Molecular Cancer Therapeutics

Highlights

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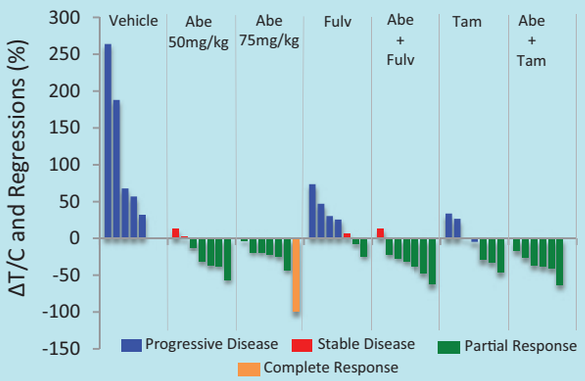
Selected Articles from This Issue



Comprehensive Analysis of Abemaciclib in Human Breast Cancer Models

O'Brien *et al.*_____Page 897

Targeting cyclinD:CDK4/6:Rb signaling pathway through CDK4/6 inhibition has proven to be a successful therapeutic approach in ER+ breast cancer. In this study, O'Brien and colleagues investigated the preclinical activity of the CDK4/6 inhibitor, abemaciclib, in each of the known molecular subtypes of breast cancer. Measurement of specific biomarkers can be used to identify sensitive sub-populations beyond the ER+ group and within the HER2-amplified and TNBC. In addition, they show that abemaciclib combinations improve upon responses observed with standard of care therapeutics in these sensitive sub-populations, including cytotoxic chemotherapies. These data support further clinical development of abemaciclib as monotherapy or as a combination partner in biomarker selected ER+, HER2-amplified and TNBCs.

Osimertinib in NSCLC Patients with EGFR Exon 20 Insertions

Floc'h *et al.*_____Page 885

Osimertinib, a third-generation EGFR TKI with activity against the activating mutations (Ex19del and L858R) and the T790M EGFR mutation, is approved for the treatment of T790M-positive NSCLC. EGFR exon 20 insertions (Ex20Ins), the 3rd most prevalent EGFR activating mutations, are unresponsive to 1st and 2nd generation EGFR inhibitors. Here, Floc'h and colleagues report that osimertinib and its metabolite inhibit proliferation in Ex20Ins mutant cell lines *in vitro* and demonstrate sustained tumor growth inhibition of EGFR-Ex20Ins mutant tumor xenograft and patient derived xenografts *in vivo*. Together, these data support clinical testing of osimertinib in patients with EGFR Ex20Ins NSCLC.

Drug Delivery for Neuroblastoma

Sagnella *et al.*_____Page 1012

Advanced stage neuroblastoma has limited therapeutic options once conventional therapy fails. Moreover, chemotherapy is not targeted, leading to dose-limiting toxicity and for neuroblastoma survivors, potential life-long side effects. Here, Sagnella and colleagues report the efficacy of bispecific antibody-targeted delivery of a bacterially-derived nanocell loaded with doxorubicin ($^{EGFR}EDV^{TM}_{Dox}$). Neuroblastoma cells grown as spheroids displayed increased sensitivity to cell death induced by $^{EGFR}EDV^{TM}_{Dox}$ compared to doxorubicin alone. *In vivo*, $^{EGFR}EDV^{TM}_{Dox}$ significantly reduced tumor growth in orthotopic models of neuroblastoma compared to free doxorubicin. The use of targeted and drug-loaded EDV^{TM} provides a potential new approach for the treatment of aggressive pediatric cancers.

IMGN853 in Type II Endometrial Cancer

Altwerger *et al.*_____Page 1003

Type II endometrial cancers, including uterine serous carcinoma, clear cell and poorly differentiated endometrioid adenocarcinoma account for a disproportionate number of endometrial cancer deaths. IMGN853 is an antibody-drug conjugate linked to DM4 targeting Folate Receptor Alpha (FRα), a receptor overexpressed in biologically aggressive endometrial tumors. Here, Altwerger and colleagues demonstrate that IMGN853 may have impressive preclinical activity against Type II endometrial cancers with high (2+) FRα expression. Due to its cleavable linker, IMGN853 may be active against heterogeneous FRα expressing tumors. Clinical studies with IMGN853 in patients harboring biologically aggressive endometrial cancers overexpressing FRα are warranted.

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