



Window Trial of Transdermal 4-OHT vs. Oral Tamoxifen for DCIS

Lee *et al.* _____ Page 3672

Effective preventive drugs are declined by most women at high risk for breast cancer because of systemic toxicity, which may be decreased by the delivery of drugs through the breast skin. Lee and colleagues randomized women awaiting DCIS resection to 6-10 weeks of oral tamoxifen or 4-hydroxytamoxifen gel applied to the breast skin. The authors observed equivalent breast concentrations of 4-hydroxytamoxifen in both groups and similar reductions in the Ki67 labelling of DCIS cells, but far lower plasma concentrations in the transdermal group. Thus transdermal delivery appears to be a viable and potentially safer approach to breast cancer prevention, requiring further study.

Chemopotentiating Effects of PARP Inhibition in GBM

Gupta *et al.* _____ Page 3730

PARP inhibitors can potentiate the efficacy of temozolomide (TMZ) in multiple tumors; however, in previous animal studies, treatment of TMZ-resistant GBM xenograft models with veliparib and TMZ was ineffective in comparison with TMZ-sensitive models. By comparing isogenic TMZ-sensitive and -resistant GBM models, Gupta and colleagues report that resistant models *in vitro* are sensitized only by supratherapeutic concentrations of veliparib and TMZ. Using clinically relevant schedules *in vivo*, veliparib promotes TMZ-induced DNA damage signaling and survival benefit only in TMZ-sensitive models. These results highlight the importance of using clinically achievable drug levels in preclinical studies of PARP inhibitor combinations.

Semi-Mechanistic PK/PD Modeling of LY2835219 in Mouse

Tate *et al.* _____ Page 3763

Selective inhibition of CDK4/6 represents an area of considerable interest for anti-cancer therapy. To explore the *in vivo* quantitative pharmacology of LY2835219, a CDK4/6 inhibitor, an integrated pharmacokinetic/pharmacodynamic (PK/PD) model was developed by Tate and colleagues, relating plasma concentration to target engagement, cell cycle arrest, and growth inhibition of colo-205 and A375 xenograft tumors. Model simulations indicate that trough plasma concentrations of 200 ng/mL are associated with robust cell cycle arrest and that continuous dosing is required to achieve sustainable *in vivo* efficacy. These findings support and reinforce the continuous dosing strategy currently adopted in LY2835219 clinical studies.

Prognostic B-Cell Signatures in Breast and Ovarian Cancer

Iglesia *et al.* _____ Page 3818

Tumor-infiltrating lymphocyte (TIL) prevalence predicts improved survival in breast and ovarian cancer. To explore the role of B-cell TILs by genomic subtype, Iglesia and colleagues assessed lymphocyte gene expression in breast and ovarian cancer mRNA-seq data. Furthermore, they developed a method to assess clonal diversity of B-cell populations from mRNA-seq. This work highlights the basal-like and HER2-enriched subtypes of breast cancer, and the immunoreactive subtype of ovarian cancer, as containing B-cell TILs that predict improved survival outcomes and are clonally restricted compared with TILs in other tumor subtypes.

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