Abstract #:036

Discovery of IACS-13909, an allosteric SHP2 inhibitor that overcomes multiple mechanisms underlying osimertinib resistance

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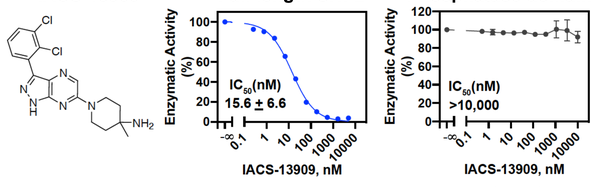
Introduction

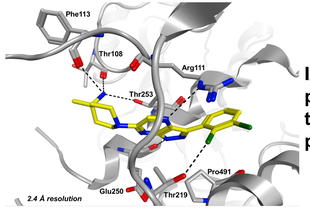
- Osimertinib, a third generation EGFR inhibitor, is a front-line therapy for *EGFR* mutated non-small lung cancer (NSCLC). The long-term effectiveness of osimertinib is limited by acquired resistance.
- Clinically identified resistance mechanisms include EGFR-dependent mechanisms such as mutations on EGFR that preclude drug binding (e.g., EGFR C797S), and EGFR-independent activation of the MAPK pathway (e.g., activation of alternate RTKs)[1]. It has also been noted that frequently a tumor from a single patient harbors more than one resistance mechanism[2].
- Src homology 2 domain-containing phosphatase (SHP2) is a phosphatase that mediates the signaling of multiple RTKs and is required for full activation of the MAPK pathway[3,4].
- Since SHP2 is required for full activation of the MAPK pathway downstream of multiple RTKs, we hypothesize that a SHP2 inhibitor may target both EGFR-dependent and EGFR-independent mechanisms for osimertinib resistance in *EGFR*^{mut} NSCLC.

IACS-13909 is a potent allosteric inhibitor of SHP2



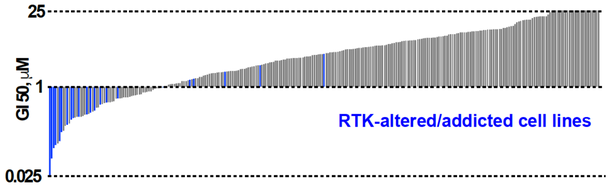
In enzymatic assays, IACS-13909 suppresses activity of the full-length SHP2, but not the truncated phosphatase domain.

Co-crystal structure of IACS-13909:human SHP2



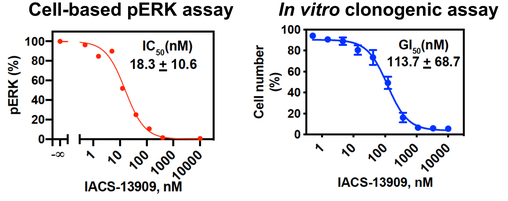
IACS-13909 binds to an allosteric pocket at the interface between the SH2 domains and phosphatase domain of SHP2.

In vitro anti-proliferative effect of IACS-13909 across a panel of human cancer cell lines

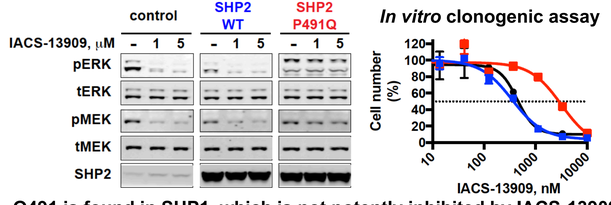


RTK-driven cell lines are sensitive to SHP2 inhibition by IACS-13909.

In vitro activity of IACS-13909 in *EGFR*^{amp} KYSE-520 cells



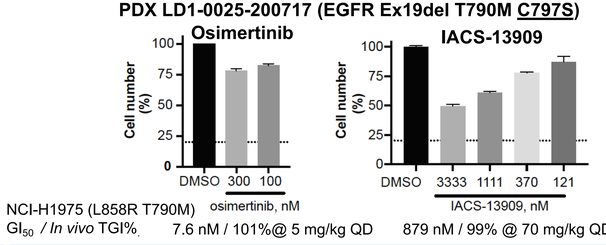
On-target activity of IACS-13909 in KYSE-520 cells



Q491 is found in SHP1, which is not potently inhibited by IACS-13909.

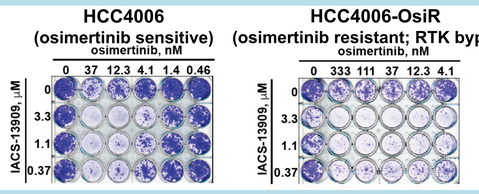
Overexpression of SHP2 P491Q that abrogates IACS-13909 binding reduces suppression of MAPK signaling and inhibition of cell proliferation.

IACS-13909 suppresses proliferation of NSCLC PDX harboring EGFR on-target resistance mutation *ex vivo*

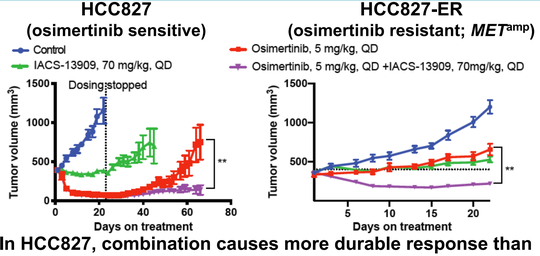


	Osimertinib	IACS-13909
NCI-H1975 (L858R T790M)		
GI_{50} / *In vivo* TGI%	7.6 nM / 101%@ 5 mg/kg QD	879 nM / 99% @ 70 mg/kg QD

In vitro anti-proliferative synergistic effect of IACS-13909 and osimertinib

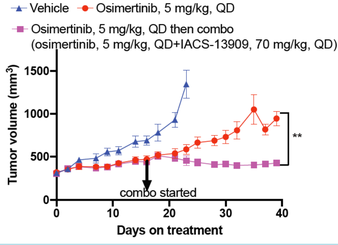


In vivo anti-tumor efficacy of IACS-13909+osimertinib in osimertinib-sensitive and -resistant models



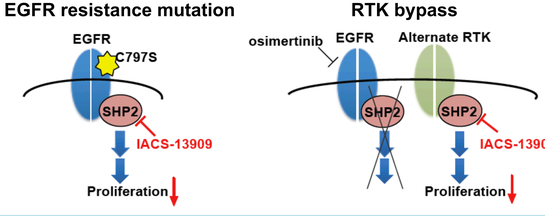
- **In HCC827, combination causes more durable response than osimertinib single agent.**
- **In HCC827-ER xenograft model with an EGFR-independent resistance mechanism (e.g., RTK bypass), IACS-13909 re-sensitizes the tumor to osimertinib treatment.**

HCC827-ER tumors that progress on osimertinib treatment remain sensitive to combination treatment



Summary

- MD Anderson and Navire pharma have developed IACS-13909, a potent and selective allosteric inhibitor of SHP2
- IACS-13909 potently suppresses the proliferation of cell lines driven by a broad range of RTKs
- IACS-13909 inhibits both EGFR-dependent and EGFR-independent resistance mechanisms towards osimertinib
- Navire is currently taking its clinical candidate SHP2 inhibitor through IND-enabling studies.



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A copy of the poster can be found at:
www.navirepharma.com