AACR: RAS Oncogenesis and Therapeutics
March 5th-8th, 2026

AB801, a Potent and Selective Clinical-Stage AXL Inhibitor, Enhances the Anti-Tumor Efficacy and Duration of Response of KRAS Inhibitors

Susan L. Paprcka, Jhansi L. Leslie, Logan Chinn, Jenna Pappalardo, Tiffany Huang, Umida Djakbarova, Dillon H. Miles, Ruben Flores, Gonzalo Barajas, Matt Wright, and Ester Fernández-Salas

ARCUS BIOSCIENCES
Hayward, CA, USA

AXL Signaling Diminishes Responses to RAS Inhibitors via Activation of the PI3K/AKT Survival Pathway

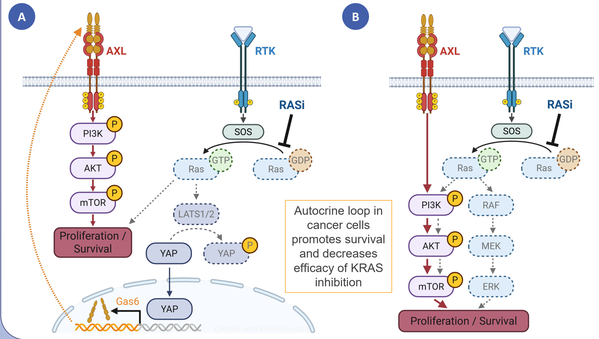


Figure 1 AXL signaling has been identified as a key survival pathway resulting in diminished sensitivity to clinical RAS inhibitors (pan-RAS ON[1] and KRAS^{G12C} OFF[2]) **A.** RAS inhibition results in decreased phosphorylation of YAP,[2] which can translocate to the nucleus and mediate transcription of Gas6, the ligand for AXL. Increased AXL signaling activates an autocrine loop that bypasses RAS pathway inhibition. **B.** AXL signaling diminishes responses to RAS inhibition by maintaining PI3K/AKT signaling[3,4], leading to cancer cell survival and proliferation despite RAS inhibition.

AXL and GAS6 Expression is High in KRASmut Tumors, Including PDAC and NSCLC

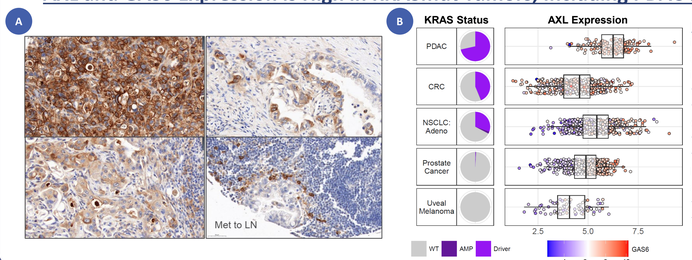
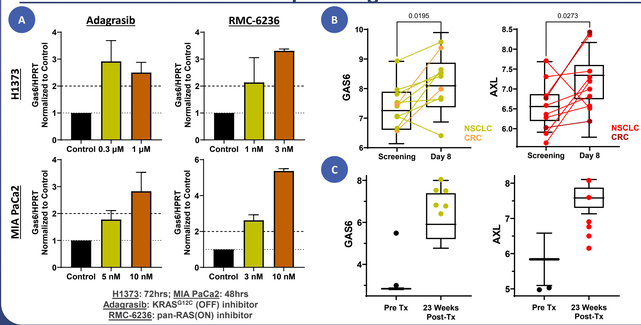


Figure 2 A. AXL Protein is highly expressed on cancer, stromal and immune cells within the TME in PDAC tumors. AXL expression was determined using the same antibody as the Ventana CDx assay. **B.** AXL and GAS6 mRNA are highly expressed in the majority of PDAC tumors and a subset of NSCLC.

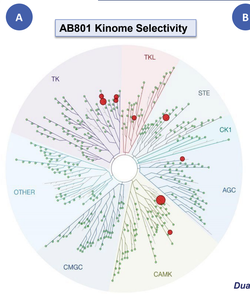
RAS Inhibition Results in Rapid & Significant Increases in AXL and Its Ligand GAS6



H1373: 72hrs; MIA PaCa2: 48hrs
Adagrasib: KRAS^{G12C} (OFF) inhibitor
RMC-6236: pan-RAS(ON) inhibitor

Figure 3 A. Gas6 mRNA rapidly increases upon treatment with Adagrasib or RMC-6236. **B.** AXL and GAS6 expression were evident in screening samples and significantly increased following KRAS inhibition with Adagrasib in NSCLC and CRC patient biopsies from the KRYSTAL-1 trial[5]. P values were calculated using paired Wilcoxon tests. **C**. Lymph node metastases from a single patient were collected prior to treatment and 23 weeks post-treatment following progression to Sotorasib[6]. AXL and GAS6 expression were substantially increased in all metastases with no additional KRAS or reactivating MAPK mutations observed.

AB801 is the Only Phase-2 Ready Potent and Selective AXL Inhibitor



B

Kinase	K_d	$K_{d,kin}$ / $K_{d,AXL}$
AXL	0.093	1
DRAK1	4.4	47
HPK1	26	280
TRKA	31	330

Assay		
Biochemical	hAXL HTRF IC_{50} (700 µM ATP)	1.75 nM
	AXL K_i	0.024 nM
	Fold selectivity over MER/TYRO3 (enzyme K_i over AXL K_i)	860x / 1400x
Cell	pAXL ELISA IC_{50} (100% serum)	68 nM

Dual AXL/MERTK inhibition resulted in ocular toxicities in patients

C

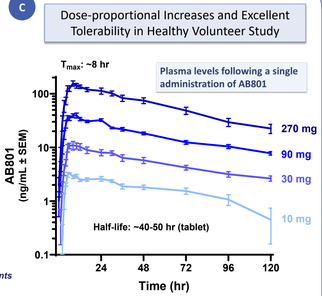


Figure 4 A. Selectivity of AB801 evaluated at Eurofins using KINOMEscan™ screening platform. AB801 was tested against 403 non-mutant kinases at 100 nM[7]. **B.** AB801 only hits one other kinase within a 200-fold window of AXL. AB801 is very potent in biochemical and cellular assays in physiological conditions (100% serum)[7]. **C.** AB801 is well-tolerated and demonstrates dose-proportional increases in exposure and a long half-life in first in human study in healthy volunteers (ARC-26).

Deeper Tumor Control and Duration of Response by Combining AB801 and Adagrasib in Human KRAS^{G12C} NSCLC Xenografts

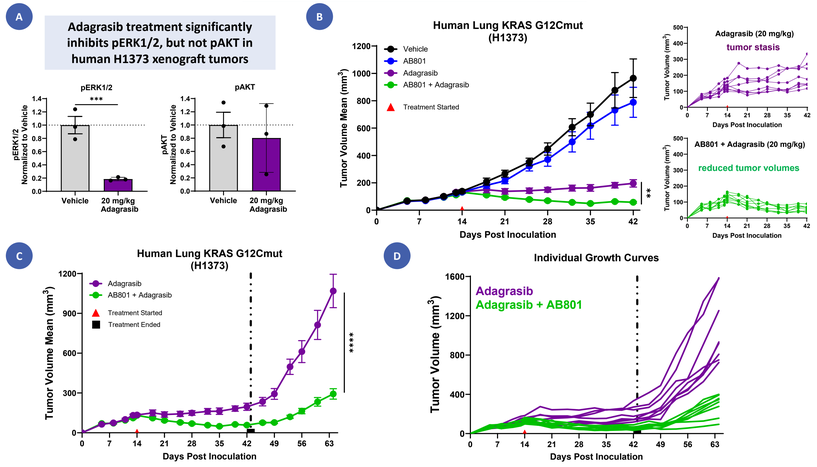


Figure 5 A. Mice bearing H1373 Human KRAS^{G12C} NSCLC Xenografts were treated with 20 mg/kg adagrasib and tumors were collected. Levels of pERK1/2 and pAKT were evaluated by western blot. Significance was determined by lognormal t tests ***<0.001. **B.** H1373 xenografts were treated with AB801 (30 mg/kg, BID, PO) or adagrasib (20 mg/kg, QD, PO) as single agents or in combination. Single agent adagrasib resulted in tumor stasis, whereas AB801 combined with adagrasib resulted in significant tumor growth reduction. Significance was determined by two-way ANOVA **< 0.01. **C.** Treatment of both AB801 and adagrasib was stopped at day 43 and tumor growth continued to be monitored. In contrast to tumors treated with single agent adagrasib, those receiving a combination of AB801 and adagrasib exhibited significantly reduced tumor regrowth. **D.** Overlaid individual growth curves. Significance was determined by two-way ANOVA ****<0.0001.

AB801 Combined with RAS Inhibition Reduces Tumor Growth and Increases Survival

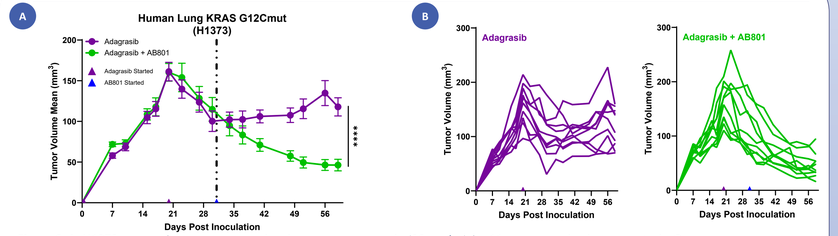


Figure 6 A. H1373 xenografts were treated with single-agent adagrasib (20 mg/kg) for 11 days, resulting in tumor stasis. One group was then treated with AB801 in combination with adagrasib. AB801 administered after single-agent adagrasib converted tumor stasis into reduced tumor growth. **B.** Individual growth curves. Significance was determined by two-way ANOVA **< 0.01, ****<0.0001

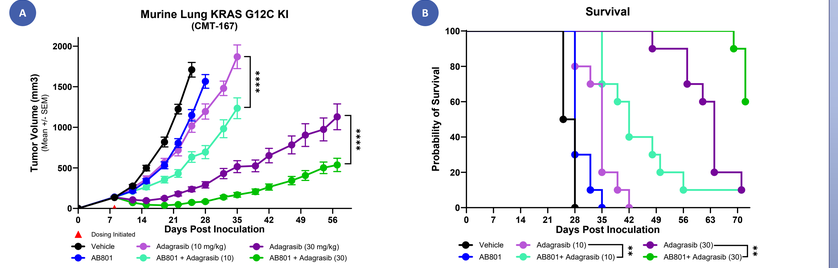
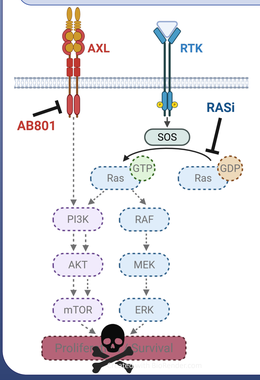


Figure 7 A. AB801 significantly inhibits tumor growth in combination with adagrasib in a syngeneic model. Significance was determined by two-way ANOVA ****<0.0001. **B.** AB801 in combination with adagrasib significantly increases survival. All remaining tumors were smaller than 1250 mm^3 when study was terminated on day 71. Significance was determined by Logrank (Mantel-Cox) test **< 0.01.

Conclusions



- AXL signaling reduces the efficacy of KRAS inhibitors via activation of the PI3K/AKT survival pathway
- In the clinic, KRAS inhibition further increases levels of AXL and Gas6, creating a feed-forward loop of increased AXL signaling to enable cancer cell survival
- AB801 combined with KRAS inhibition results in significant inhibition of tumor growth and increased survival in vivo
- AB801 is the only clinical-stage inhibitor with the appropriate potency, selectivity, and pharmacokinetics profile to fully target AXL
- Combination of KRAS and AXL inhibition will produce deeper and longer responses in patients with driver KRAS mutations

References

1. Der C.J., et al. KRAS Inhibitor Resistance Mechanisms and Combinations. *European Journal of Cancer* 211S1 (2024) S1–S188
2. Morimoto K., et al. AXL signal mediates adaptive resistance to KRAS G12C inhibitors in KRAS G12C-mutant tumor cells. *Cancer Letters* (2024)
3. Fridell Y-W., et al. Differential Activation of the RAS/Extracellular-Signal-Regulated Protein Kinase Pathway is Responsible for the Biological Consequences Induced by the Axl Receptor Tyrosine Kinase. *Molecular and Cellular Biology* (1996)
4. Taniguchi H., et al. AXL confers intrinsic resistance to osimertinib and advances the emergence of tolerant cells. *Nature Communication* (2019)
5. Klomp J A., et al., Defining the KRAS- and ERK-dependent transcriptome in KRAS-mutant cancers. *Science* (2024)
6. Tsai Y S., et al., Rapid idiosyncratic mechanisms of clinical resistance to KRAS G12C inhibition. *Journal of Clinical Investigation* (2022)
7. Miles D H., et al. Discovery of AB801, a Potent and Selective Inhibitor of AXL Receptor Tyrosine Kinase for Use in Cancer Therapy. *Journal of Medicinal Chemistry* (2025)