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NEWS

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### RECEPTOR TYROSINE KINASE-DEPENDENT INDUCIBLE DEGRADATION OF MUTANT PI3KA DRIVES INAVOLISIB EFFICACY: TOWARD PRECISION TARGETING OF PI3K IN BREAST CANCER

*PIK3CA* is one of the most frequently mutated oncogene in cancer. Phosphoinositide 3-kinase (PI3K) is a heterodimer comprising two subunits: a catalytic subunit (p110) and a regulatory subunit (p85). Activating mutations in *PIK3CA* are found in ∼30%-40% of patients with breast cancer (BC) and induce hyperactivation of the catalytic subunit.[1] This mutation has been associated with endocrine therapy resistance in luminal BC, and also with anti-HER2 therapy in HER2+ BC. In May 2019, alpelisib, an α-specific PI3K inhibitor, was approved for the treatment of patients with advanced *PIK3CA*-mutant luminal BC.[2] However, the efficacy has been modest, in part due to a limited therapeutic index.

Song et al.[3] published in *Cancer Discovery* an impressive article showing a unique mechanism of action of PI3K inhibitors. The authors demonstrated that taselisib and inavolisib were stronger inducers of cell antiproliferation in *PIK3CA*-mutant cancer cells than other inhibitors. Furthermore, inavolisib in combination with endocrine treatment plus CDK4/6 inhibitors showed efficacy and tolerability in preclinical *PIK3CA*-mutant luminal BC models. To explain this differential efficacy in *PIK3CA* mutant models between different PI3K inhibitors, they described a novel mechanism. Taselisib and inavolisib depleted the mutant p110α protein. The molecular process underlying this degradation was through ubiquitination. Thereby, mutant p110α oncoprotein was less stable and more vulnerable to inhibitor-mediated degradation in a ubiquitin- and proteasome-dependent manner.

Interestingly, they showed that receptor tyrosine kinase (RTK) activity plays a key role in regulating p110α degradation by recruiting p110α to the membrane through p85b (an isoform of p85 regulatory subunit) for ubiquitination. In fact, low RTK activity resulted in inefficient mutant p110α degradation, suggesting that the degrader mechanism of action may not provide additional benefit over drugs with a nondegrader mechanism in HER2-negative mutant cells. To complete the analysis, they explored the activity of inavolisib in HER2-amplified BC. In these tumors, HER2-targeted therapy is the standard of care. However, patients with *PIK3CA* mutations are less responsive to anti-HER2 therapies. As they expected, degrader inhibitors in combination with trastuzumab plus pertuzumab or T-DM1 showed better response in *in vitro* and *in vivo* models. Overall, this work reveals a new mechanism of action to exploit in *PIK3CA*-mutant tumors, and opens an exciting path to pushing PI3Kα degraders in patients with HER2-positive BC.

### A BETTER UNDERSTANDING OF IMMUNE-RELATED TOXICITY TO IMMUNE CHECKPOINT BLOCKADE IN MELANOMA THROUGH CD4 T-CELL CHARACTERIZATION

Immune checkpoint inhibitors (ICIs) have revolutionized the medical therapy of malignant melanoma. Nevertheless, ∼10%-60% of patients experience severe immune-related adverse events (irAEs). So far, no predictive factors for these toxicities have been clearly identified and it is still unknown whether a common baseline immunological state precedes irAEs development.[4]

In a relevant article published in *Nature Medicine* by Lozano et al.,[5] the role of potential factors able to predict irAEs was studied by focusing attention on the common baseline immunological state. Patients with advanced melanoma ($n = 78$) who were treated with ICI monotherapy or in combination were recruited in this analysis to assess the risk factors associated with severe irAEs. For this purpose, the authors studied different white cells population with a single-cell RNA technology. In their analysis, a significant and high abundance of CD4 T-cell effector memory (EM) and CD4 T-cell central memory was observed in the blood of patients experiencing severe irAEs versus those without presenting no toxicities. Likewise, the authors showed how the specific activation stages of CD4 T cell 5 + 3 are those that have a high abundance in patients with severe irAEs. Through differential expression analysis against CD4 T cell 5 + 3, the authors demonstrated a gene enrichment of markers associated with CD4 T-cell EM. Consequently, by sequencing analysis of the V(D)J receptor, the authors showed that increased T-cell receptor (TCR) clonotype diversity is significantly associated with severe irAEs, in contrast to increased B-cell receptor clonotype diversity. By integrating a model between the abundance of activated CD4 T-cell EM and the diversity of TCR, the authors demonstrated the ability to predict the behavior of patients about severe irAEs before ICIs therapy. Based on the developed model, patients were divided into the low or high models. The authors observed that patients classified as 'low model' rarely developed severe irAEs after treatment in both monotherapy and combination, in contrast to patients classified as 'high model'. Furthermore, the authors showed that the clonal diversity of TCRs increases after treatment in patients who develop severe irAEs, emphasizing that those with high clonal expansion developed severe irAEs sooner.

This work provides robust information on the mechanisms associated with the development of severe irAEs before treatment with ICIs. A predictive model based on the abundance of specific T cells and the variability of TCRs was designed and demonstrated its high sensitivity and specificity to determine this adverse event. This study

allows future analyses using single-cell technology, facilitating optimal treatment of patients at risk of developing severe irAEs after treatment with ICIs, and therefore preventing associated toxicities.

## MULTIOMIC PROFILING OF CHECKPOINT INHIBITOR-TREATED MELANOMA: IDENTIFYING PREDICTORS OF RESPONSE AND RESISTANCE AS WELL AS MARKERS OF BIOLOGICAL DISCORDANCE

Immunotherapy has deeply changed the treatment of both high-risk localized and advanced melanoma. In the metastatic setting, the use of ICIs has achieved a 5-year overall survival rate of ∼52%.[6] However, primary or acquired resistance to treatment appears and its mechanisms are still not fully elucidated. As a general statement, those tumors with high programmed death-ligand 1 (PD-L1) expression, high tumor mutational burden (TMB), and tumor-infiltrating lymphocytes are expected to benefit the most from ICIs. More recently, EOMES+CD69+CD45RO+ EM T cells have been also associated with response to ICIs in a large cohort of patients. On the contrary, JAK mutations, PTEN loss, WNT/b-catenin overexpression, neoantigen heterogeneity T-cell dysfunction, and nonredundant signaling pathways[7] have been related to resistance to those treatments.

Newell et al.[8] in an interesting paper recently published in *Cancer Cell* comprehensively examined the landscape of response and resistance to ICIs and combination of ICIs and cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitors therapy in a large cohort of patients with advanced melanoma. In this study, 77 pretreatment samples were studied using whole-genome sequencing, RNA sequencing, methylome profiling, and immunohistochemistry to correlate genome, transcriptome, methylome, and immune cell infiltrates of tumors from this cohort with an extensive response and other clinical data.

In this interesting study, the authors showed that, as expected, the high TMB, neoantigen load, expression of γ-interferon-related genes, PD-L1 expression, low PSMB8 methylation, and T cells in the tumor microenvironment are associated with response to immunotherapy. No specific mutation correlates with therapy response. No correlation with certain molecular events previously associated with a poor immunotherapy response, including somatic mutation of specific genes, for example, JAK1, JAK2, SERPINB3, and the BAF/PBAF family, or expression of genes, including β-catenin, or the IPRES score, were detected. All these suggest a heterogenous scenario for the non-responders. A multivariable model combining the TMB and γ-interferon-related genes expression robustly predicted response [89% sensitivity; 53% specificity; area under the curve (AUC), 0.84]. Tumors with high TMB and a high γ-interferon-related signature showed the best response to immunotherapy. This model was validated in an independent cohort (80% sensitivity; 59% specificity; AUC, 0.79). Except for a JAK3 loss-of-function mutation, there is no obvious biological mechanism that clearly relates to the lack of response, suggesting a heterogeneous landscape. To better understand the heterogeneity of poor responders, the authors performed a comprehensive annotation and analysis focusing on 12 patients who had molecularly and clinically discordant findings (eight poor responders with TMB high IFNg-6 low or TMB low IFNg-6 high, and four good responders with TMB low IFNg-6 low). Interestingly the whole-genome sequencing and methylation profiling detected some new features associated with a poor response, including high numbers of structural rearrangements, the potential role chromothripsis, as well as high PSMB8 promoter methylation (and low PSMB8 expression) in poor responders. Furthermore, all the results obtained in the metastatic setting were robust and generalizable to other cohorts as they demonstrated across patients enrolled in a neoadjuvant trial.[9] These findings support that resistance to checkpoint inhibition is extremely heterogeneous. Despite being interesting, the results of this study need to be further evaluated due to the small sample size cohort included in this analysis. A larger prospective confirmatory study to examine the genomic features of the ICI-naïve population is warranted.

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