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Angiogenesis contributes to chemoimmunotherapy resistance in immune-high and immune-low triple-negative breast cancer (TNBC): Biomarker analysis of the NeoPACT trial

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Background

- Although benefit of immunotherapy in early TNBC has been observed regardless of PD-L1 expression, compared to immune-high TNBC, immune-low TNBC has lower pathologic complete response (pCR) rates and higher recurrence rates after neoadjuvant chemoimmunotherapy.[1-4]
- Development of more effective therapies for immune-low early-stage TNBC is an area of unmet clinical need.
- Angiogenesis enables tumor growth/metastasis and leads to immune suppression and treatment resistance in breast cancer.[5-7]
- Bispecific antibodies targeting PD-1/PD-L1 plus vascular endothelial growth factor (VEGF) have shown promising activity in advanced TNBC irrespective of PD-L1 expression.[8-9]

Aim

Examine the prognostic role of angiogenesis pathway expression signature in early-stage TNBC treated with chemoimmunotherapy on the NeoPACT trial.

Methods

- Study population included 109 patients treated with neoadjuvant chemoimmunotherapy (Carboplatin + Docetaxel + Pembrolizumab x6 cycles) on the phase II NeoPACT trial (NCT03639948)[3] for whom pre-treatment +/- residual tumor whole-exome RNA sequencing (Illumina TruSeq® RNA Exome Panel) was available (Table 1).
- Stromal tumor-infiltrating lymphocytes (sTILs) were centrally scored by standard criteria,[10] and tumors were defined as immune-high (sTILs ≥30%) or immune-low (sTILs <30%).
- Previously published 10-gene angiogenesis signature and 10-gene hypoxia signature scores were computed from RNA sequencing data.[11]
- Logistic regression was used to examine the independent prognostic utility of sTILs and angiogenesis signature for pCR. Event-free survival (EFS) was assessed by Kaplan-Meier method, with groups compared by log-rank test.

References: 1. Schmid et al, *N Engl J Med* 2022. 2. Loibl et al, *Ann Oncol* 2022. 3. Sharma et al, *JAMA Oncol* 2024. 4. Geyer et al, SABCS 2024. 5. Madu et al, *J Cancer* 2020. 6. Badodekar et al, *Cell Biochem Funct* 2021. 7. Zhang et al, *Front Oncol* 2024. 8. Ouyang et al, ESMO 2024. 9. Wu et al, ESMO 2024. 10. Salgado et al, *Ann Oncol* 2015. 11. Franzini et al, *Clin Cancer Res* 2015.

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Table 1. Patient characteristics

Characteristic – N (%)		All (N=109)
Age, y - median (range)		51 (27-70)
Race	White	85 (79%)[a]
	Black	20 (19%)
	Asian	3 (3%)
T stage	T1-2	89 (82%)
	T3-4	20 (18%)
Nodal positivity		41 (38%)
pCR		63 (58%)[b]
Immune status	High (sTILs ≥30%)	50 (47%)
	Low (sTILs <30%)	57 (53%)
Angiogenesis status[c]	High	65 (61%)
	Low	42 (39%)

[a]Race unknown for N=1 patient. [b]pCR not evaluable for N=1 patient. [c]Cutpoint for high vs low determined through ROC analysis.

Figure 1. Association of angiogenesis with pathologic response

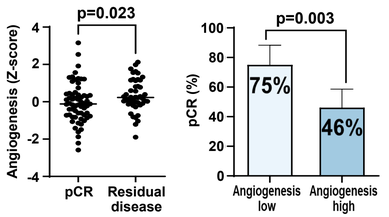


Figure 2. EFS by angiogenesis

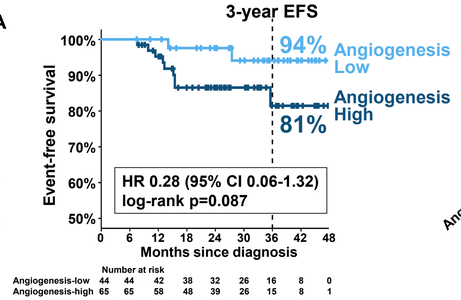


Figure 3. Angiogenesis by immune group

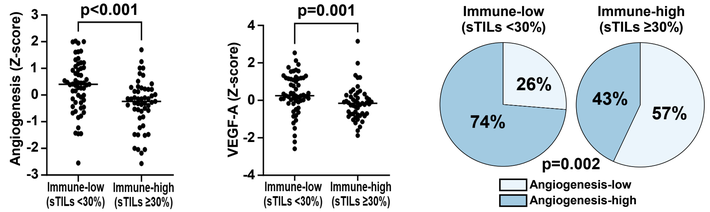


Figure 4. Immune cell composition

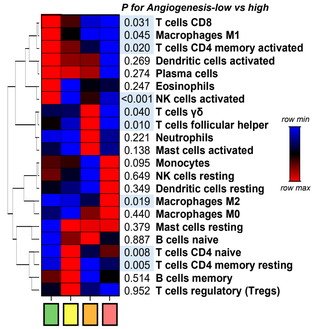


Figure 5. pCR by dual classification

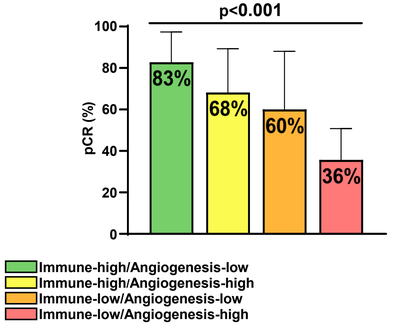
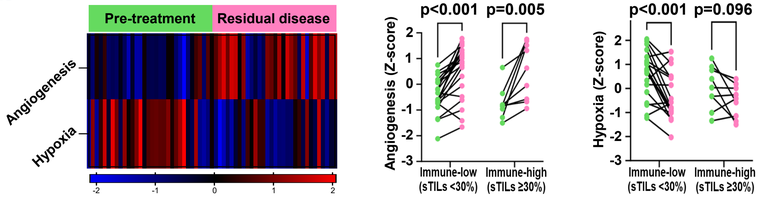


Table 2. Multivariable analysis for pCR

Model	Variable(s)	OR	95% CI	*p*	AUC
Model 1	sTILs (≥30% vs <30%)	4.47	1.94-10.3	<0.001	0.676
Model 2	Angiogenesis (low vs high)	3.50	1.51-8.10	0.003	0.642
Model 3 (joint model)	sTILs (≥30% vs <30%)	3.60	1.52-8.54	0.004	0.720
	Angiogenesis (low vs high)	2.48	1.02-6.05	0.046	

Figure 6. Angiogenesis and hypoxia in pretreatment vs residual tumor



Results

- Angiogenesis signature was inversely associated with pCR both as a continuous variable and as high/low categories (Figure 1).
- Numerically lower EFS was noted in patients with angiogenesis-high tumors compared to those with angiogenesis-low tumors (Figure 2).
- sTILs were inversely correlated with angiogenesis and VEGF-A. Compared to immune-high tumors, a higher proportion of immune-low tumors were angiogenesis-high (Figure 3).
- On CIBERSORTx cell type gene expression analysis, angiogenesis-low tumors demonstrated significantly more robust infiltration of anti-tumor immune cells (e.g., TH follicular helper, CD8+ T_{CTL}, M1 macrophages), and angiogenesis-high tumors exhibited a more immune-suppressive environment (e.g., M2 macrophages) (Figure 4).
- When included in a joint model with sTILs, angiogenesis was independently predictive of pCR, and the two markers combined predicted pCR more accurately compared to each individually (Table 2).
- Dual classification based on sTILs and angiogenesis was highly prognostic for pCR (Figure 5).
- Adequate residual tumor was available for RNA sequencing in 67% (31/46) of patients with residual disease (RD). Paired analysis of pre-treatment and RD showed high angiogenesis and low hypoxia signatures in RD compared to pre-treatment samples in both immune-high and -low tumors (Figure 6).

Conclusions

- Our data show that angiogenesis plays an important role in contributing to primary chemoimmunotherapy resistance in TNBC.
- Consistent with known association between angiogenesis and immune suppression, we noted higher angiogenesis signature score and VEGF-A expression in immune-low compared to immune-high tumors. Angiogenesis-high and -low tumors demonstrated differential tumor immune microenvironment composition.
- Angiogenesis and sTILs are complementary prognostic markers. Patients with immune-high/angiogenesis-low tumors experienced pCR rate exceeding 80%, and those with immune-low/angiogenesis-high tumors had pCR rates below 40%.
- Paired pre-treatment/residual tumor analysis indicates that induction of angiogenesis may be an escape mechanism contributing to acquired chemoimmunotherapy resistance.
- These findings lay a strong biological rationale for targeting VEGF in addition to PD-1/PD-L1 in early-stage TNBC. An upcoming neoadjuvant trial (NeoASPECT: Neoadjuvant Angiogenesis-Targeting Bispecific Chemoimmunotherapy for TNBC) will evaluate a bispecific PD-1/VEGF antibody in combination with chemotherapy in immune-low and immune-high early TNBC.

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