AACR-NCI-EORTC
Annual Meeting
Oct 23rd, 2025

AXL Inhibitor AB801 Increases the Anti-Tumor Efficacy of KRAS Inhibition

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Background

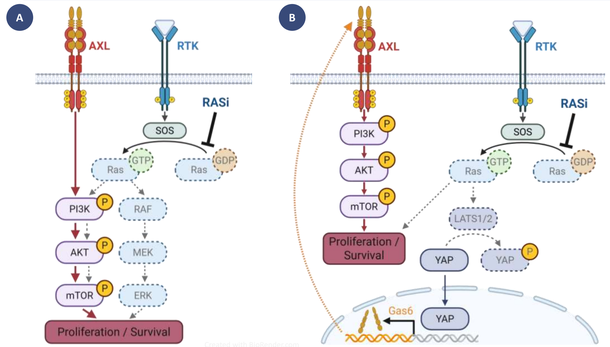


Figure 1. A. AXL signaling mediates resistance to RAS inhibition by maintaining PI3K/AKT signaling[1,2], leading to cancer cell survival and proliferation despite RAS inhibition. **B.** Inhibition of RAS results in the lack of YAP phosphorylation[3]. Unphosphorylated YAP translocates the nucleus where it mediates transcription of Gas6. Increased levels of Gas6 result in increased AXL signaling, resulting in a feed-forward loop of AXL activation and signaling that bypasses RAS pathway inhibition.

Clinical Inhibition of RAS Increases Both AXL and GAS6 Expression in Tumors

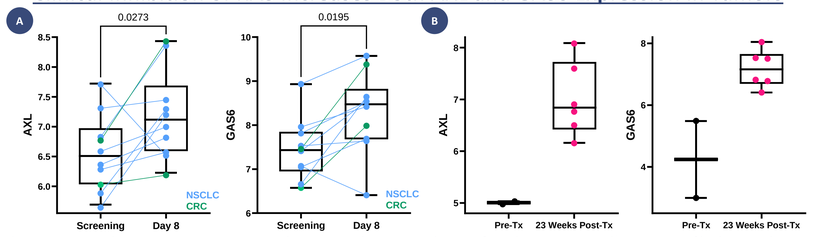


Figure 2. A. AXL and GAS6 expression were assessed in NSCLC and CRC patient biopsies from the KRYSTAL-1 trial[4]. Expression of both AXL and GAS6 were evident in screening samples and significantly increased following KRAS inhibition with adagrasib. P values were calculated using paired Wilcoxon tests. **B.** Lymph node metastases from a single patient were collected prior to treatment and 23 weeks post-treatment following progression to sotorasib treatment[5]. AXL and GAS6 expression were substantially increased in all metastases evaluated with no additional KRAS or reactivating MAPK mutations observed.

AXL Inhibition Prevents Bypass RAS Pathway Signaling

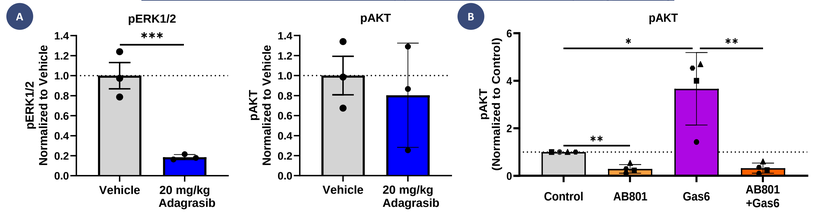


Figure 3. A. Adagrasib treatment significantly inhibits phosphorylation of ERK1/2, but not AKT in human H1373 xenograft tumors. **B.** Inhibition of AXL by AB801 significantly reduces both basal and Gas6-induced AKT phosphorylation in H1299 cancer cells. Significance was determined by lognormal t tests *<0.05, **< 0.01, ***<0.001.

AB801 Combined with RAS Inhibition Significantly Increases Tumor Control

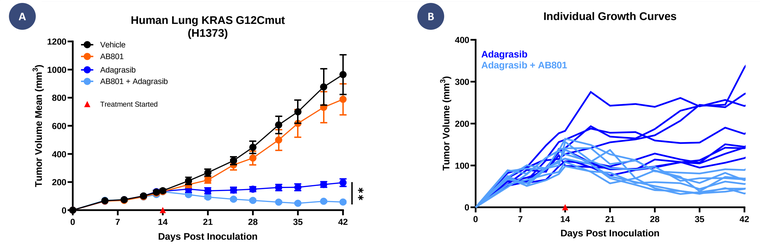


Figure 4. A. H1373 xenografts were treated with AB801 (30 mg/kg, BID, PO) or adagrasib (20 mg/kg, QD, PO) as single agents or in combination. Single agent adagrasib resulted in tumor stasis, whereas AB801 combined with adagrasib resulted in significant tumor growth reduction. **B.** Overlaid individual growth curves demonstrate consistent results among mice in each treatment group. Significance was determined by two-way ANOVA **< 0.01

Tumor Control is More Durable when RAS Inhibition is Combined with AB801

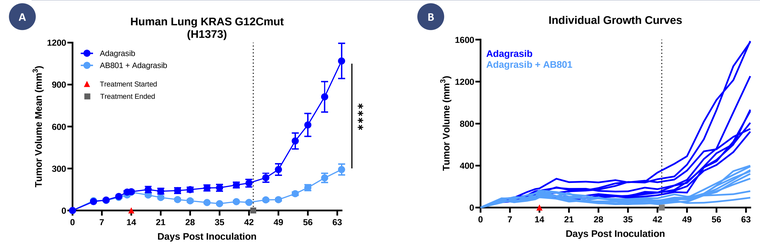


Figure 5. A. Treatment of both AB801 and adagrasib was stopped at day 43 and tumor growth continued to be monitored. In contrast to tumors treated with single agent adagrasib, those receiving a combination of AB801 and adagrasib exhibited significantly reduced tumor regrowth. **B.** Overlaid individual growth curves demonstrate consistent results among mice in each treatment group. Significance was determined by two-way ANOVA ****<0.0001.

Significantly Greater Tumor Control Achieved by Adding AB801 to a Maximally Effective Dose of Adagrasib

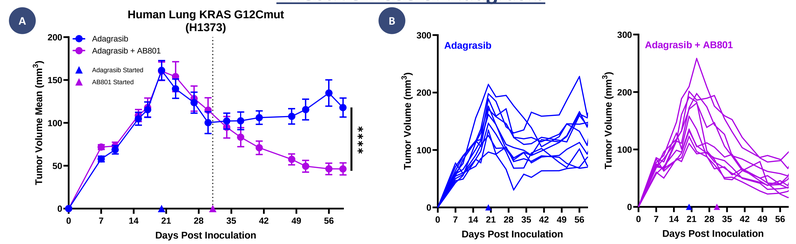


Figure 6. A. H1373 xenografts were treated with single-agent adagrasib (20 mg/kg) for 11 days, resulting in tumor stasis as previously observed. One group was then treated with AB801 in combination with adagrasib, resulting in significant tumor growth reduction compared to adagrasib monotherapy. This demonstrates that AXL inhibition with AB801 is effective even after maximal efficacy is achieved by single agent RAS inhibition. **B.** Individual growth curves. Significance was determined by two-way ANOVA **< 0.01, ****<0.0001

AB801 Combined with RAS Inhibition Significantly Reduces Tumor Growth and Increases Survival

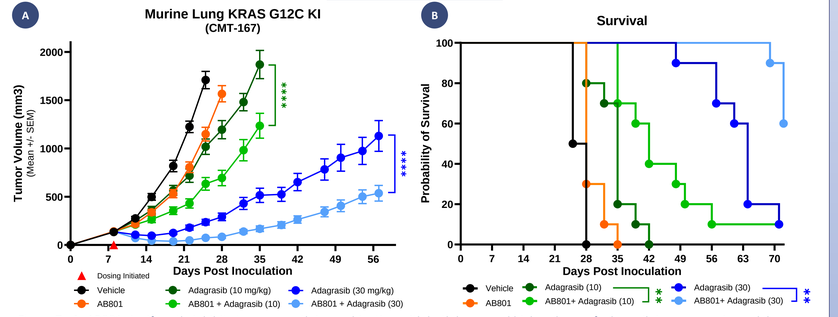
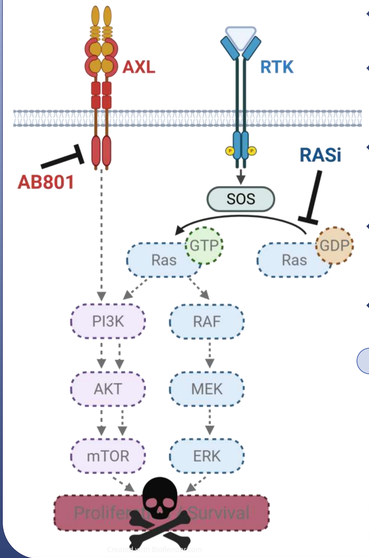


Figure 7. A. AB801 significantly inhibits tumor growth in combination with both lower and higher doses of adagrasib in a syngeneic model. Significance was determined by two-way ANOVA ****<0.0001 **B.** AB801 in combination with adagrasib significantly increases survival with both lower and higher doses of adagrasib. All remaining tumors were smaller than 1250mm^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 RAS inhibitors, leading to decreased efficacy and resistance
- RAS inhibition results in increased levels of Gas6, creating a feed-forward loop of increased AXL signaling and RAS inhibitor resistance[3]
- AB801 is the first drug with the ability to evaluate the effects of maximal, selective AXL inhibition to restore responses to anti-tumor therapies[6]
- AB801 combined with RAS inhibition results in significant inhibition of tumor growth and increased survival in vivo
- There is strong scientific evidence supporting the clinical combination of AB801 and RAS inhibition

References

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