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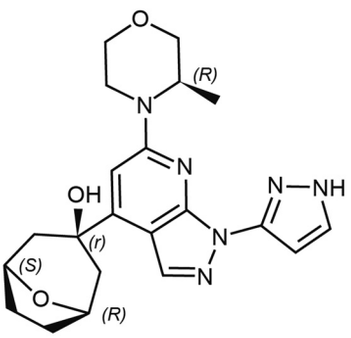
MOLECULAR CANCER THERAPEUTICS
HIGHLIGHTS

Selected Articles from This Issue

Novel, Potent, Selective and Effective ATR Inhibitor RP-3500



Roulston *et al.* | Page 245

ATR is essential to protect genome integrity during DNA replication in cancer cells. In this first disclosure, Roulston and colleagues identify RP-3500 (NCT04497116), a highly potent and selective oral ATR inhibitor with efficacy as a monotherapy and in combination with PARP inhibitors in several xenograft models. Preclinically, intermittent dosing of RP-3500 maintains efficacy without inducing anemia, a dose-limiting toxicity observed clinically for ATR inhibitors. Furthermore, concurrent administration of RP-3500 with PARP inhibitors on an intermittent schedule provides greater efficacy and reduced toxicity compared to sequential administration, providing an opportunity to maximize clinical benefit for this class of anti-cancer agent.

Precision Medicine of Triplatin in Breast Cancer

Hampton *et al.* | Page 271

Hampton and colleagues describe an approach for precision medicine of platinums in the treatment of triple-negative breast cancer (TNBC) through exploitation of the glycosaminoglycan (sGAG) expression of the tumor. The *in vivo* accumulation and antitumor efficacy of the paradigmatic polynuclear platinum complex Triplatin (BBR3464) in TNBC cells positively correlated with sGAG levels, representing a discrete mechanism of selective tumor accumulation not shared by the mononuclear agents. The paper validates the exploitation of sGAG profile as biomarker predicting response to therapy suggesting personalized approaches for TNBC patients—enhancement of neoadjuvant and adjuvant treatment will likely improve clinical outcome of TNBC.

Tissue Penetration of ADC Bystander Payloads

Khera *et al.* | Page 310

After decades of slow progress in the clinic, antibody drug conjugates (ADCs) have catapulted into the spotlight with 7 approvals in the past 3 years. One theme of recent approvals is the use of 'bystander' payloads capable of diffusing into adjacent cells after antibody targeting. However, the distribution of these payloads after release is unclear. This study quantifies and compares the tissue penetration and efficacy of all 3 classes of ADC payloads used in the clinic in a 3D tissue culture system. These results provide the necessary data to design more efficient next generation ADCs for clinical efficacy.

FLASH Irradiation Enhances PD-1 Immune Checkpoint Inhibition

Eggold *et al.* | Page 371

There is a critical need for treatment modalities that improve immune checkpoint blockade responses in ovarian cancer. Radiation therapy has been shown to synergize with PD-1/PD-L1 blockade in some cancers but has not been utilized in ovarian cancer due to the toxicity associated with conventional abdominopelvic irradiation. Eggold and Chow et al. demonstrate that ultra-high dose rate FLASH irradiation combined with PD-1 inhibition enhances intratumoral T-cell infiltration and tumor control with minimal toxicity in preclinical models of ovarian cancer. These data suggest that FLASH irradiation may improve the therapeutic efficacy of checkpoint inhibition in the treatment of ovarian cancer.

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