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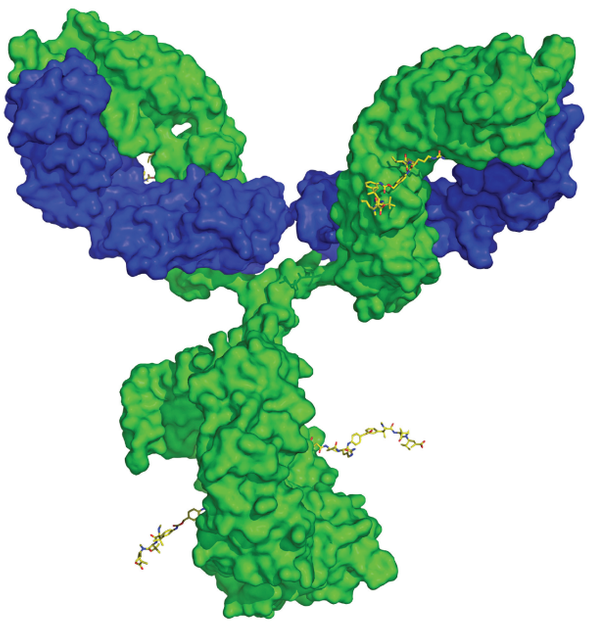
MOLECULAR CANCER THERAPEUTICS
HIGHLIGHTS

Selected Articles from This Issue

STRO-002, a Novel Homogeneous ADC Targeting FolRα



Li *et al.* | Page 155

FolRα is a cell-surface glycoprotein that is frequently over-expressed in multiple cancer indications including ovarian and endometrial cancers, which are the most lethal cancers for female reproductive system. Here we reported the discovery of STRO-002, a homogeneous antibody-drug-conjugate (ADC) that binds to FolRα with high affinity, internalizes, and releases a novel tubulin-targeting cytotoxin (hemiasterlin) to kill FolRα expressing tumor cells. With superior stability and favorable pharmacokinetic (PK) profile, a single dose of STRO-002 induced significant tumor growth inhibition in xenograft and PDX models. Phase I studies for STRO-002 are in progress in ovarian and endometrial cancer patients (NCT03748186 and NCT05200364).

Endo180 ADC for the Treatment of Sarcoma

Evans *et al.* | Page 240

Sarcomas comprise over 100 different subtypes which have significant genetic, morphological and histological heterogeneity, posing a substantial challenge to developing personalized therapies. Immunohistochemical staining identifies strong tumor cell expression of the recycling receptor, Endo180, in a high proportion of soft tissue sarcomas. Here, Evans and colleagues develop an antibody-drug conjugate (ADC) using an anti-Endo180 antibody conjugated to the anti-mitotic agent, MMAE. This ADC causes cell death specifically in Endo180-expressing sarcoma cell lines and, in a sarcoma xenograft model, results in tumor regression and impaired metastasis. This identifies Endo180 as a promising pharmacological target for a broad range of sarcoma subtypes.

Retinoblastoma Expression and Targeting in SCLC

Dowlati *et al.* | Page 264

In small cell lung cancer (SCLC) loss of *TP53* and *RB1* function were felt to be universal. The Dowlati laboratory had previously identified that a subset of SCLC is *RB1* wild type (WT). What was not clear was that if this subgroup had a functional RB pathway. They have now identified that a subset of SCLC indeed retains RB function by both transcriptomics and protein expression. Using cell lines and animal studies they demonstrate that this subgroup of SCLC is sensitive to CDK 4/6 inhibitors. To prove the point, they demonstrate a dramatic antitumor response in a patient with RB functional SCLC to abemaciclib.

High-throughput Functional Evaluation of Variants of MAP2K1

Kohsaka *et al.* | Page 227

Activating mutations in mitogen-activated protein kinase kinase 1 (MAP2K1) are involved in a variety of cancers. Here, functional analysis of 100 MAP2K1 variants indicated that 67 variants including 16 variants of unknown significance were oncogenic or likely oncogenic. Sensitivity to BRAF inhibitors was associated with the RAF dependency of the MAP2K1 variants, whereas resistance was strong in RAF-regulated and independent variants compared with RAF-dependent variants. This approach facilitates an understanding of the function of oncogenic variants in combination and will drive new drug development as well as personalized medicine for individual patients.

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