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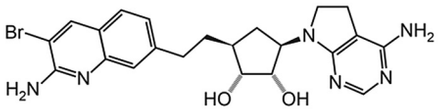
MOLECULAR CANCER THERAPEUTICS

HIGHLIGHTS

Selected Articles from This Issue

PRMT5 Inhibitor with Potent Anti-tumor Activity

JNJ-64619178



Brehmer *et al.* | Page 2317

Dysregulation of the protein arginine methyltransferase 5 (PRMT5) is associated with lymphomas, lung cancers, and breast cancers. In this First Disclosure, Brehmer and colleagues outline JNJ-64619178, an inhibitor of PRMT5 with potent anti-proliferative activity. JNJ-64619178 occupies the SAM and substrate pockets of PRMT5, trapping it in a catalytically inactive state. PMRT5 inhibition by JNJ-64619178 increased alternatively spliced events and resulted in the killing of primary AML samples *ex vivo*. Taken together, the results support the continued clinical study of JNJ-64619178 (NCT03573310).

Preclinical Evaluation of Dato-DXd, a TROP2-directed ADC

Okajima *et al.* | Page 2329

The approval of Trastuzumab deruxtecan demonstrates the potency of the DNA topoisomerase I inhibitor DXd in antibody-drug conjugates (ADCs). DXd-ADCs exhibit a short systemic half-life and ability to optimize the drug-antibody ratio. In this First Disclosure, Okajima and colleagues outline the design of another DXd-containing ADC targeting Trophoblast cell surface antigen 2 (TROP2). Datopotamab deruxtecan is designed to have a shorter half-life than sacituzumab govitecan, a TROP2-directed ADC approved by the FDA for TNBC. Dato-DXd showed potent anti-tumor activity and was absent of severe gastrointestinal toxicity. The results support the first-in-human phase 1 study for patients with advanced solid tumors (NCT03401385).

Combination of CRM1 Inhibitor Selinexor and Olaparib

Handley *et al.* | Page 2352

Chromosome region maintenance 1 is overexpressed in ovarian cancer and its inhibition has been shown to achieve a 30% disease control rate in recurrent disease. Here, Handley and colleagues seek to enhance the effects of selinexor through synergistic drug combinations. Their screen found the PARP inhibitor olaparib as the most likely candidate. Selinexor decreased the expression of DNA damage repair proteins, generating an increased susceptibility to PARP inhibitors. The combination reduced tumor nodules and weight *in vivo* in a mouse model. Their results outline an actionable combination for advanced ovarian cancer patients.

Characterization of KRAS Mutation Subtypes in NSCLC

Judd *et al.* | Page 2577

The advent of KRAS inhibitors, as well as the disagreement between retrospective studies in immunotherapy and KEYNOTE-189, demonstrate the need to characterize the KRAS mutational landscape of non-small cell lung cancer (NSCLC). Therefore, Judd and colleagues sequenced 592 genes from 17,095 NSCLC specimens to assess co-occuring genomic alterations, tumor mutational burden (TMB), and PD-L1 expression. They demonstrate the rate of co-mutation depends on the KRAS mutation type. Mutated KRAS was significantly increased in PD-L1 expression compared to wild type, with KRAS G12C the most likely to be PD-L1 positive. These studies inform future therapeutic intervention for KRAS-mutated NSCLC.

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