Personalized Medicine

Major Finding: Targeted therapies matched to genomic alterations can improve breast cancer progression-free survival.

Concept: Alteration-matched drugs can improve patient outcomes if clinical data support target actionability.

Impact: Sequencing results should only guide treatment if genomic alterations have firm clinical evidence.

PRECISION MEDICINE IN BREAST CANCER MUST CONSIDER TARGET ACTIONABILITY

Precision cancer medicine aims to tailor treatment by basing decisions on the characteristics of an individual patient's tumor. Recent advances in DNA sequencing and cancer genomics have enabled the study of how different genomic alterations impact disease trajectory and govern sensitivity to targeted therapies. Multigene panels are common in clinical practice with frameworks, including the European Society for Medical Oncology (ESMO) Scale for Clinical Actionability of Molecular Targets (ESCAT), having been developed to help prioritize alterations as actionable targets based on clinical evidence; however, it remains unclear how to best interpret sequencing results to guide treatment. To address this, Andre, Filleron, Kamal, and colleagues conducted the randomized, multicenter phase II SAFIR02-BREAST clinical trial, comparing targeted therapies matched to genomic alterations with chemotherapy in the maintenance setting for patients with HER2-negative metastatic breast cancer. The primary objective was to assess whether targeted therapy improved progression-free survival (PFS) as compared to maintenance chemotherapy, with secondary objectives being overall survival and response rates, safety, and correlation of molecular characteristics with efficacy endpoints. Of the 1,462 patients who received genomic profiling, 646 patients (44%) presented with a targetable genomic alteration, and 238 patients (16%) were subsequently randomized to receive targeted therapy (n = 157) or chemotherapy (n = 81). In patients presenting with an ESCAT tier I/II genomic alteration (48%)—the highest levels of actionability indicative of a matched drug having either established or preliminary clinical evidence of efficacy—targeted therapy led to a significantly longer PFS than chemotherapy (9.1 months vs. 2.8 months). Notably, targeted therapies matched to genomic alterations ranking lower on the ESCAT scale, indicating hypothetical actionability at best, had no significant difference in PFS compared with chemotherapy. In summary, this work demonstrates that genomic alterations can effectively guide targeted treatment to improve patient outcomes if there is prior clinical evidence of target actionability. ■

Andre F, Filleron T, Kamal M, Mosele F, Arnedos M, Dalenc F, et al. Genomics to select treatment for patients with metastatic breast cancer. Nature 2022 Sep 7 [Epub ahead of print].

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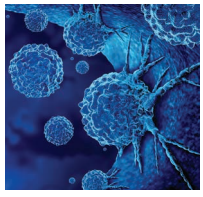
Immunotherapy

Major Finding: Rapid immune context changes occur in the tumor microenvironment after axicabtagene ciloleucel treatment.

Concept: Responders had increased markers of T-cell infiltration and activity but decreased B-cell lineage genes.

Impact: These findings provide potential predictive biomarkers of CAR T clinical response in patients with B-cell lymphoma.

TUMOR MICROENVIRONMENT IMMUNE CHANGES SUPPORT ANTI-CD19 CAR T-CELL EFFICACY



The anti-CD19 chimeric antigen receptor (CAR) T-cell therapy axicabtagene ciloleucel (axi-cel) has shown efficacy, but over half of patients relapse or develop resistance within the first year, indicating a clinical need for markers of response. Therefore, Scholler and colleagues assessed how the interactions between tumor and immune cells influence axi-cel outcome through evaluation of the tumor microenvironment (TME) both before and after treatment of 51 patients enrolled in the ZUMA-1 phase II clinical trial. Key immune features associated with clinical outcome were observed using transcriptomics with differences in genes involved in innate and adaptive immunity. Patients who responded to axi-cel treatment showed early and rapid alterations of cytotoxic T cell–related genes, T-cell growth factor genes like IL15, and IFNγ-regulated immune checkpoint encoding genes, while B-cell lineage markers were decreased. Conversely, nonresponders did not show these immune changes. Moreover, patients who achieved a complete response had a low tumor burden and higher helper T-cell densities, while patients who relapsed on axi-cel demonstrated a shift toward expression of T cell–related and other immune-related genes as compared to the early posttreatment TME along with an increase in B-cell lineage gene expression. Evaluation of pretreatment T-cell infiltration and chemokine secretion indicated a correlation with survival, with a more T cell–involved immune contexture supporting TME sensitivity to CAR T-cell therapy. Specifically, activated $CD8^+$ T cells were associated with an overall response, while nonresponders had increased expression of B-cell lineage genes. Furthermore, regulatory T-cell (T_{reg}) density was reduced in patients who exhibited high-grade neurologic events, but a high density of T_{regs} was correlated with positive TME features and clinical response. In conclusion, these results show that axi-cel treatment leads to rapid immune changes within the TME that can alter clinical outcome and suggest potential predictive markers of response. ■

Scholler N, Perbost R, Locke FL, Jain MD, Turcan S, Danan C, et al. Tumor immune contexture is a determinant of anti-CD19 CAR T cell efficacy in large B cell lymphoma. Nat Med 2022;28:1872–82.

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