: absence of invasive breast cancer in breast and axilla (ypT0/is ypN0)

Statistical analysis: Association between TIL and clinicopathological variables was studied using the χ2 test. Association of TIL with pCR was evaluated with binary logistic regression models. All p values were two-sided, p values <0.05 were considered as statistically significant.

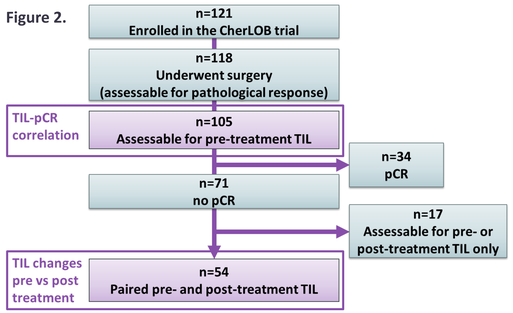
References: 1. Loi S et al, J Clin Oncol 2013; 2. Adams S et al, J Clin Oncol 2014; 3. Denkert C et al, J Clin Oncol 2010; 4. Denkert C et al, SABCS 2013; 5. Dieci MV et al, Ann Oncol 2014; 6. Loi S et al, Ann Oncol 2014; 7. Guarneri V et al, J Clin Oncol 2012

Results

1. Study flow

The flow of patients through the Cher-LOB TIL evaluation study and the sample size of the populations considered for each analysis are reported in **Figure 2**.

Figure 2.



2. Clinicopathological characteristics

16% of the 105 tumors assessable for TIL on the diagnostic core-biopsy were LPBC. ER-negative tumors were significantly more frequently LPBC compared to ER-positive cases (**Table 1**).

Table 1.		All n(%)	non-LPBC n(%)	LPBC n(%)	p
All patients		105 (100)	88 (84)	17(16)	
Age (years)	>=50	49 (47)	39 (80)	10 (20)	
	<50	56 (53)	49 (87.5)	7 (12.5)	0.272
Grade	1-2	20 (19)	18 (90)	2 (10)	
	3	69 (66)	55 (79.5)	14 (20.5)	
	Unkown	16 (15)			0.291
N status	Neg	41 (39)	37 (90)	4 (10)	
	Pos	63 (60)	50 (79.5)	13 (20.5)	
	Unkown	1 (1)			0.143
T size	<=5cm	83 (79)	67 (80.5)	16 (19.5)	
	>5cm	22 (21)	21 (95.5)	1 (4.5)	0.095
Ki67	<15%	13 (12.5)	12 (92.5)	1 (7.5)	
	≥15%	92 (87.5)	76 (82.5)	16 (17.5)	0.374
ER	Neg	40 (38)	29 (72.5)	11 (27.5)	
	pos	65 (62)	59 (90.5)	6 (9.5)	**0.014**
Treatment	CT+Trast	32 (30.5)	27 (84.5)	5 (15.5)	
	CT+Lap	34 (32.5)	28 (84)	6 (17.5)	
	CT+Trast+Lap	39 (37)	33 (84.5)	6 (15.4)	0.961

3. Correlation between TIL and pCR

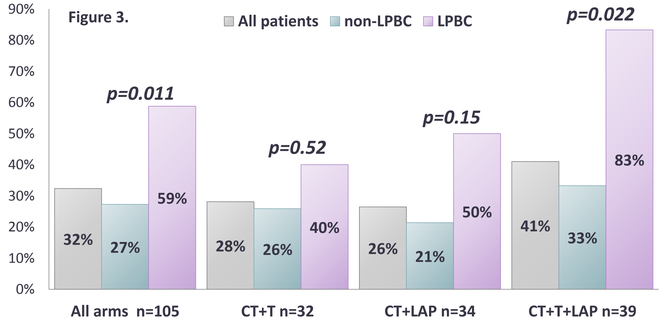
Both It-TIL and Str-TIL as continuous variables (10% increase) were significantly associated with a higher probability of achieving pCR (**Table 2**).

Table 2.		OR*	95% CI	p
It-TIL	*per 10%*	2.64	1.46-4.79	***0.001***
Str-TIL	*per 10%*	1.32	1.08-1.60	***0.006***

*It-TIL and Str-TIL were the only variables that correlated with pCR in univariate analysis. Other factors that were tested: N, ER status, T size, Stage, grade, age.

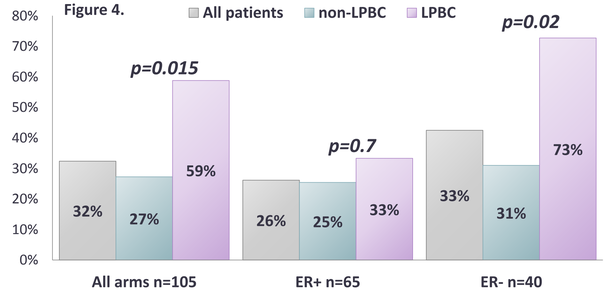
LPBC phenotype significantly predicted for pCR. According to treatment, the difference in pCR rate between LPBC and non-LPBC was particularly evident for patients treated with chemotherapy and double anti-HER2 blockade (**Figure 3**).

Figure 3.



According to estrogen receptor (ER) status, no difference in pCR rates between LPBC and non-LPBC was observed in the ER-positive population, whereas pCR rate was more than doubled for ER-negative LPBC compared to ER-negative non-LPBC patients (**Figure 4**).

Figure 4.



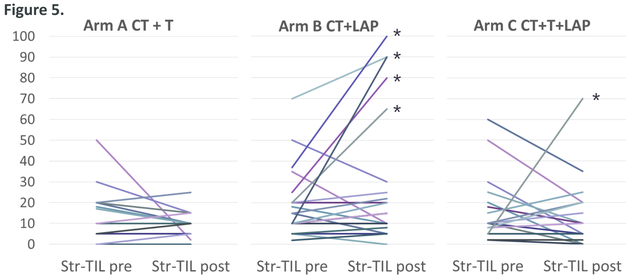
4. TIL changes before and after neoadjuvant treatment

No significant change in It-TIL and Str-TIL before and after treatment was observed overall, per arm and per ER status. In 10 cases, a ≥10% increase in Str-TIL on residual disease compared to baseline was reported. All these patients received lapatinib as part of the neoadjuvant treatment and were more likely ER-negative (**Table 3**). No other factor was significantly associated with Str-TIL increase.

Table 3.		Overall	Str-TIL increase ≥10%	no Str-TIL increase	p
Overall		54 (100%)	10 (18.5%)	44 (81.5%)	
Treatment	with LAP	39	10 (25.6%)	29 (74.4%)	
	without LAP	15	0	15 (100%)	**0.03**
ER	negative	16	7 (43.8%)	9 (56.2%)	
	positive	38	3 (7.9%)	35 (92.1%)	**0.002**

Changes in Str-TIL according to treatment are reported in **Figure 5**. Four patients treated with CT+LAP and 1 patient treated with CT+T+LAP (*) changed from non-LPBC to LPBC.

Figure 5.



Conclusions

- The presence of a lymphocyte tumor infiltration at baseline predicts pCR rates after neoadjuvant chemotherapy plus anti-HER2 agents for HER2-positive tumors.
- The predictive effect of TIL for pCR was more evident in case of dual HER2 blockade: LPBC patients treated with CT+Tras+Lap achieved 83% pCR rate.
- Correlation between LPBC phenotype and pCR was limited to ER-negative patients.
- Tumor lymphocyte infiltration may increase after neoadjuvant CT + anti-HER2 agents; this was observed especially for HER2+/ER- patients and for patients treated with Lapatinib.
- Lapatinib-containing treatments may be able to convert from non-LPBC to LPBC.
- Confirmation of these data in larger datasets is warranted. Updating of follow-up is ongoing, correlations between TIL and survival are planned.

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