Molecular Cancer Therapeutics

Highlights

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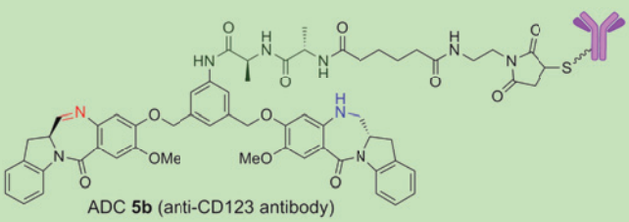
Selected Articles from This Issue



A Novel DNA-Alkylating Payload Class for Antibody-Drug Conjugates

Miller *et al.* Page 650

A novel DNA alkylating payload of antibody-drug conjugates (ADCs) was designed and evaluated in preclinical cancer models by Millers and colleagues. Changing the mechanism of action of the cytotoxic agent from a crosslinker to a DNA alkylator, along with linker optimization, provided ADCs with improved bystander killing and greater in vivo activity. ADCs with the DNA alkylator also displayed better in vivo tolerability than those with a DNA crosslinker, and thus, a higher in vivo therapeutic index was achieved. These findings represent a significant advancement in ADC technology designed to ultimately offer cancer patients a safer, yet highly active, therapeutic option.

Therapeutic Potential of EZH2 in Ovarian Cancer

Jones *et al.* Page 591

Recent advances in cancer genomics and transcriptomic analysis of ovarian cancer suggest dysregulation of many critical genes regulating ovarian cancer cell growth. Among them, histone methyl transferase, EZH2, acts as a global transcriptional repressor and downregulates the expression of many tumor suppressor genes. Multiple specific inhibitors of EZH2 have been identified and are currently in clinical trials. EZH2 expression has been shown to induce platinum resistance in ovarian cancer, and recent studies have suggested that EZH2 inhibition may be a valuable therapeutic approach. This review article summarizes the current literature pertaining to EZH2 in ovarian cancer.

Afatinib Targets EGFR and Brachyury in Chordoma

Magnaghi *et al.* Page 603

Chordomas are rare bone tumors marked by an unfavorable prognosis in most cases, with no efficacious therapy beyond surgery. Magnaghi and colleagues identified afatinib as the only EGFR inhibitor with activity across a panel of chordoma cell lines. The treatment of afatinib also led to tumor regression in different chordoma models in vivo. Further mechanistic studies found that afatinib could promote the degradation of EGFR and brachyury proteins, and the sensitivity of chordoma cell lines to afatinib is correlated with high EGFR phosphorylation and low AXL and STK33 expression. These data provided the preclinical rationale for the upcoming European Phase II clinical study with afatinib in chordoma.

Targeting Hormone Positive Breast Cancer with a GFRA1 ADC

Bhakta *et al.* Page 638

Luminal A (hormone receptor-positive) breast cancer constitutes 70% of total breast cancer patients. Bhakta and colleagues identified and characterized GFRA1, a luminal A (hormone receptor-positive) breast cancer target for its use as an antibody-drug conjugate (ADC) therapeutic. A humanized anti-GFRA1 ADC demonstrated specific *in vitro* and *in vivo* killing of GFRA1 expressing cells and displayed ideal therapeutic features, including a target safety profile and pharmacokinetic properties that would enable its progress towards further development into the clinic. GFRA1 ADC has potential utility as a targeted therapy for many-relapsed luminal A breast cancer patients.

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