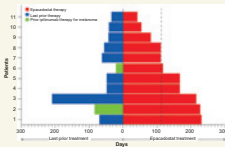


### IDO1 Inhibitor in Advanced Solid Cancers

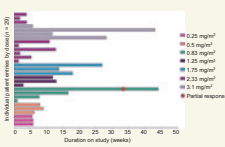


The enzyme indoleamine 2,3-dioxygenase-1 (IDO1), which catabolizes tryptophan degradation, can promote tumor escape from host immunosurveillance through T-cell suppression. In this first-in-human phase 1 study, Beatty and colleagues investigated the maximum tolerated dose, safety, pharmacokinetics, pharmacodynamics, and antitumor activity of epacadostat (INCB024360), a potent and selective IDO1

enzyme inhibitor. Epacadostat achieved potent inhibition of IDO1 at tolerable doses; a maximum tolerated dose was not established. By disrupting the IDO1-induced immunosuppression within the tumor microenvironment, epacadostat may provide enhanced antitumor activity in combination with other immunotherapies. Ongoing clinical studies are evaluating epacadostat in combination with immune checkpoint inhibitors. ■

See article by Beatty et al., p. 3269

### Phase 1 Trial of LB-100, an Inhibitor of PP2A

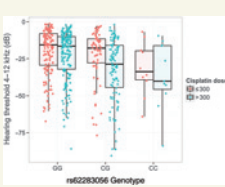


Protein phosphatase 2A (PP2A), a regulator of cell division and DNA-damage-response/repair, has been recognized as a potentially important cancer target, although its inhibition had been hypothesized as too toxic for clinical use. Numerous preclinical studies have shown that inhibition of this multifunctional enzyme selectively enhances antitumor activity

of cytotoxic drugs and radiation. This phase 1 study from Chung and colleagues demonstrates the safety, tolerability, and anticancer activity of LB-100, a novel small molecule inhibitor of PP2A, in patients with refractory solid tumors, supporting further development of LB-100 alone and with cytotoxic regimens as a new therapeutic approach to a broad spectrum of cancers. ■

See article by Chung et al., p. 3277

### Genetics of Cisplatin-Associated Ototoxicity

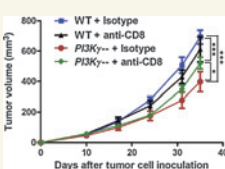


Genetic predictors of cisplatin-associated ototoxicity (CAO) could inform treatment decisions to avoid unnecessary toxicity. Wheeler and colleagues performed a genome-wide association study (GWAS) of CAO among testicular cancer survivors. One SNP in *WFS1* met genome-wide significance, and the *WFS1* functional association replicated in an independent cohort. They also show

that CAO shares underlying genetic etiology with both related Mendelian disorders and multi-cause, common phenotypes available in electronic health records. These results provide a framework for study design in clinical pharmacogenomics: following a GWAS of an adverse drug event, a related general phenotype with a larger sample size could be used for replication. ■

See article by Wheeler et al., p. 3325

### PI3K Promotes Tumor Growth and Impairs Antitumor Immunity



The PI3K pathway is activated in many breast cancers, either due to intrinsic genetic changes or alternative pathway activation. Sai and colleagues show that pan-inhibition of PI3K in mouse models of breast cancer mouse and in humanized PDX models results in reduced tumor growth and metastasis. Moreover, the antitumor immune

response was enhanced either with BKM120 inhibition of PI3K, or with genetic loss of PI3K in the host alone. Combining pan-PI3K inhibition with check-point inhibition (anti-PD1) further reduced tumor growth. The combined approach of blocking immune checkpoint inhibitors with PI3K pathway inhibition shows promise for patients who have failed single-agent immune or targeted therapies. ■

See article by Sai et al., p. 3371

# Clinical Cancer Research

## Highlights of This Issue

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