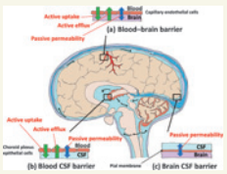
Clinical Cancer Research

Highlights

December 15, 2017 • Volume 23 • Number 24 Selected Articles from This Issue

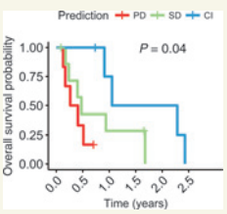
PBPK Modeling of AZD1775 Penetration into Brain Tumors



Prospective prediction and mechanistic understanding of drug penetration across human blood-brain barrier (BBB) are critical to rational drug development and therapy for brain cancer. By using a translational research strategy that leverages preclinical studies, pharmacokinetic modeling, and clinical trials, Li and colleagues developed an IVIVE-PBPK modeling approach for quantitatively and mechanistically understanding tumor penetration of AZD1775 in glioblastoma patients. The knowledge and tool generated are of enormous value to the field of quantitative pharmacology and also to the development of more effective therapies for brain cancer, where sufficient drug brain penetration is the prerequisite for efficacy. ■

See article by Li et al., p. 7454

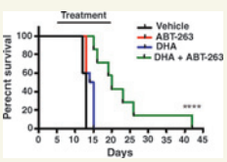
HRD and Platinum Outcomes in Advanced Breast Cancer



Mutation signatures of homologous recombination deficiency (HRD) have recently been shown to be prevalent in many cancer types. To examine their clinical implications, Zhao and colleagues performed whole-genome sequencing of 93 breast cancers, 33 of which were treated with platinum-based chemotherapy. They quantified 6 HRD-associated mutation signatures shown to robustly predict *BRCA1/2* status. Their observational analysis found that these HRD signatures also were associated with improved outcomes and treatment durations on platinum-based chemotherapy. They demonstrate an approach for computing HRD signatures, which may aid in the clinical translation of this potential predictive biomarker. ■

See article by Zhao et al., p. 7521

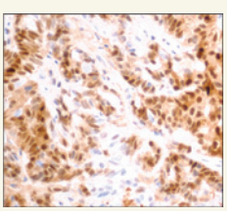
DHA Sensitizes Leukemia to Navitoclax



Philadelphia chromosome positive acute lymphoblastic leukemia (BCR-ABL$^+$ B-ALL) has poor prognosis in both pediatric and adult patients with the disease-free survival of 25%–30% in children and less than 20% in adults. Antiapoptotic MCL-1 is essential for the survival of BCR-ABL$^+$ leukemic cells and they are resistant to BH3-mimetic navitoclax. Budhraja and colleagues identified that dihydroartemisinin (DHA), an antimalarial drug, represses MCL-1 expression and sensitizes BCR-ABL$^+$ B-ALL cells to synergistic killing by navitoclax *in vitro* in patient-derived xenografts and in mouse models. The data suggested that combination of DHA and navitoclax could have implications to improve therapeutic response in BCR-ABL$^+$ B-ALL. ■

See article by Budhraja et al., p. 7558

SARM Inhibits AR/ER$^+$ Breast Cancer



The high prevalence of AR in ER$^+$ breast cancer along with the preclinical and clinical efficacy of classic androgens provide rationale for developing a new generation of selective AR agonist for this indication. Yu and colleagues report that RAD140, an oral, tissue-selective androgen receptor modulator (SARM), significantly inhibits the growth of AR/ER$^+$ breast cancer models, an effect further enhanced by the coadministration of CDK4/6 inhibitor. Importantly, RAD140 treatment led to substantial decrease in *ESR1* mRNA, suggesting a distinct AR-mediated mechanism of action compared with the agents targeting ER protein. RAD140 is now being evaluated in recurrent ER$^+$ breast cancer. ■

See article by Yu et al., p. 7608