ABSTRACT: Small cell lung cancer (SCLC), accounts for 15% of all lung cancer cases. Initially, most patients respond to first-line chemotherapy, but relapse occurs in nearly all patients and is fatal. Overexpression of the MYC family of oncogenes occurs in a subset of chemoresistant SCLC. While MYC amplification accounts for some of these phenotypes, c-MYC overexpression is frequently seen, suggesting that c-MYC transcriptional activation drives aggressive disease. We identified a novel pathway of c-MYC activation via DNA-PKcs-mediated phosphorylation of OCT4 at Ser93. We present a novel cell-based screening assay to identify inhibitors of the OCT4-DNA-PKcs interaction. We screened ~80,000 compounds and identified 56 “hits” inhibiting kinase-substrate binding. We validated narciclasine as a potent inhibitor of DNA-PKcs-mediated phosphorylation of OCT4 at Ser93. Narciclasine impairs c-MYC expression and induces apoptosis in high c-MYC-expressing SCLC and augments the activity of ABT-199, a BH3-mimetic, in vitro and in vivo in high c-MYC-expressing SCLC models.

Persons with disabilities who may need auxiliary aids or services are requested to contact Tiffany Denton, 806.743.4008 at least 24 hours prior to this meeting so that appropriate arrangements can be made.