AB801, a Potent and Highly Selective Clinical Stage AXL Inhibitor, Sensitizes Tumors to Standard of Care Therapies

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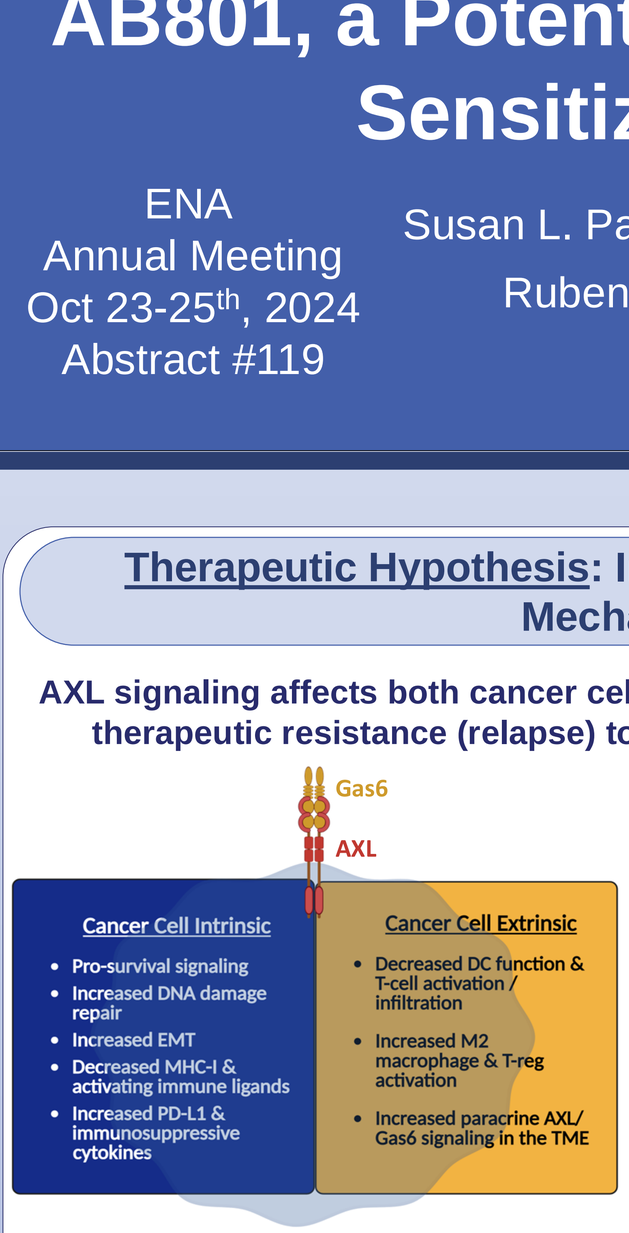
Therapeutic Hypothesis: Inhibiting AXL Signaling Will Overcome Multiple Mechanisms of Drug-Resistance

AXL signaling affects both cancer cells and the TME mediating therapeutic resistance (relapse) to multiple therapeutics



- **Targeted therapy**
  - Upregulation of AXL expression
  - Homo- and hetero-dimerization with TAM receptors and RTKs
- **Chemotherapy**
  - Increases DNA repair
  - Increases anti-apoptotic and survival signaling
- **Immunotherapy**
  - Decreases antigen presentation
  - Secretion of immunosuppressive chemokines

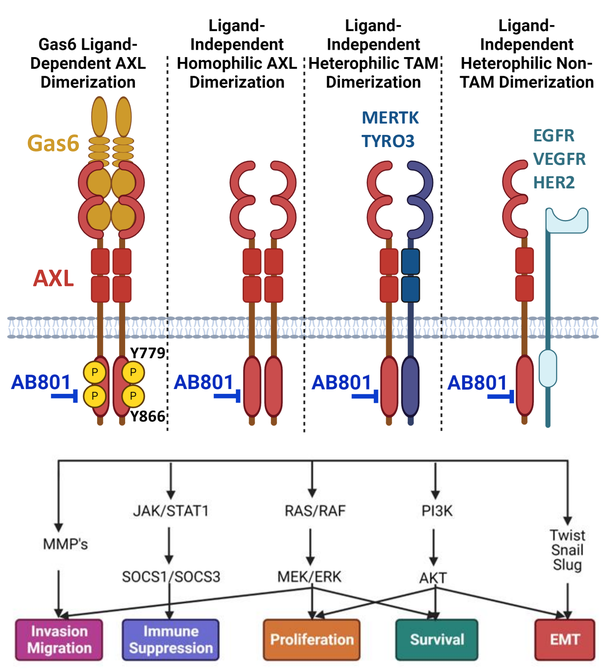


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Figure 1: AXL signaling results in drug resistance and attenuated immune responses mediated though both cancer cell intrinsic and extrinsic biology. Activation of AXL can occur in a ligand-dependent as well as ligand-independent manner and initiates signaling cascades promoting cancer cell proliferation, survival, migration, EMT and an immunosuppressive microenvironment.

AB801 Inhibits Ligand-Dependent and Ligand-Independent AXL Signaling

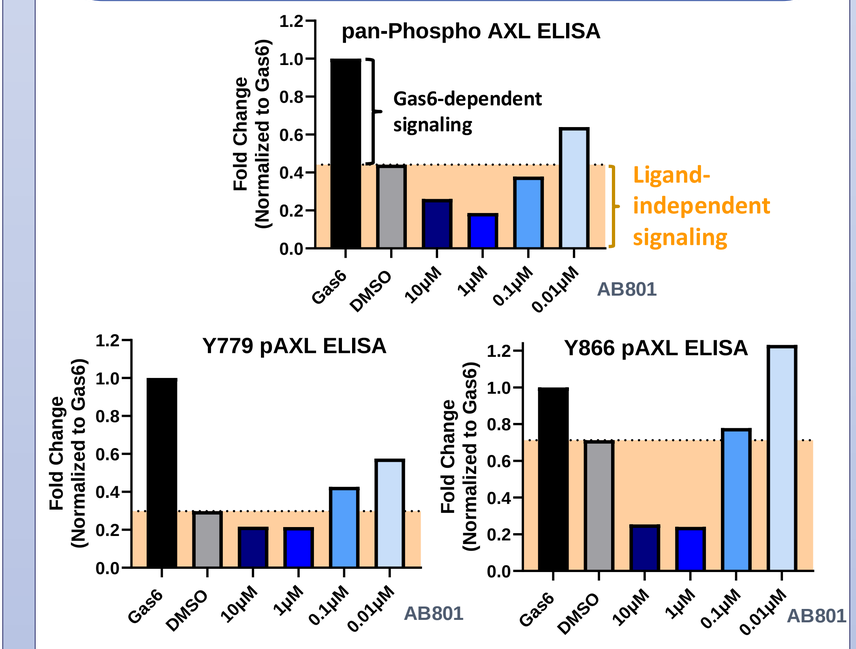
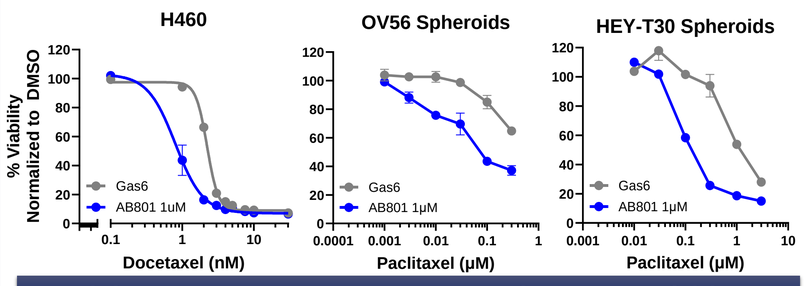


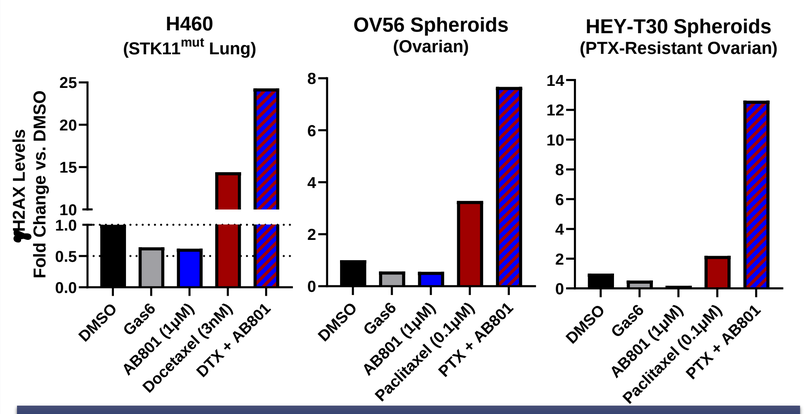
Figure 2: Proprietary phospho-AXL specific antibodies demonstrate that AB801 inhibits the phosphorylation of key signaling residues in the AXL cytoplasmic tail

AB801 Restores Sensitivity to Chemotherapy

(A) AB801 Increases Chemosensitivity to Taxane Chemotherapies in Human Cancer Cells



(B) AB801 Increases DNA Damage (γH2AX Levels) in Combination with Chemotherapy



(C) AB801 Combined with Paclitaxel Demonstrates Tumor Growth Inhibition in Paclitaxel-Resistant HEY-T30 Xenografts

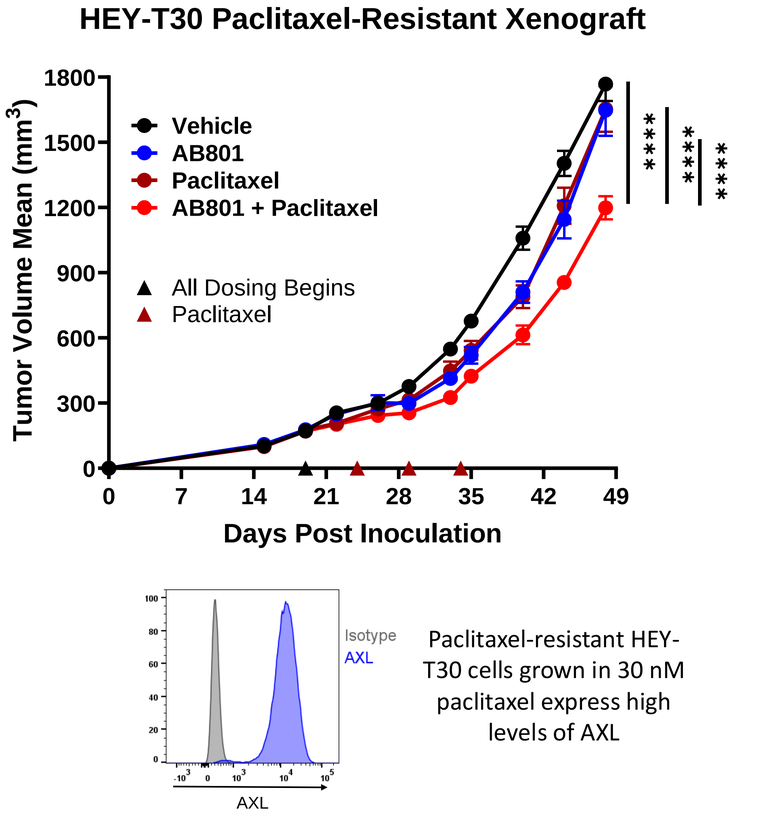
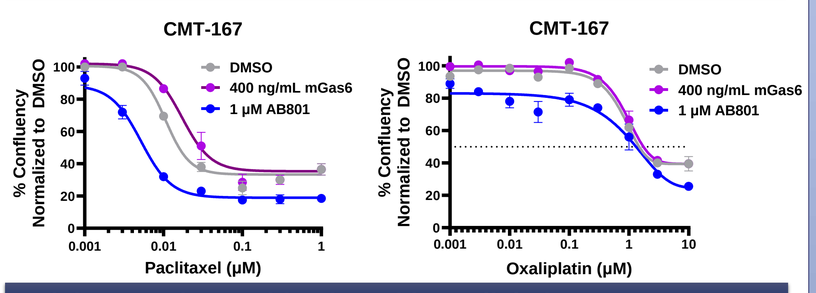


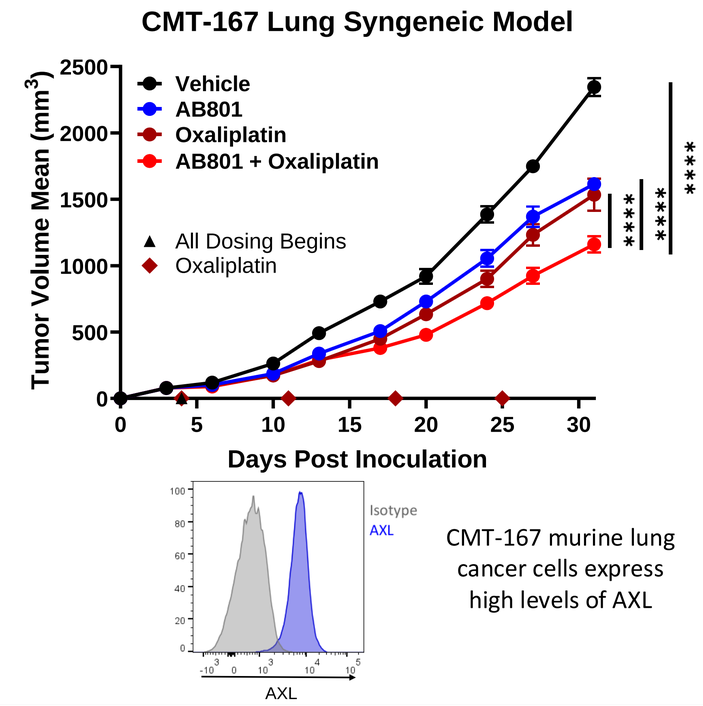
Figure 3: **AB801 increases sensitivity to chemotherapy *in vitro* and *in vivo*** **(A)** AB801 increases sensitivity to taxane chemotherapies in STK11^{mut} NSCLC (H460) ovarian (OV-56) and Paclitaxel-resistant ovarian (HEY-T30) cancer cell lines *in vitro*. **(B)** AB801 in combination with taxane chemotherapies greatly increases DNA damage (levels of γH2AX) *in vitro* (72 h). **(C)** Significant tumor growth inhibition is observed with Paclitaxel in combination with AB801 in the Paclitaxel-resistant HEY-T30 xenograft model. (P<0.001), 2way ANOVA with Tukey's multiple comparisons test.

AB801 Enhances Responses to Immuno-Chemotherapies

(A) AB801 Increases Sensitivity to Chemotherapy in CMT-167 Murine Lung Cancer Cells



(B) AB801 in Combination with Oxaliplatin Demonstrates Significant Tumor Growth Inhibition in CMT-167 Model



(C) AB801 in Combination with Oxaliplatin and αPD1 Demonstrates Significant Efficacy in CMT-167 Model

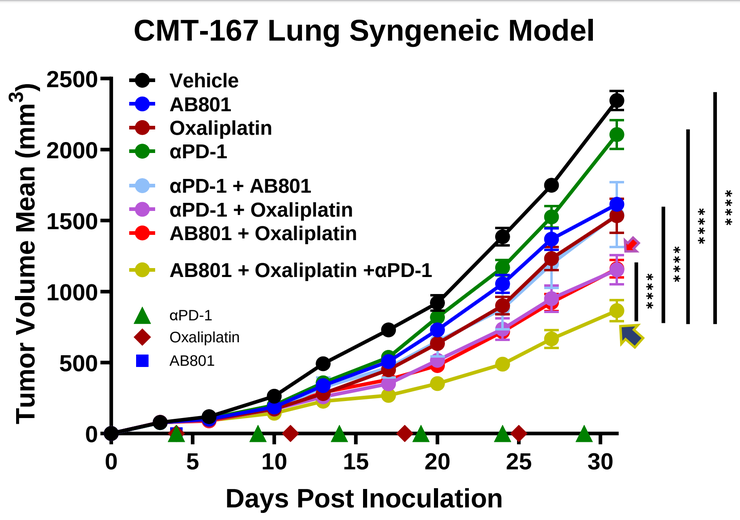
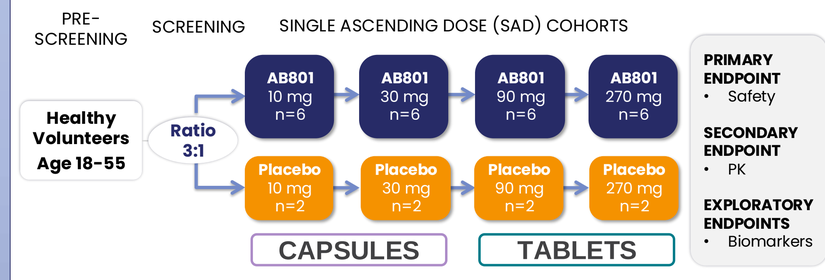


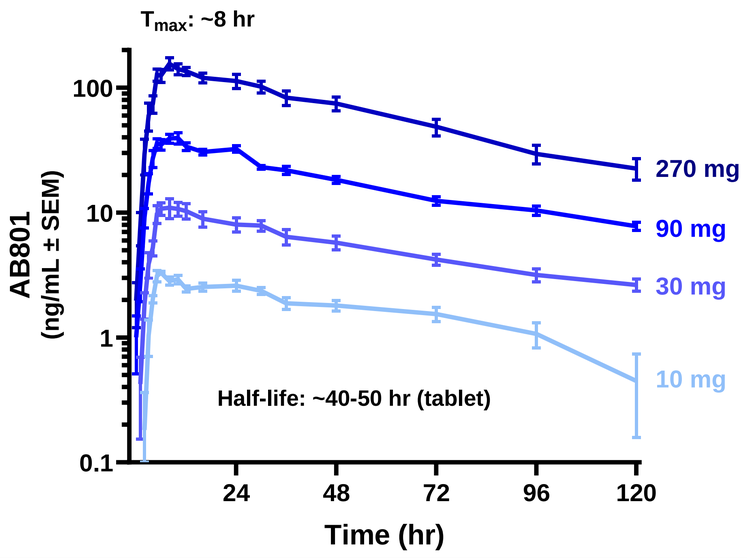
Figure 4: **AB801 increases sensitivity of murine lung CMT-167 cancer cells to standard of care therapies. (A)** AB801 increases sensitivity of CMT-167 cells to taxane and platinum chemotherapies *in vitro*. **(B)** Combination of AB801 and oxaliplatin produced significant tumor growth inhibition compared to either single-agent or vehicle-treated mice. **(C)** Tumor growth inhibition observed with the combination of AB801 and oxaliplatin is comparable to that observed with αPD-1 and oxaliplatin. The triplet combination of AB801, αPD-1 and oxaliplatin demonstrates significant additional benefit compared to either doublet therapy. (P<0.001), 2way ANOVA with Tukey's multiple comparisons test.

AB801 Exposure Increased Dose-Proportionally in a FIH SAD HV Study



Single doses of AB801 up to 270 mg were well tolerated with no safety signals observed in any of the cohorts

AB801 First in Human Study in Healthy Volunteers Demonstrated Dose-Proportional Increases in Exposure



Geometric Mean (CV%) AB801 Plasma PK Parameters

DOSE	$T_{1/2}$† [hr]	T_{max}‡ [hr]	C_{max} [ng/mL]	AUC_{0-120h} [hr*ng/mL]
270 mg (Tablet)	40 (18)	8 (8-12)	153 (27)	7,490 (30)
90 mg (Tablet)	54 (18)	8 (5-10)	40 (23)	2,090 (14)
30 mg (Capsule)	72 (25)	8 (5-10)	12 (34)	614 (30)
10 mg (Capsule)	70 (50)	6 (5-24)	3 (11)	180 (18)

Exposure caps for highest dose: C_{max} = 961 ng/mL, AUC_{0-24}=20700 ng*h/mL
† Reported as estimates due to incomplete elimination
‡ T_{max} reported as median (range)

Conclusions

- **AXL signaling mediates therapeutic resistance via cancer cell intrinsic and immune-mediated mechanisms**
- **AB801 enhances sensitivity to chemotherapy *in vitro* and *in vivo* by increasing DNA damage**
- **Efficacy of AB801 in combination with chemotherapy is further improved with the addition of αPD-1 in the CMT-167 lung model**
- **AB801 is well-tolerated, demonstrates dose-proportional increases in exposure, and a long half-life in healthy volunteers**
- **A Ph1/1b trial evaluating AB801 as a single-agent and in combination with chemotherapy in NSCLC is ongoing and actively enrolling patients (ARC-27; NCT06120075)**