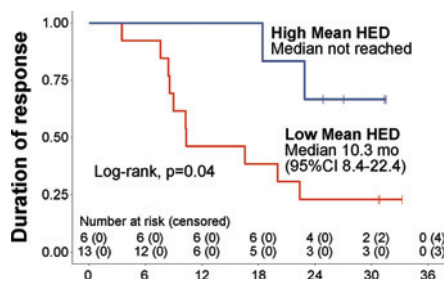


## MOLECULAR CANCER RESEARCH

## HIGHLIGHTS

Selected Articles from This Issue

## Genomic Biomarkers for Lenvatinib/Pembrolizumab in RCC

Lee *et al.* | Page 1510

Immunotherapy with immune checkpoint inhibitors (ICI) has become a cornerstone of the clinical management of some tumor types, particularly those with high PD-L1 expression, an unstable genome, or high mutational burden. By contrast to ICI monotherapy, few biomarkers exist to identify patients who may respond better to combination therapy with ICI and other targeted agents. In this study, Lee and colleagues report clinically effective stratification of renal cell carcinoma (RCC) patients who derived benefit from combination of lenvatinib, a multi-kinase inhibitor targeting VEGFR and FGFR, and the anti-PD-1 immunotherapeutic pembrolizumab. The authors found that patients with a diverse HLA-I genotype derived the most benefit from the combination. Specifically, HLA-I evolutionary divergence—a measure of the breadth of antigens and neoantigens that a patient's immune system can recognize—was a critical factor in determining outcomes in this phase Ib/II clinical trial, which was validated in an independent cohort that received ICI monotherapy. These observations offer valuable insight into the genetic and immunologic factors underlying the application of ICI combinations in the clinic and open new avenues for testing ICI combinations in RCC and beyond.

## LINC00239 Regulates EMT in ESCC

Liang *et al.* | Page 1465

Long non-coding RNAs (lncRNA) have emerged as a key regulatory element in cell biology, fine-tuning gene expression and activity through interactions with target proteins and RNAs. The mechanisms underlying their roles in cell biology are varied and often context-dependent, leading to substantial variation in their functions across tissue and tumor types. Here, Liang and colleagues identify a novel oncogenic role for one such lncRNA, *LINC00239*, in esophageal squamous cell carcinoma (ESCC). Specifically, *LINC00239* expression was upregulated via the TGFβ pathway in ESCC cells, with the end result of increasing tumor cell proliferation and promoting epithelial-mesenchymal transition. Once expressed, *LINC00239* competitively bound with MBP-1, an inhibitory transcription factor that represses the expression of MYC. By preventing MBP-1 from binding to the MYC promoter, *LINC00239* releases a critical brake on cell proliferation in ESCC cells, which could be restored with therapies targeting the TGFβ signaling pathway.

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## Characterization of p53 Frameshift Mutations

Tong *et al.* | Page 1522

Truncating or frameshifting mutations in p53 typically result in loss of function, but the specific implications of the various products resulting from each unique frameshift are poorly understood. Here, Tong and colleagues perform functional characterization of a group of p53 frameshift mutants to assess their relative activities in cancer cells. While DNA binding remained intact for each mutant, most were rendered unable to initiate a classical anti-proliferative response due to abrogated oligomerization. However, one mutant—I332fs\*14—produced a product with high similarity to endogenous TAp53 isoforms. This variant displayed anti-proliferative and pro-senescent activity when tested in cancer cells, with implications for downstream biological readouts such as migration and invasion. The authors conclude that truncating and frameshifting mutations occurring downstream of the p53 DNA binding domain, while generally implying a loss of function, can result in differential transcriptional activity depending on the specific product. This suggests that individual mutations observed in the clinic should be assessed on a case-by-case basis, as they could be differentially targeted for therapeutic benefit.

## EMT-Induced Drug Sensitivity in Breast Tissue

Karvelsson *et al.* | Page 1546

Metabolic requirements vary across cell and tissue types, as well as across the stages of tumor initiation, development, and progression. In the context of metastasis, cells undergoing epithelial-mesenchymal transition (EMT) become more motile and adaptable to new microenvironmental conditions, facilitating their spread throughout the body. In this study, Karvelsson and colleagues employ a breast cell model spanning the epithelial and mesenchymal states to query metabolic changes associated with EMT. In this context, cells re-route their metabolic flux through the TCA-cycle, de-emphasizing glycolysis and instead upregulating reductive carboxylation of glutamine to increase lipid biosynthesis via IDH2. This rewired metabolic network was accompanied by differential drug sensitivities, suggesting that cells which have undergone EMT may express a suite of molecular targets that are de-emphasized in epithelial cell biology but are crucial for cell survival in the mesenchymal state. In particular, mTOR inhibitors were found to be more efficacious against cells with a mesenchymal phenotype. Taken together, these findings offer new insights into metabolic requirements at different stages of cancer progression.