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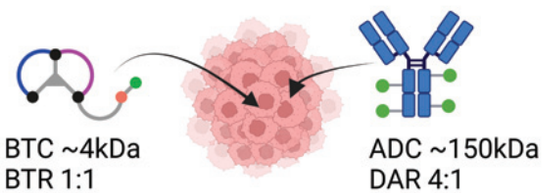
MOLECULAR CANCER THERAPEUTICS
HIGHLIGHTS

Selected Articles from This Issue

BT8009; a Bicycle® Toxin Conjugate for Treating Solid Tumors



Rigby *et al.* | Page 1747

Nectin-4 is a validated cancer target through ADC enfortumab vedotin. Rigby and colleagues have identified BT8009, a *Bicycle*® Toxin Conjugate that selectively binds Nectin-4 providing robust activity, and affording similar, or improved, activity over an ADC based on enfortumab vedotin, in several preclinical xenograft cancer models. The small, hydrophilic, nature of BT8009 results in a pharmacokinetic profile very different from an ADC, with a high Cmax, rapid extravasation from systemic circulation and rapid renal elimination. These different physical and PK characteristics may provide benefit for tumor penetration and reduced systemic exposure. BT8009 is in an ongoing Phase 1/2 clinical trial.

A Small Molecule CYP11A1 Inhibitor

Karimaa *et al.* | Page 1765

In metastatic castration-resistant prostate cancer (CRPC), altered expression of steroidogenesis enzymes, androgen receptor (AR) overexpression and mutations in AR ligand binding domain lead to increased AR sensitivity against various different steroids. ODM-208 is a highly selective inhibitor of the rate-limiting enzyme of steroidogenesis, CYP11A1. By inhibiting CYP11A1 it is possible to prevent the synthesis of all steroid ligands that could activate AR. ODM-208 leads to rapid, complete, durable, and reversible inhibition of the steroid hormones in multiple preclinical models and in patients with CRPC (NCT03436485). In addition, tumour growth inhibition has been shown in CRPC xenograft model.

ABX196 Cancer Immunotherapy in HCC and Melanoma Mouse Models

Scherrer *et al.* | Page 1788

Scherrer and colleagues investigated the effects of a stimulator of invariant natural killer T-cells, ABX196, on mouse models of B16F10 melanoma and hepatocarcinoma Hepa 1-6. ABX196 combined with anti-PD-1 resulted in increased melanoma and hepatocarcinoma control and survival. In both models, efficacy was associated with a generation of a more advantageous T-effector to Treg cell ratio within the tumor, resulting in the proliferation and accumulation of cells that would otherwise be anergized. ABX196 plus anti-PD-1 antibody may be a novel strategy to overcome the immunosuppressive microenvironment and to produce anti-tumor activity.

Targeted Alpha Therapy of HER2-positive Cancer

Rodak *et al.* | Page 1835

Human epidermal growth factor receptor type 2 (HER2) is overexpressed in various cancers. There is an urgent need for novel strategies overcoming resistance to HER2-targeted therapies and single-domain antibodies (sdAbs) could offer a useful platform for radioimmunotherapy. Here, a complete preclinical evaluation of 2Rs15d-sdAb radiolabeled with α-particle-emitting ^{225}Ac radionuclide is reported. [^{225}Ac]Ac-DOTA-2Rs15d efficiently targeted HER2^{pos} cells and was effective in treatment of intraperitoneal disseminated tumors, both alone and as an add-on combination with trastuzumab. [^{225}Ac]Ac-DOTA-2Rs15d holds promise for further investigation, and with the recent successful introduction of ^{225}Ac-labeled peptides in the clinic, might also find its way towards clinical translation.

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