Clinical Cancer Research
Highlights
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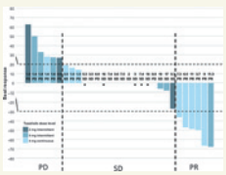
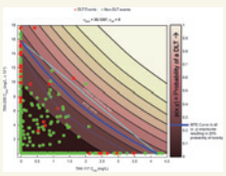
POSEIDON Phase 1b: Taselisib Combined with Tamoxifen



Endocrine therapy combined with PI3K-mTOR inhibition has been considered promising for estrogen receptor-positive breast cancer treatment, but toxicities have limited the clinical application of this strategy. Baird and colleagues report the results of a phase Ib trial in which estrogen receptor-positive, metastatic breast cancer patients were treated with tamoxifen and escalating doses of taselisib, a selective PI3K inhibitor. This combination was well tolerated, with no dose-limiting toxicities. Objective responses were seen in 24% of patients, and 40% of patients had disease control for at least 6 months. This combination was deemed successful and is currently under examination in a phase II trial. ■

See article by Baird et al., p. 6598

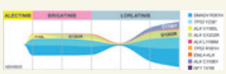
Modeling Optimal Dose Combinations of Anticancer Agents



Selecting the recommended phase II dose (RP2D) that provides maximal antitumor effect and tolerability is challenging, especially in the setting of combination treatment. Because phase I studies are underpowered for efficacy, Bottino and colleagues developed a modeling methodology that uses preclinical antitumor activity data and phase I clinical toxicity data to predict an optimal RP2D for combination therapy. The approach was applied to a PI3K and TORC1/2 inhibitor combination, illustrating the potential for this method to guide combination RP2D determination. ■

See article by Bottino et al., p. 6633

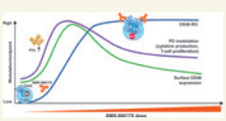
Treatment with Next-Generation ALK Inhibitors Fuels Plasma *ALK* Mutation Diversity



Patients with advanced *ALK*-positive lung cancer typically receive a second-generation ALK inhibitor followed by lorlatinib and develop compound *ALK* mutations. Dagogo-Jack and colleagues hypothesized that sequencing plasma would reveal a broader spectrum of *ALK* mutations than tissue. To this end, they assessed over 100 plasma specimens and demonstrated that the accumulation of *ALK* mutations during sequential treatment with next-generation ALK inhibitors promotes formation of refractory compound mutations. Plasma was more likely than tissue to harbor multiple detectable *ALK* mutations. This study highlights the potential for plasma genotyping to monitor the molecular evolution of therapeutic resistance. ■

See article by Dagogo-Jack et al., p. 6662

Defining Optimal Administration of OX40 Agonist Antibodies



OX40 is an important costimulatory receptor for T-cell survival and function. BMS-986178, a fully human agonistic anti-OX40 antibody, was well tolerated when administered alone or in combination with checkpoint blockade in patients with advanced cancers. Wang and colleagues assessed pharmacodynamic biomarkers in patients treated with BMS-986178, alone or in combination with checkpoint blockade, to identify the optimal dose and schedule of T-cell agonists for cancer treatment. Patients receiving BMS-986178 with or without checkpoint blockade harbored increased proliferating $CD4^+$ effector memory cells and activated $HLA\text{-}DR^+CD38^+$ effector cells. OX40 receptor occupancy between 20% and 50% correlated with the highest T-cell activity. This work will have implications for dose selection of immune modulators in future clinical trials. ■

See article by Wang et al., p. 6709