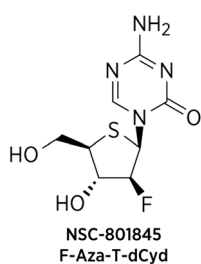


MOLECULAR CANCER THERAPEUTICS

HIGHLIGHTS

Selected Articles from This Issue

F-aza-T-dCyd, a Novel Cytidine Analog

Morris *et al.* | Page 625

Cytidine analogs remain an area of active drug discovery and development with five FDA-approved drugs. Herein F-aza-T-dCyd (NSC801845), a novel fluorine-containing cytidine analog, is first disclosed and compared in cell culture and human tumor xenograft studies with gemcitabine and several investigational cytidine agents currently undergoing clinical development. In the 3 of 5 xenograft studies (HCT-116 colon, HL-60 leukemia, PDX BL-0382 bladder), F-aza-T-dCyd produced complete regression of the tumors in all mice with a response that proved durable beyond post-implant day. These findings indicate that further development of F-aza-T-dCyd as a potential chemotherapeutic is warranted.

LY3214996-based Treatment for RAS-driven Lung Cancer

Köhler *et al.* | Page 641

The oncogene RAS remains an attractive target due to its widespread occurrence in cancer and its effect on pathways such as MAPK, PI3K, and cyclins. In this highlighted manuscript, Köhler and colleagues propose the ERK1/2 inhibitor LY3214996 to potentially prevent these RAS-driven pathways without the bypass and feedback activation of MEK inhibitors. They demonstrate the potency of LY3214996 in patient-derived and genetically engineered mouse models of RAS mutant lung cancers alone and in combination with the PI3K/mTOR inhibitor LY023414 or CD4/6 inhibitor abemaciclib. LY3214996 is currently undergoing Phase I clinical trials (NCT02857270).

Targeting BET and PI3K in Ovarian Clear Cell Carcinoma

Shigeta *et al.* | Page 691

Ovarian clear cell carcinoma (OCCC) represents a subtype of ovarian cancer that remains difficult to treat at advanced stages. Shigeta and colleagues employed a high-throughput siRNA screening platform to patient-derived cell lines and identified BRD2 and BRD3 as targets for treating OCCC. They demonstrate synergy via the Bliss Independence model for BET inhibitors and PI3K-AKT inhibitors. Therefore, combined therapy with BET inhibitors and PI3K-AKT inhibitors are a viable strategy for OCCC.

Bispecific Antibody for the Treatment of Ovarian Cancer

Lo *et al.* | Page 716

Antibodies directed at programmed cell death proteins PD-1/PD-L1 checkpoint pathway have had modest results to date in ovarian cancer. Lo and colleagues propose CD3 bispecific antibodies may accomplish a more robust immunotherapy response in ovarian tumors due to their unique triggering of polyclonal, MHC independent T cell responses. In this manuscript, they examine the use of a LYPD1/CD3 T cell dependent bispecific antibody in mice and human CD3 transgenic models. The LYPD1 was well-tolerated in the mice models. Taken together, their evidence supports further development of anti-LYPD1/CD3 T cell dependent bispecific antibodies for ovarian cancer patients.