



A covalent-binding, selective inhibitor of HER2 kinase

Irie *et al.* _____ Page 733

HER2 is a promising therapeutic target for various cancers. Although several reports have described HER2 inhibitors, no covalent-binding inhibitor selective for HER2 kinase has been reported. The high specificity for HER2 kinase inhibition may prevent EGFR-related toxicity and achieve more effective dosing in HER2-targeted therapy. In this study, Irie and colleagues demonstrated TAS0728 as a covalent-binding kinase inhibitor that showed the high selectivity for HER2 and reduced activity for EGFR. These results may provide a rationale to offer a new therapeutic option for the treatment of cancers harboring HER2 gene abnormalities.

Effective bladder tumor growth control by PDT with THPTS

Berndt-Paetz *et al.* _____ Page 743

The recommended therapy for muscle-invasive urothelial cancer includes radical cystectomy with or without chemotherapy. Photodynamic therapy (PDT) presents a promising option as an organ-sparing therapy for muscle-invasive urothelial cancer but is limited by the short excitation wavelengths of typical photosensitizers. In this study, Berndt-Paetz and colleagues utilize the near-infrared excitation wavelength of the photosensitizer Tetrahydroporphyrin-Tetratosylat (THPTS) to penetrate up to 15 mm into tissue. They demonstrated that PDT with THPTS generates tumor reductions in an immunocompetent rat model of muscle-invasive urothelial cancer while sparing healthy tissue. These results suggest PDT with the photosensitizer THPTS is worthy of clinical consideration as an organ-sparing therapy in muscle-invasive urothelial cancer.

P16/CDKN2A predicts CDK4/6 inhibitor target engagement and sensitivity

Green *et al.* _____ Page 771

While CDK4/6 inhibitors have demonstrated therapeutic efficacy for ER+/HER2- advanced breast cancer, biomarkers are still needed to predict patient response and to extend the treatments to other cancers. Here, Green and colleagues assessed CDK4/6 target engagement in a panel of cell lines with known CDKN2A-CDK4 binding alterations and found that the interaction limits target engagement by CDK4/6 inhibitor drugs. Further research showed that high CDKN2A correlated with a biological insensitivity in a diverse panel of cell lines, but not in the ER+ subset. Therefore, high p16/CDKN2A could serve as an ER-independent biomarker to identify patients unlikely to respond to CDK4/6 inhibitors.

The tumor-growing mice may take antibodies away

Li *et al.* _____ Page 780

Preclinical assessment of therapeutic antibodies relies on immune-deficient mouse strains, which allow various tumor models to engraft. However, the choice of these mice may have impact on the pharmacokinetics profile. In this study, Li and colleagues contrast the half-life of antibodies in various mouse models. Surprisingly, the half-life of an antibody was only 1.4 days in the NSG mice, in contrast to a 7-day half-life in other strains. Mechanic studies found that Fc-FcγR interaction was responsible for the abnormal clearance in NSG mice. This shortened exposure resulted in reduced efficacy of an antibody-drug conjugate in NSG mice. The authors propose to pretreat mice with immunoglobulin to normalize antibody pharmacokinetics. Integrating strain-specific clearance parameters may help better guide the dose selection for clinical studies.

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