AP26113 is a dual ALK/EGFR inhibitor: Characterization against EGFR T790M in cell and mouse models of NSCLC

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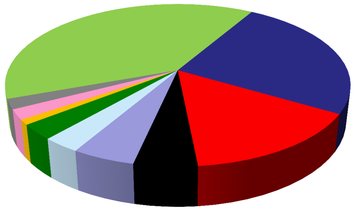
AACR 2012 Abstract 1794

Background

- The genomics revolution has stratified lung adenocarcinoma into a series of molecularly defined diseases characterized by unique genomic alterations

Distribution of somatic genomic alterations identified in lung adenocarcinoma

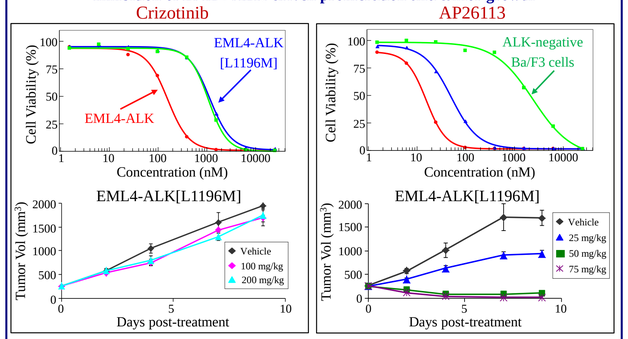


- Clinically effective agents targeting mutant EGFR (erlotinib, gefitinib) and ALK fusions (crizotinib) now exist but in almost all cases resistance inevitably occurs
- Resistance to targeted agents is commonly mutation-based and defines a new disease
- Novel inhibitors that target new molecular drivers of adenocarcinoma or resistance mutations are urgently required to improve clinical outcomes

Results: ALK

AP26113 potently inhibits EML4-ALK and the crizotinib resistant L1196M gatekeeper mutant *in vitro* and *in vivo*

Inhibition of EML4-ALK-driven proliferation and tumor growth

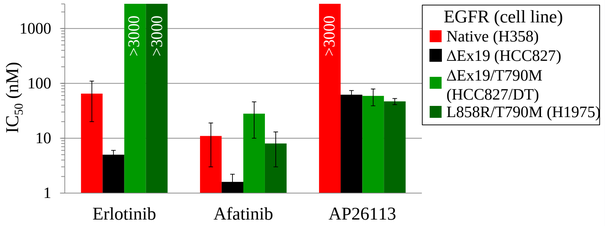


- The cMET/ ALK inhibitor crizotinib is approved for the treatment of ALK+ NSCLC
- AP26113 potently inhibits EML4-ALK and ALK mutants including L1196M (Zhang *et al*. 101st AACR Meeting, 2010, Abstract LB298).

Results: EGFR

AP26113 potently inhibits phosphorylation of mutant but not native EGFR in NSCLC cell lines

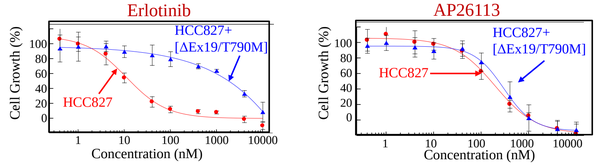
Inhibition of EGFR phosphorylation assessed in a panel of NSCLC lines by western blot



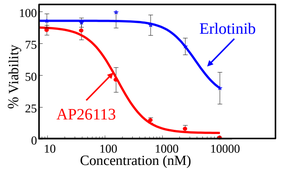
- Erlotinib is efficacious in patients harboring EGFR activating mutations but acquired resistance can occur through second site mutation of T790 (Pao *et al.*, PLoS Med, 2005)
- Inhibition of native EGFR is associated skin rash and diarrhea
- AP26113 potently inhibited all mutant forms of EGFR but was inactive vs native EGFR

AP26113 effectively targets both activating and resistance EGFR mutations *in vitro*

Inhibition of proliferation in HCC827 & HCC827+[ΔEx19/T790M] cells



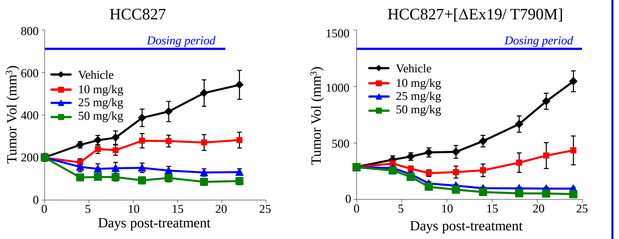
Inhibition of Ba/F3+[ΔEx19/T790M] cells



- Erlotinib selectively inhibits proliferation of cells expressing EGFR ΔEx19
- AP26113 inhibits proliferation driven by either ΔEx19 or ΔEx19/ T790M

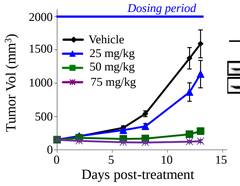
AP26113 regresses multiple EGFR-driven *in vivo* models harboring the T790M gatekeeper mutation

AP26113 mediated inhibition of HCC827 and HCC827+[ΔEx19/ T790M] tumor growth

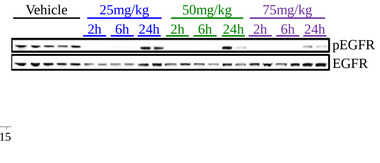


Inhibition of NIH3T3+[ΔEx19/ T790M] tumor growth & signaling

AP26113 Efficacy (Once daily oral dosing)

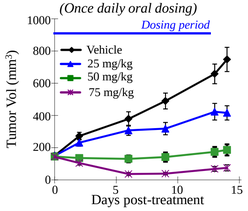


AP26113 Pharmacodynamics (Single oral dose)

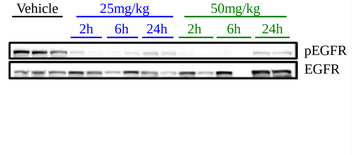


Inhibition of Ba/F3+[ΔEx19/ T790M] tumor growth & signaling

AP26113 Efficacy (Once daily oral dosing)



AP26113 Pharmacodynamics (Single oral dose)

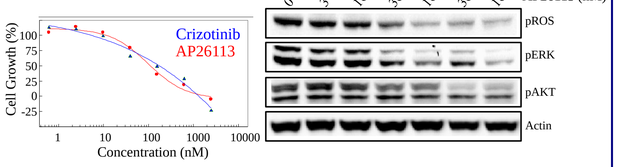


- Once daily, oral dosing of AP26113 induces regressions in tumors driven by either EGFR ΔEx19 or EGFR ΔEx19/ T790M
- A single dose of AP26113 effectively inhibits tumor EGFR activity in a dose dependent manner in multiple ΔEx19/ T790M *in vivo* models

Results: ROS

AP26113 potently inhibits SLC34A2-ROS-driven signaling and proliferation in a dose dependent manner

Inhibition of HCC78 proliferation and signaling by AP26113



- HCC78 NSCLC cells have previously been demonstrated to possess an activating ROS fusion (SLC34A2-ROS) that is sensitive to crizotinib
- AP26113 potently inhibits ROS-driven signaling and proliferation in a dose-dependent manner
- Further work to explore the impact of AP26113 upon ROS-driven tumor growth is currently underway

Conclusions

- AP26113 is a potent ALK/ EGFR inhibitor with the unique ability to inhibit clinically relevant gatekeeper mutants
  - AP26113 potently inhibits ALK [L1196M]
  - AP26113 effectively inhibits EGFR [T790M]
- AP26113 potently inhibits mutant EGFR but not native EGFR
  - Potent inhibition of native EGFR by next-generation EGFR agents, such as afatinib, is associated with EGFR-related toxicities (e.g. skin rash and diarrhea)
- AP26113 induces regressions in EGFR & ALK driven *in vivo* models
- AP26113 demonstrates promising *in vitro* activity versus the recently identified SLC34A2-ROS fusion
- AP26113 may have clinical utility in multiple NSCLC sub-sets and is currently in Phase 1/ 2 testing (ClinicalTrials.gov: NCT01449461)

Potential clinical utility of AP26113 in lung adenocarcinoma