Elaborating the Mechanism of PARP Synthetic Lethality Following ATM Loss in DLD-1 Cell Line

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Background and the Findings
PARP inhibitors (PARPi) have demonstrated the potential to overcome cancer which is known to have high incidence in BRCA1 and BRCA2 carriers. Synthetic lethality (SL) induced by PARPi was initially observed in tumors bearing BRCA1/2 germline mutations caused by germline or somatic alterations. PARPi inhibits nuclear cell death in HR-deficient cell lines through the formation of DNA breaks and cell cycle arrest.

The results from our recent in vivo studies indicate that ATM loss in DLD-1 cells increases sensitivity in vivo as assessed by tumor growth and tumor burden with exposure to Piraspare (NPX202). These data support the use of ATM loss in DLD-1 cells as a model system to determine PARPi sensitivity.

S.H. capacity is impaired in both DLD-1 ATM(-/-) and ABRAC2(-/-) cell lines.

Results 1. Homologous Loss of ATM Causes a Marked Increase in the TGI and Viable Cell Loss in NSCLC PDX models. Differences in ATM, a novel therapeutic pathway in NSCLC PDX models, and in ATM(-/-) cell lines. Approximately 2% of cells were targeted with ATM inhibitors in multiple tumor indications such as prostate, lung, and colorectal cancer.

Inactivation of ATM mediated by a frameshift mutation in NBN is associated with genome instability and increased sensitivity against PARPi inhibition. ATM deficiency is associated with markedly increased sensitivity against PARPi inhibition.

Conclusions
ATM loss in DLD-1 cell line caused a reduced increase in sensitivity in vivo and monotherapy (30 mg/kg) and induced a SKBR3 cell line to regress in vivo. The results obtained from the DLD-1 cell line were consistent with the increased sensitivity to PARPi in multiple tumor indications. These findings support the use of ATM loss in DLD-1 cells as a model system to determine PARPi sensitivity.