Splenomegaly and response to chemo-immunotherapy in Triple-Negative Breast Cancer: Findings from *MMTV-R26^{Met}* mouse model and patients

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CRCM CENTRE DE RECHERCHE EN CANCÉROLOGIE Marseille

POSTER #2025-A-2031-SABCS

SAN ANTONIO BREAST CANCER SYMPOSIUM® — UT Health San Antonio Mays Cancer Center — AACR American Association for Cancer Research

ABSTRACT

The *MMTV-R26^{Met}* model spontaneously develops triple-negative breast cancer (TNBC) and enables multi-parametric analysis (histology, genomics, proteomics, transcriptomics, immunophenotyping) identifying four distinct immune-molecular clusters with unique signatures correlating with clinical outcomes. Combined chemotherapy (epirubicin) and anti-PD-1 immunotherapy revealed cluster-specific therapeutic responses. Neutrophil-enriched tumors responded dramatically to combination therapy, while macrophage-enriched tumors showed differential sensitivity, highlighting innate immunity's critical role in treatment efficacy. Neutrophil-enriched tumors exhibited marked splenomegaly with systemic neutrophilia and extramedullary hematopoiesis. Spleen size correlated with treatment response, suggesting systemic immune activation could predict therapeutic benefit. These findings suggest splenomegaly as an accessible biomarker for patient stratification in precision immuno-oncology approaches.

BACKGROUND

TNBC exhibits marked heterogeneity in immune microenvironments and variable response to immunotherapy. Chemo-immunotherapy achieves pathological complete response (pCR) in only 65% of patients, highlighting need for predictive biomarkers. Current preclinical models fail to recapitulate the full spectrum of immune diversity observed in human TNBC. The *MMTV-R26^{Met}* mouse model spontaneously develops TNBC (Lamballe et al. 2021). Identification of accessible biomarkers is critical for patient stratification and treatment optimization.

OBJECTIVES

1) Characterize immune heterogeneity in *MMTV-R26^{Met}* model to identify immune-clusters and validate its clinical relevance

2) Evaluate cluster-specific responses to epirubicin, anti-PD-1, and combination therapy, with focus on systemic immune activation (splenomegaly)

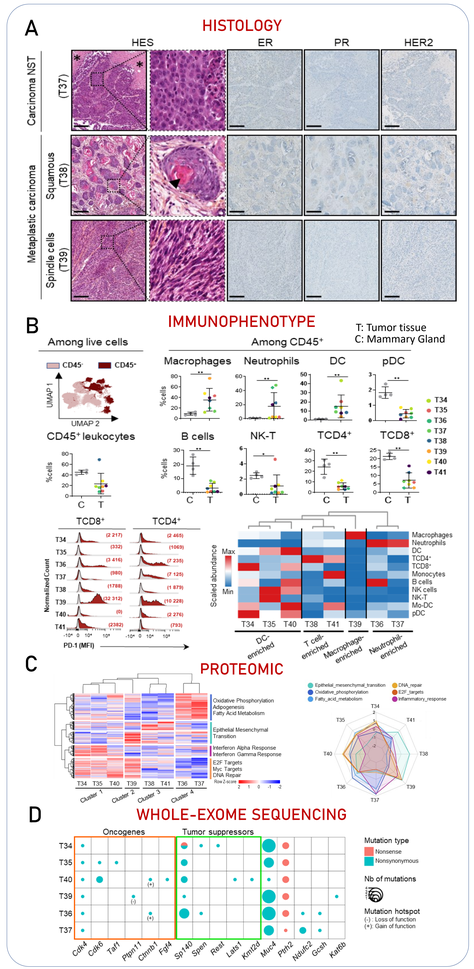
3) Translate preclinical findings to clinical validation in 125 stage II-III TNBC patients receiving neoadjuvant pembrolizumab plus chemotherapy

4) Develop predictive models for patient stratification and treatment optimization using accessible imaging biomarkers

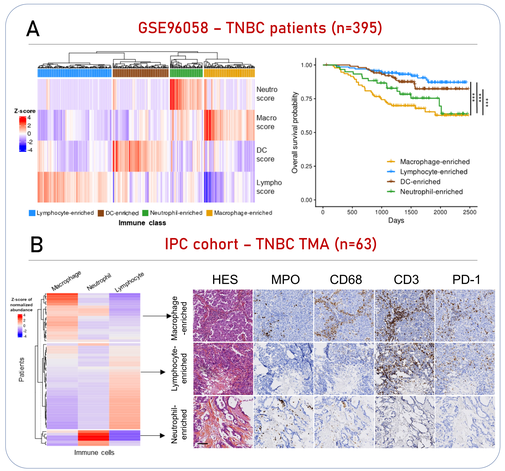
METHOD

We developed the immunocompetent *MMTV-R26^{Met}* mouse model, which mimics key TNBC features. Multi-parametric characterization (histology, proteomics, genomics, immunophenotyping, scRNA-seq) enabled direct comparison with human TNBC. We generated syngeneic orthotopic transplants that preserved tumor-immune heterogeneity across passages. Treatment studies evaluated the effects of epirubicin, anti-PD-1 and combination therapy. Clinical validation involved RNAseq public dataset, 63 TMA and 125 stage II-III TNBC patients receiving neoadjuvant pembrolizumab plus chemotherapy, with comprehensive clinical, pathological, and imaging data collection. Predictive models used machine learning approaches (logistic regression).

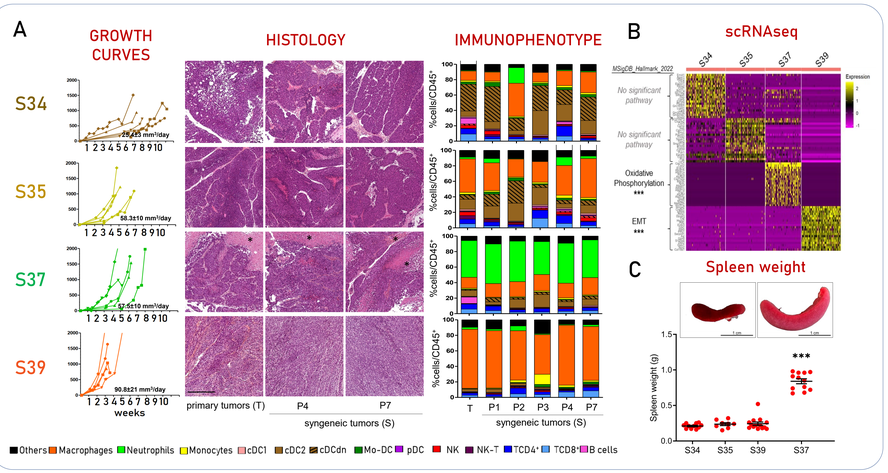
1) *MMTV-R26^{Met}* tumors multi-modal analysis



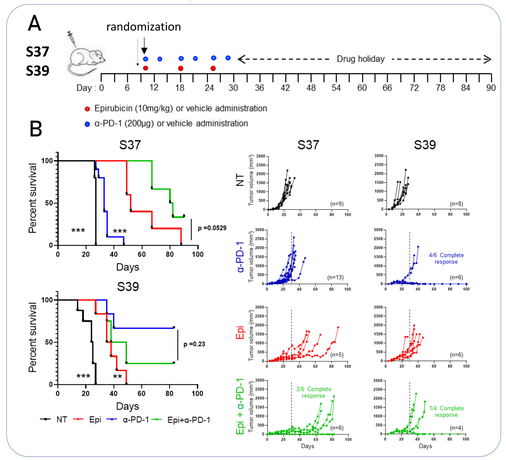
2) Clinical validation of 4 immune-clusters



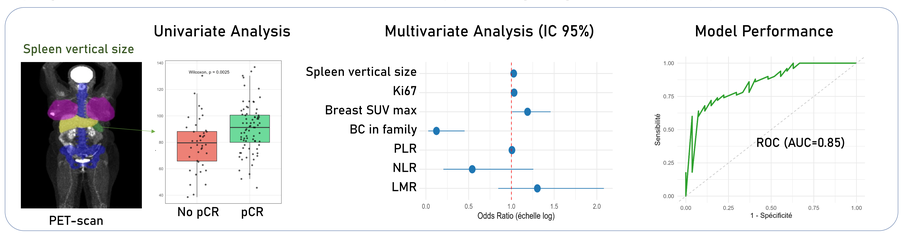
3) Syngeneic grafts maintain immuno-molecular features



4) Differential response to chemo-immuno



5) Spleen as biomarker to chemo-immuno (IPC hospial patients, n=125)



CONCLUSION

1) Four TNBC immune-molecular clusters identified in *MMTV-R26^{Met}* model are conserved in human patients.

2) Syngeneic transplantation system allows rigorous assessment of cluster-specific features

3) Neutrophil-enriched tumors respond to chemo-immunotherapy while Macrophage-enriched show differential sensitivity

4) Splenomegaly appears as a clinically accessible imaging biomarker

PERSPECTIVES

Dissect mechanistic response to chemo-immuno in TNBC

National multi-centric study to confirm spleen as predictive biomarker

ACKNOLEDGMENT

- IPC-CRCM Experimental pathology Platform (ICEP)
- CRCM core facilities for their essential technical support on mouse, cytometry, and microscopy
- Transcriptomic and Genomic Marseille Luminy (TGML) platform
- The CRCM Flow Cytometry Platform
- The CRCM Integrative BioInformatics (Cibi) platform

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FUNDING

Inserm cnrs amU Aix Marseille Université REGION SUD INSTITUT PAOLI-CALMETTES un cancer Marseille