San Antonio Breast Cancer Symposium® - December 9-12, 2025, Abstract #SESS-2364

Exploratory Analysis of Immune Cell Subsets in Luminal B HER2-negative Breast Cancer and Their Association with Pathologic Response

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Background

Although tumor-infiltrating lymphocytes (TILs) are associated with better outcomes in triple-negative and HER2-positive breast cancer, their prognostic value in luminal HER2-negative subtype remains unclear. This study aimed to evaluate TIL subpopulations in luminal breast cancer and their association with pathologic response.

Materials and methods

This prospective trial included 72 pts with ER+ (>10%), HER2 negative breast cancer II-III stages. Both stromal and intratumoral subpopulations of TILs were assessed with flow cytometry on a tumor sample obtained by core-biopsy directly before the start of neoadjuvant chemotherapy. We analyzed CD3-CD8+, CD3+HLA- DR+, CD3-HLA-DR+, HLA-DR+, CD8+CD28+, CD8+CD28-, CD8+CD28+/CD8+CD28-, CD4+/CD8+, 11b+28-, 11b+28+, 11b- 28-, 11b-28+, CD8+CD4+, CD4+CD152+ minor subpopulations and other linear subpopulations (CD3+, CD19+, CD56+). Given the different distribution of variables and the lack of established reference values, all data is presented as the median (Me) and the 25th and 75th percentiles (quartiles). All the pts received NACT with 4 cycles of dose-dense AC every 2 weeks then 4 cycles of docetaxel every 3 weeks.

Results

The mean value of TIL is 2.58% (median 0.9%; range 0–30.6%). Stage II was diagnosed in 7 patients (9.7%), and stage III in 65 patients (90.3%). G2 tumors were found in 58 patients (80.6%), G3 in 14 (19.4%). The mean age was 46 ± 9 years (range 25–70), with most patients being premenopausal (72.2%). No significant differences in TIL levels were observed across age groups (median 0.9% in patients ≤50 years vs. 0.8% in >50 years; p=0.450). Nevertheless, older patients showed a numerical increase in CD16+ and CD8+CD279+(PD-1+) cells, along with a decrease in CD4+CD25+ lymphocytes, consistent with previous reports. There was no significant difference in mean value of total TIL levels between patients with good (RCB 0–1) and poor (RCB 2–3) pathologic response (3.92% vs. 2.09%, p=0.137). Most analyzed subpopulations (including CD3+CD4+, CD3+CD8+, CD4+CD25^{high}CD127$^{-/low}$, and others) showed no significant association with treatment response. However, CD4+CD25+ (11.2% vs. 7.5%; p=0.013) and CD8+PD-1+ lymphocytes (9.5% vs. 16.3%; p=0.041) significantly differed between the RCB 0–1 and RCB 2–3 groups. Higher levels of CD4+CD25+ (more than median) lymphocytes were significantly associated with favorable response (RCB 0-1 - 57.1% vs. 8.3%, p=0.001), while lower levels of CD8+PD-1+ lymphocytes were also associated with a better outcome (RCB0-1 46.2% vs. 12.0%, p=0.007).

Univariate regression analysis identified the following as predictors of better pathologic response: absence of lymph node involvement (N0), G3 tumor grade, age ≤50 years, progesterone receptor expression <20%, low CD8+PD-1+, and high CD4+CD25+ levels. However, none of these factors retained independent predictive value in multivariate analysis.

Subpopulation	RCB 0-1		RCB 2-3		p
	Me (quartiles), %	n	Me (quartiles), %	n	
CD3+CD4+	45,7 (42,9-51,1)	16	45,0 (36,4-53,5)	39	0,574
CD3+CD8+	39,9 (34,9-44,5)	17	44,6 (37,5-52,2)	41	0,093
CD3+	88,6 (85,5-92,8)	17	87,8 (83,3-93,5)	41	0,953
CD8+	42,9 (39,8-46,4)	17	45,5 (38,9-54,5)	41	0,225
CD4+CD25^{high}CD127$^{-/low}$	11,0 (7,8-19,0)	10	9,9 (5,1-12,4)	30	0,242
CD3-CD19+	4,5 (2,8-7,4)	17	2,2 (1,3-5,1)	37	0,087
CD3-CD16+CD56+	2,7 (1,8-5,9)	17	4,2 (2,6-9,2)	41	0,055
CD3+CD16+CD56+	7,8 (6,7-8,6)	17	7,4 (5,9-10,8)	40	0,626
CD4+CD25+	11,2 (8,9-12,3)	14	7,5 (3,7-10,8)	31	**0,013**
CD4+CD279+	12,4 (10,3-18,5)	12	14,6 (8,2-20,5)	34	0,990
CD8+CD279+	9,5 (5,5-11,2)	15	16,3 (6,5-23,3)	36	**0,041**

Fig.1 Association of subpopulation level with pathologic response

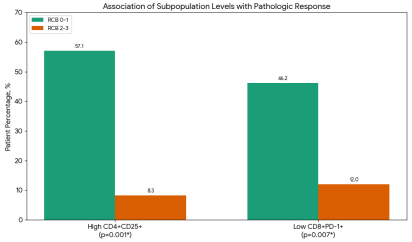
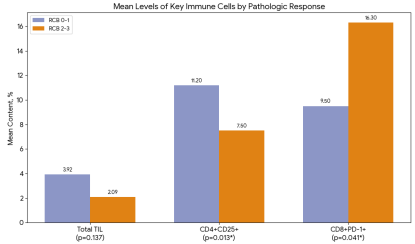


Fig.2 Mean levels of key immune cells by pathologic response



Conclusion

These findings suggest a potential prognostic relevance of specific TIL subpopulations, particularly CD4+CD25+ and CD8+PD-1+ lymphocytes, in luminal breast cancer. Further studies with larger cohorts are needed to validate these observations.

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