RESEARCH HIGHLIGHT

Precision medicine for metastatic TNBC: the FUTURE is now

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Cell Research (2023) 33:491–492; https://doi.org/10.1038/s41422-023-00815-1

Despite well-described molecular heterogeneity of triple negative breast cancer (TNBC), management of metastatic disease primarily relies on cytotoxic chemotherapies, in some cases combined with immunotherapy, without consideration of molecular subtypes. In a recent *Cell Research* article, Liu et al. show the feasibility and promise of a precision medicine-guided treatment approach for heavily pretreated metastatic TNBC.

Triple negative breast cancer (TNBC) is clinically defined by lack of expression of estrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 (HER2) and is associated with high risk of early metastatic recurrences, worse prognosis, and fewer therapeutic options than other subtypes. Most TNBCs are high grade and lack targetable alterations; thus systemic therapy is largely comprised of cytotoxic chemotherapy. Recently novel agents have been added as potential treatment options: the Trop2-targeting antibody–drug conjugate (ADC), sacituzumab govitecan (SG),[1] immune checkpoint inhibitors for tumors with high expression of programmed death-ligand 1 (PD-L1),[2] poly (ADP-ribose) polymerase (PARP) inhibitors for patients with germline *BRCA* (*gBRCA*) mutations[3] and the HER-targeting ADC, trastuzumab deruxtecan, for HER2-low expressing tumors.[4] However, chemotherapy remains the primary option in later line settings, where response rates are poor at 5%–10%,[1] highlighting the need for research in heavily pretreated metastatic TNBC (mTNBC).

For over a decade distinct molecular subtypes of TNBC have been described, initially with Lehmann's six subtypes[5] followed by Burstein's four subtypes.[6] A revision of the four-subtype classification known as the Fudan University Shanghai Cancer Center (FUSCC) classification, incorporated messenger and long noncoding RNA profiling to describe immunomodulatory (IM), luminal androgen receptor (LAR), mesenchymal (MES) and basal-like immune-suppressed (BLIS) subtypes.[7] Jiang et al.[8] expanded on the latter study by proposing additional biomarkers and therapeutic targets in each subtype using multi-omics profiling of 465 TNBCs. The LAR-subtype was enriched with *ERBB2* mutations, potentially sensitive to HER2-targeted tyrosine kinase inhibitors. Immune-related signatures were common in the IM-subtype, while the BLIS-subtype had a high prevalence of genomic instability and homologous recombination-deficient tumors. Fig. 1 summarizes the FUSCC TNBC subtypes with biomarker characteristics.

To develop a subtyping method for the clinical setting, an immunohistochemistry (IHC)-based classification approach, which sequentially stains for androgen receptor (AR), CD8 and FOXC1, was developed with moderate to substantial agreement with the mRNA-based method.[9] The IHC-classifier was utilized in the innovative FUTURE umbrella trial, which employed IHC-based subtyping along with genomic sequencing to select among potential therapies for heavily pretreated mTNBC. Bayesian predictive probability modeling was used to predefine efficacy criteria based on overall response rates (ORRs) for seven treatment cohorts. The LAR-subtype patients with *ERBB2* mutations received pyrotinib plus capecitabine (A) while those without *ERBB2* mutations received AR inhibitor with a CDK4/6 inhibitor (B). The IM-subtype patients received camrelizumab (anti-PD-1 antibody) plus nab-paclitaxel (C). The BLIS-subtype patients with *gBRCA1/2* mutations received a PARP inhibitor (D) while those without a mutation received VEGFR inhibitor (E). The MES-subtype patients without PI3K/AKT pathway alterations also received VEGFR inhibitor (F) while those with PI3K/AKT alterations received everolimus plus nab-paclitaxel (G).

An interim analysis (IA) reporting ORR and safety after 69 patients had been enrolled was previously published.[10] Median lines of prior therapy were 3, with 99% of patients receiving prior taxanes, 86% anthracyclines, and 88% platinum agents. The majority had 6-month or less progression-free interval on initial chemotherapy. In 19 IM patients ORR was 53% and based on the activity the arm remained open to accrual. In 23 BLIS patients treated with 500 mg apatinib (VEGFR inhibitor) ORR was 26%, but high-grade adverse events (AEs) were excessive. Treatment was modified to either 250 mg apatanib or famitinib with oral VP-16 for the remainder of the trial.

In the paper by Liu et al.,[11] final efficacy results in 141 patients with heavily pretreated mTNBC and an expected ORR of 5%–10% with conventional chemotherapy are presented. Arms A, C, E and G reached predefined efficacy boundaries, with the highest ORR in the infrequent LAR-subtype with *ERBB2* mutations (3/4, 75%), followed by the more common IM-subtype (20/46, 43.5%), BLIS without *gBRCA1/2* mutations (13/46, 28.3%) and MES with PI3K/AKT pathway alterations (3/9, 33%). In addition to the ORR of 43.5% in the IM-subtype, median duration of response was 8.6 months and median overall survival was a remarkable 16.1 months. For context, the Phase Ib KEYNOTE-012 study in a similar population reported ORR of 18.5% with pembrolizumab.[12]

The authors provided a wealth of correlative data demonstrating the potential to develop hypotheses for testing in subsequent trials. Analysis of CD8 staining score and various biological processes revealed strong enrichment of immune-related pathways in tumors with high $CD8^+$ T cell infiltration, while angiogenesis enrichment was present with lower CD8 scores, suggesting that anti-angiogenesis therapy may

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Published online: 8 May 2023

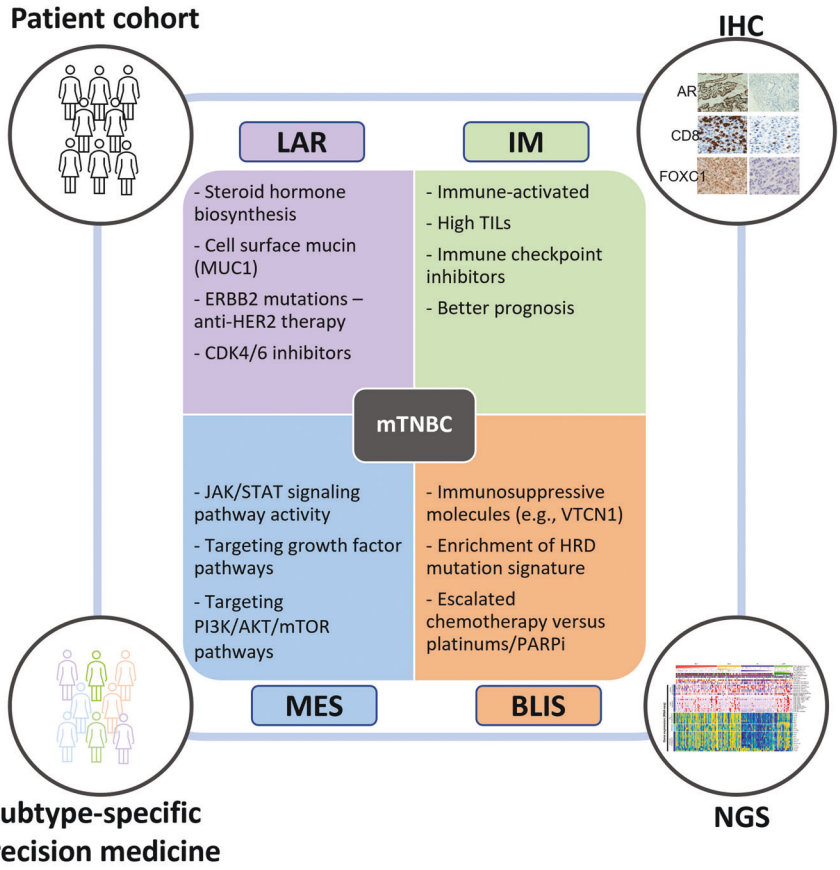

Fig. 1 FUSCC TNBC subtypes. Graphical representation of the FUSCC molecular classification of metastatic TNBC used in Liu et al.[11] Classification into four molecular subtypes — LAR, IM, BLIS and MES — was based on IHC staining for AR, CD8 and FOXC1, followed by additional next-generation sequencing (NGS) analysis to identify actionable alterations. Selected characteristics and potential treatment targets of each molecular subtype are highlighted in the colored boxes.

facilitate immune-based therapies. Based on this hypothesis, the authors designed the FUTURE-C-Plus trial,[13] adding the angiogenesis inhibitor, famitinib, to camrelizumab plus nab-paclitaxel, as first-line therapy for IM-mTNBC. They observed a remarkable ORR of 81.3% with median progression-free survival of 13.6 months, albeit with 50% of patients experiencing grade ≥3 AEs.

Patient-derived organoids from biopsy specimens were used to explore predictors of response and resistance and to test the efficacy of the ADC, SG, among the subtypes. This revealed the highest efficacy of SG in the LAR and BLIS subtypes, which had notably derived minimal benefit from initial treatment strategies in FUTURE, suggesting future trials evaluating SG in these challenging subtypes.

FUTURE highlights the potential of precision medicine-guided treatment to both address urgent needs in clinical breast cancer research and provide a platform for translational research to develop and test new hypotheses. It employed a novel IHC-based approach to classify patients with heavily pretreated mTNBC into molecular subtypes as well as to select treatment strategies. Groundbreaking studies generate new questions and opportunities. Challenges raised by FUTURE include the validation and quality assurance of IHC-based TNBC subtyping into routine clinical practice; utility of TNBC subtyping and genomic sequencing in the first-line metastatic setting and the early, potentially curative setting for high-risk patients with residual invasive breast cancer following optimal neoadjuvant therapy comprised of chemotherapy and checkpoint inhibitor; identifying more effective therapies for the LAR, BLIS and MES subtypes; and understanding how this work conducted exclusively in Chinese patients translates to more diverse populations.

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ADDITIONAL INFORMATION

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