Clinical Trials

**Major finding:** Birabresib achieved partial responses in 3 of 10 patients with NUT midline carcinoma.

**Concept:** Birabresib did not achieve responses in patients with prostate cancer or non–small cell lung cancer.

**Impact:** BET inhibition with birabresib may be beneficial in patients with NUT midline carcinoma.

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**THE BET INHIBITOR BIRABRESIB IS SAFE IN PATIENTS WITH SOLID TUMORS**

The bromodomain and extraterminal (BET) proteins (including BRD2, BRD3, BRD4, and BRD7) are essential epigenetic regulators of transcription, and BET inhibition has antitumor activity in a variety of preclinical tumor models including nuclear protein in testis (NUT) midline carcinoma (NMC), which is characterized by BRD4–NUT fusions, non–small cell lung cancer (NSCLC), and androgen-resistant and androgen-sensitive prostate cancer. A selective small-molecule BET inhibitor, birabresib (OTX015), demonstrated antitumor activity in patients with hematologic malignancies, but has not yet been evaluated in solid tumors. Lewin and colleagues evaluated the safety and efficacy of birabresib in an open-label phase Ib dose-escalation study. A total of 46 patients were treated with birabresib: 26 with castration-resistant prostate cancer (CRPC), 10 with NMC, and 10 with NSCLC. Twenty-four patients were enrolled in cohort A and received continuous birabresib (starting at 80 mg per day), and the 22 patients in cohort B received 100 mg birabresib for 7 consecutive days in 21-day cycles. The primary objective was determination of dose-limiting toxicities and the recommended phase II dose, and secondary objectives were assessment of the safety, efficacy, and pharmacokinetics of birabresib. In the 42 evaluable patients, there was a 67% disease control rate, with partial responses achieved in 3 of 10 patients with NMC. Overall, 38 patients (83%) experienced treatment-related adverse events, including grade 3–4 treatment-related adverse events in 35% of patients and serious adverse events in 22% of patients. Pharmacokinetic analysis showed that birabresib had a dose-proportional increase in exposure and rapid absorption. Collectively, the results of this phase Ib trial indicate that birabresib has a favorable safety profile in solid tumors and warrants further investigation for the treatment of patients with NMC.

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**Breast Cancer**

**Major finding:** Inhibiting p38α blocks DNA repair by HR and increases CIN to suppress tumor progression.

**Mechanism:** p38α phosphorylates CtIP to promote DNA double strand break resection and repair.

**Impact:** Breast tumors with high levels of CIN may benefit from treatment with p38α inhibitors plus taxanes.

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**p38α LIMITS CHROMOSOMAL INSTABILITY IN BREAST CANCER CELLS**

Chromosomal instability (CIN) can be induced by defects in DNA repair and increased DNA replication stress, but the effects of CIN on tumor progression are context dependent. Cánovas, Igea, and colleagues investigated the role of p38α, a ubiquitously expressed kinase involved in mediating the stress response to replication defects and DNA damage, in breast cancer cell survival and CIN. In a mouse model of breast cancer, p38α was required for tumor progression, and deletion of Mapk14 (encoding p38α) resulted in tumor regression with increased levels of DNA damage. In vitro, p38α was required to prevent cell death and maintain efficient cell-cycle progression in mammary tumor epithelial cells. p38α directly phosphorylated CtIP, which is involved in DNA double strand break (DSB) resection. Thus, depletion of p38α reduced ATR activation and suppressed DNA repair by homologous recombination (HR), resulting in an increase in replication stress, DNA damage, and CIN. Further, depletion of p38α sensitized cells to treatment with paclitaxel or docetaxel, taxane drugs that trigger missegregation in proliferating cells to promote CIN. Consistent with these findings, treatment with the p38α inhibitor PH797804 plus paclitaxel or docetaxel suppressed tumor growth in an autochthonous mouse model of breast cancer, whereas single-agent taxane treatment had only a cytostatic effect. Moreover, combined treatment was associated with increased DNA damage and missegregation events, suggesting that p38α contributes to the DNA damage response and promotes the survival of cancer cells with high levels of CIN. p38α inhibition also enhanced CIN and reduced tumor growth in combination with taxane treatment in breast cancer patient-derived xenograft models. In addition to elucidating a role for p38α in limiting replication stress and CIN, these findings suggest that tumors with high levels of aneuploidy may benefit from combination therapy with p38α inhibitors plus taxanes.

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The BET Inhibitor Birabresib Is Safe in Patients with Solid Tumors

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