

## BT2

### Drug Discovery for Atypical Pulmonary Carcinoid Using a Library of Targeted Agents

Curtis R. Chong<sup>1</sup>; Bruce E. Johnson<sup>1</sup>; Pasi A. Jänne<sup>1</sup>

<sup>1</sup>Dana-Farber Cancer Institute, Boston, MA 02215

**BACKGROUND:** On average it costs ~\$1 billion and takes > 15 years to develop a new drug; this is a major challenge to drug discovery for rare forms of lung cancer like atypical pulmonary carcinoid. One way to overcome this challenge is to identify existing drugs active against multiple types of neuroendocrine lung cancers.

**METHODS:** We created a library of 292 targeted agents that inhibit 104 different cellular pathways, including drugs that are FDA-approved (31 drugs, 11%), in phase III (29 drugs, 10%), phase II (51 drugs, 18%), or phase I (30 drugs, 10%) clinical trials or in pre-clinical drug development (150 agents, 51%). We screened this collection on a panel of pulmonary neuroendocrine tumor cell lines: atypical carcinoid (NCI-H720 and H835) and small cell lung cancer (G1C, H69).

**RESULTS:** Navitoclax, which targets Bcl-2/BCL-XL, showed potent inhibition against NCI-H720 vs. NCI-H835 ( $IC_{50}$  = 66 and 460 nM, respectively). The BCL-XL-specific agents 334092 and 354961 also inhibited NCI-H720 ( $IC_{50}$  = 80 and 350 nM, respectively), while the Bcl-2 specific inhibitor ABT-199 was much less potent ( $IC_{50}$  ~ 5  $\mu$ M). Other promising inhibitors of NCI-H720 and H835 include the HSP-90 inhibitor AUY-922 ( $IC_{50}$  = 4 nM for both), the PI3 kinase/mTOR inhibitor GSK-2126458 ( $IC_{50}$  = 7 and 38 nM, respectively), and the polo-like kinase inhibitor volasertib ( $IC_{50}$  = 6 nM and > 1  $\mu$ M, respectively), which was also active against the small cell lines tested (11 nM and 24 nM for G1C and H69, respectively).

**CONCLUSION:** Our screen of a collection of targeted agents identifies navitoclax, AUY-922, GSK-2126458, and volasertib as inhibitors of atypical pulmonary carcinoid cell lines. As this form of lung cancer is quite rare, a clinical trial may need to include patients with other types of neuroendocrine lung cancers. We are expanding our screening efforts to include every available targeted therapy.