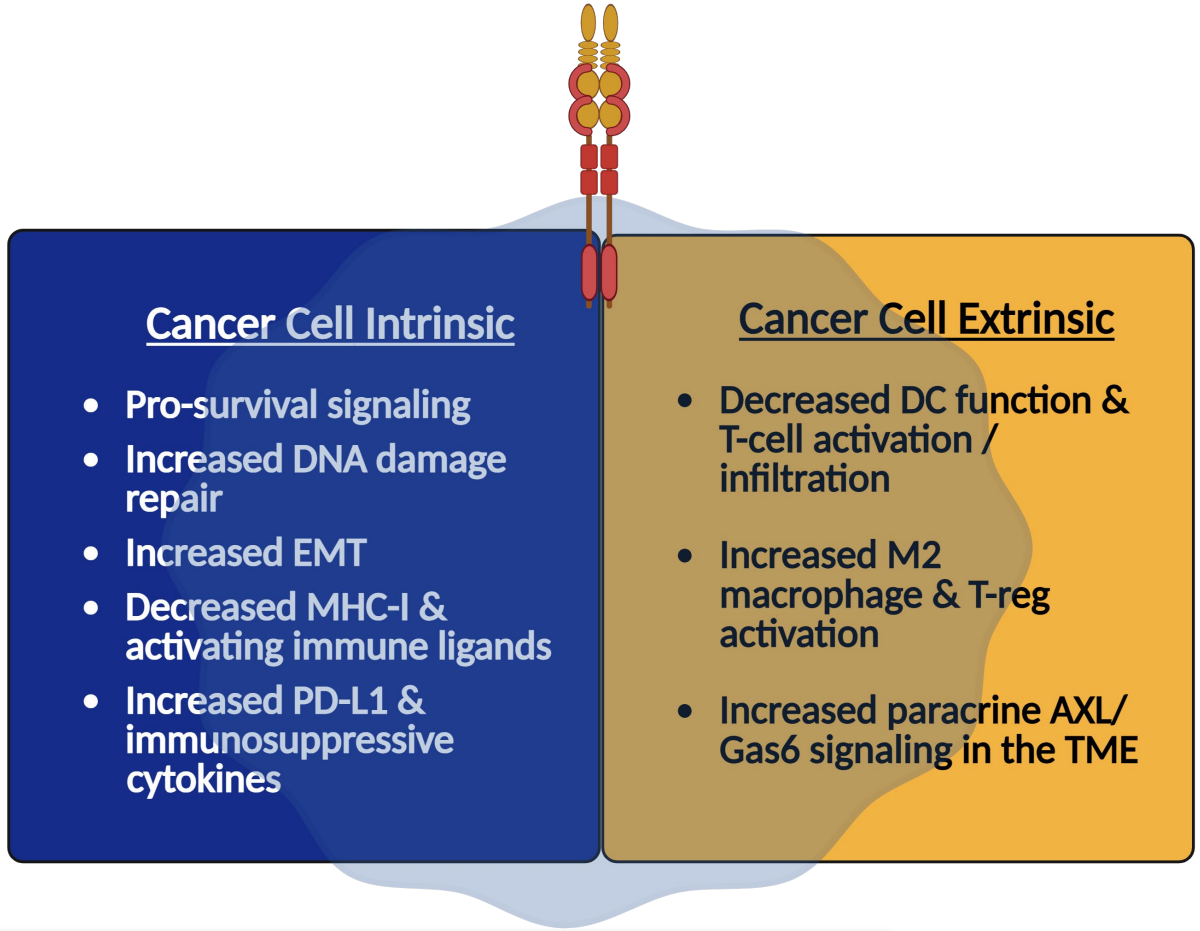
AB801 POTENTLY & SELECTIVELY INHIBITS AXL TO OVERCOME THERAPEUTIC RESISTANCE

Susan Paprcka
Associate Director, Arcus Biosciences

AXL Signaling Is a Common Mechanism of Resistance to Standard of Care Therapies

AXL signaling supports therapeutic resistance (relapse) to multiple therapeutics:

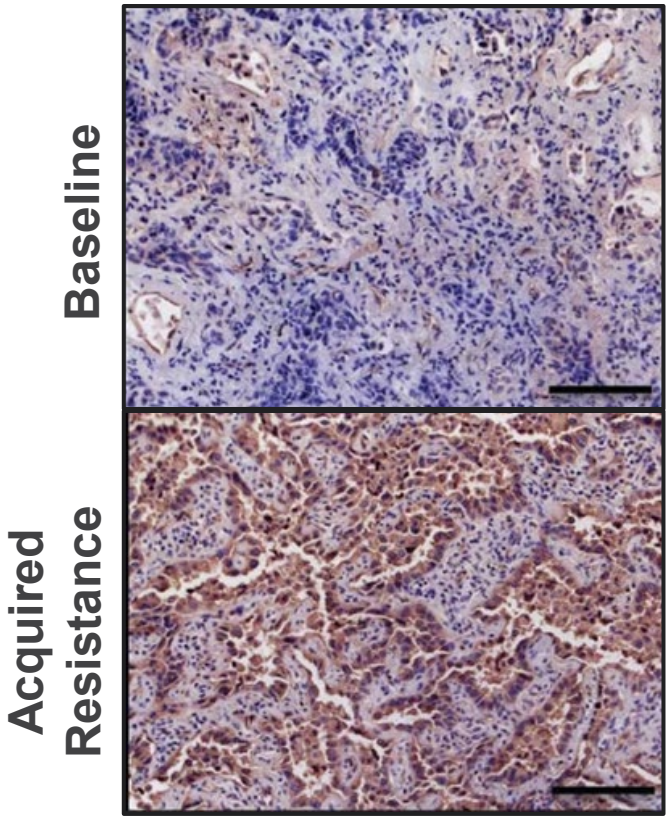
- **Targeted Therapy**
  - Upregulation of AXL expression
  - Homo- and hetero-dimerization with other TAM receptors and RTKs
- **Chemotherapy**
  - Increases DNA repair
  - Increases anti-apoptotic and survival signaling
- **Immunotherapy**
  - Decreases antigen presentation
  - Secretion of immunosuppressive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



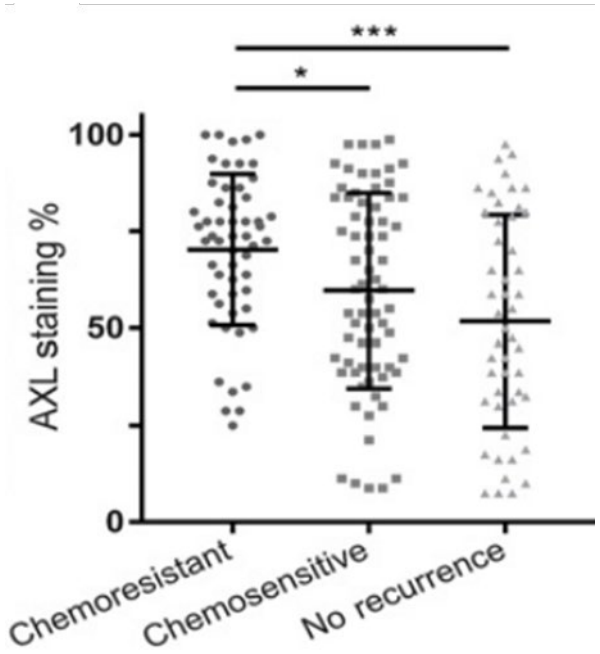
Therapeutic Hypothesis: Inhibiting AXL signaling will overcome multiple mechanisms of drug-resistance

AXL Signaling Supports Therapeutic Resistance in Multiple Indications

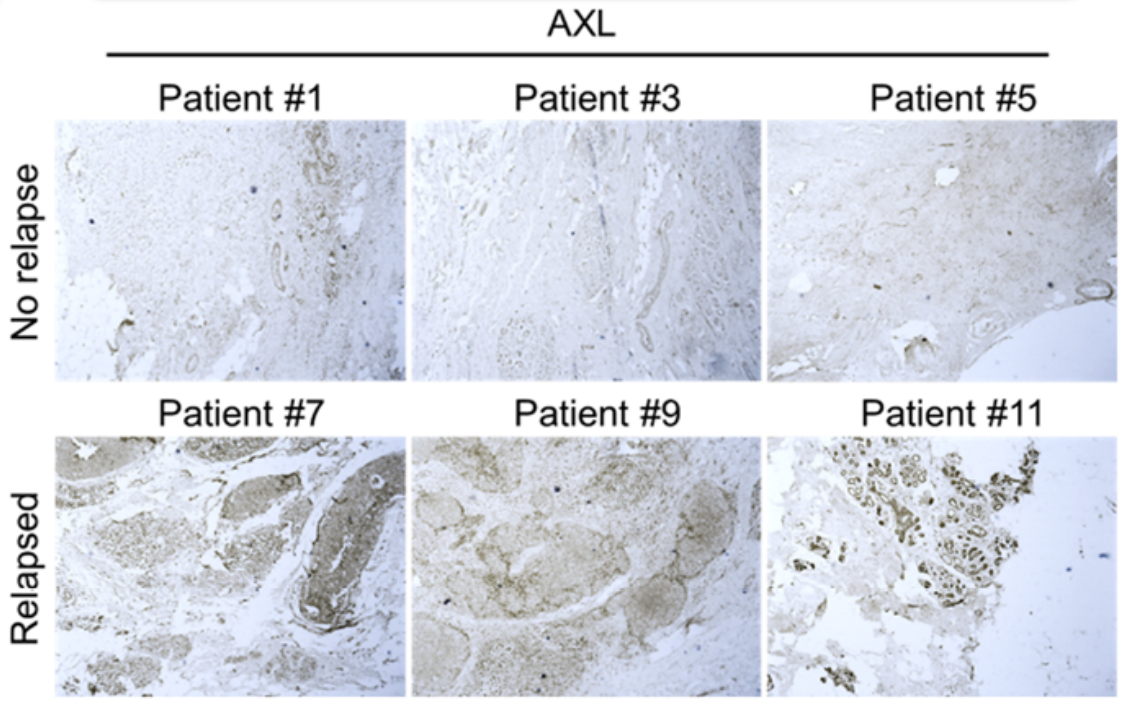
EGFR^{mut} NSCLC (Erlotinib)



Ovarian (Taxanes)



Breast (Chemotherapy)



High expression of AXL results in therapeutic resistance

NSCLC data: Zhang, et al., Nat Genet 2012
Ovarian data: Quinn, et al., Mol Cancer Ther. 2019
Breast data: Aldonza, et al., Scientific Reports. 2021

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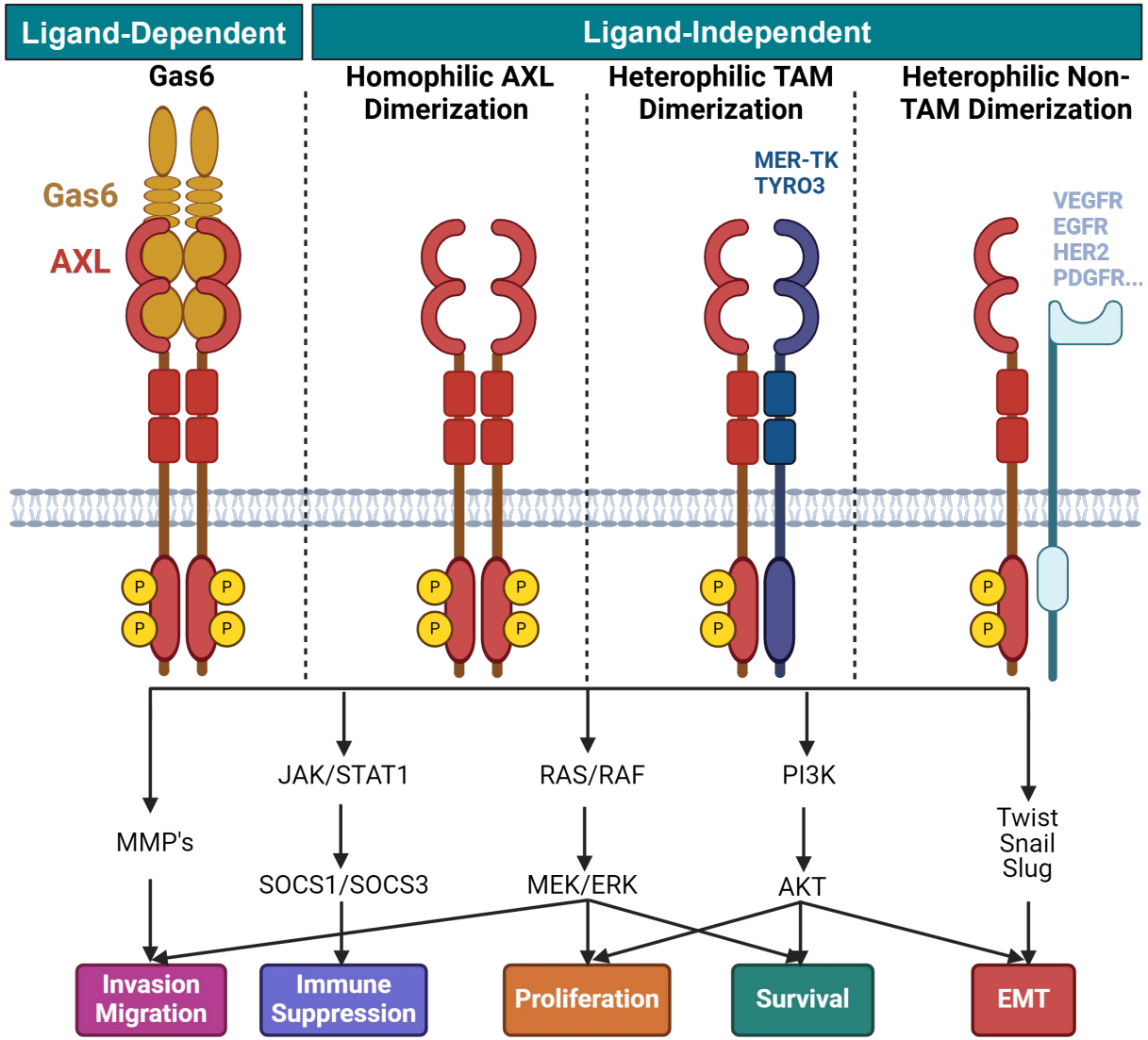
AXL Signaling is Mediated by Both Ligand-Dependent and Ligand-Independent Dimerization



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- **AXL phosphorylation**
  - **Ligand-dependent** via Gas6
  - **Ligand-independent** via AXL homodimerization or heterodimerization with other TAM family members or RTK's
- **AXL signaling promotes cancer cell proliferation, survival, migration, EMT, and an immunosuppressive microenvironment**

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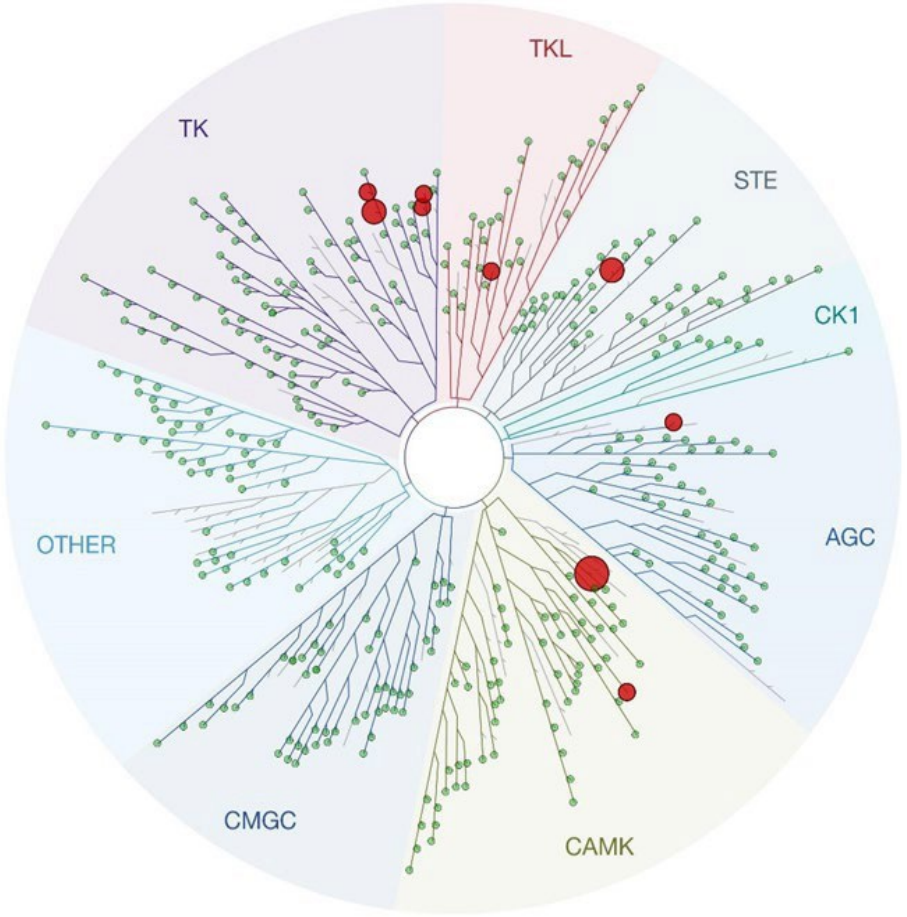
AB801 Is a Highly Potent and Selective AXL Inhibitor

AB801



Selectivity of AB801 evaluated at Eurofins using KINOMEscan™ screening platform; tested against 403 non-mutant kinases @ 100 nM

AB801 only hits one other kinase within a 200-fold window of AXL

AB801 Is Highly Selective for AXL

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

AB801 is a Potent Inhibitor of AXL

	Assay	AB801
Biochemical	hAXL HTRF IC_{50} (700 µM ATP)	1.75 nM
	AXL K_i	0.024 nM
	Fold selectivity over hMERTK / hTYRO3 (enzyme K_i over AXL K_i)	860x / 1400x
Cell Based	pAXL ELISA IC_{50} (100% serum)	68 nM

But Haven't AXL Inhibitors Already Been Used in the Clinic?

- **Several multi-TKIs, like cabozantinib, have been described as AXL inhibitors, however they inhibit many other kinases as or more potently than AXL**
- **Clinically, lack of selectivity results in dose-limiting toxicities (DLTs) making complete inhibition of AXL unachievable**
  - Inhibition of LCK or FLT3 (and associated myelosuppression) by several multi-TKIs limit their ability to combine with standard of care treatments like chemo- and immunotherapy

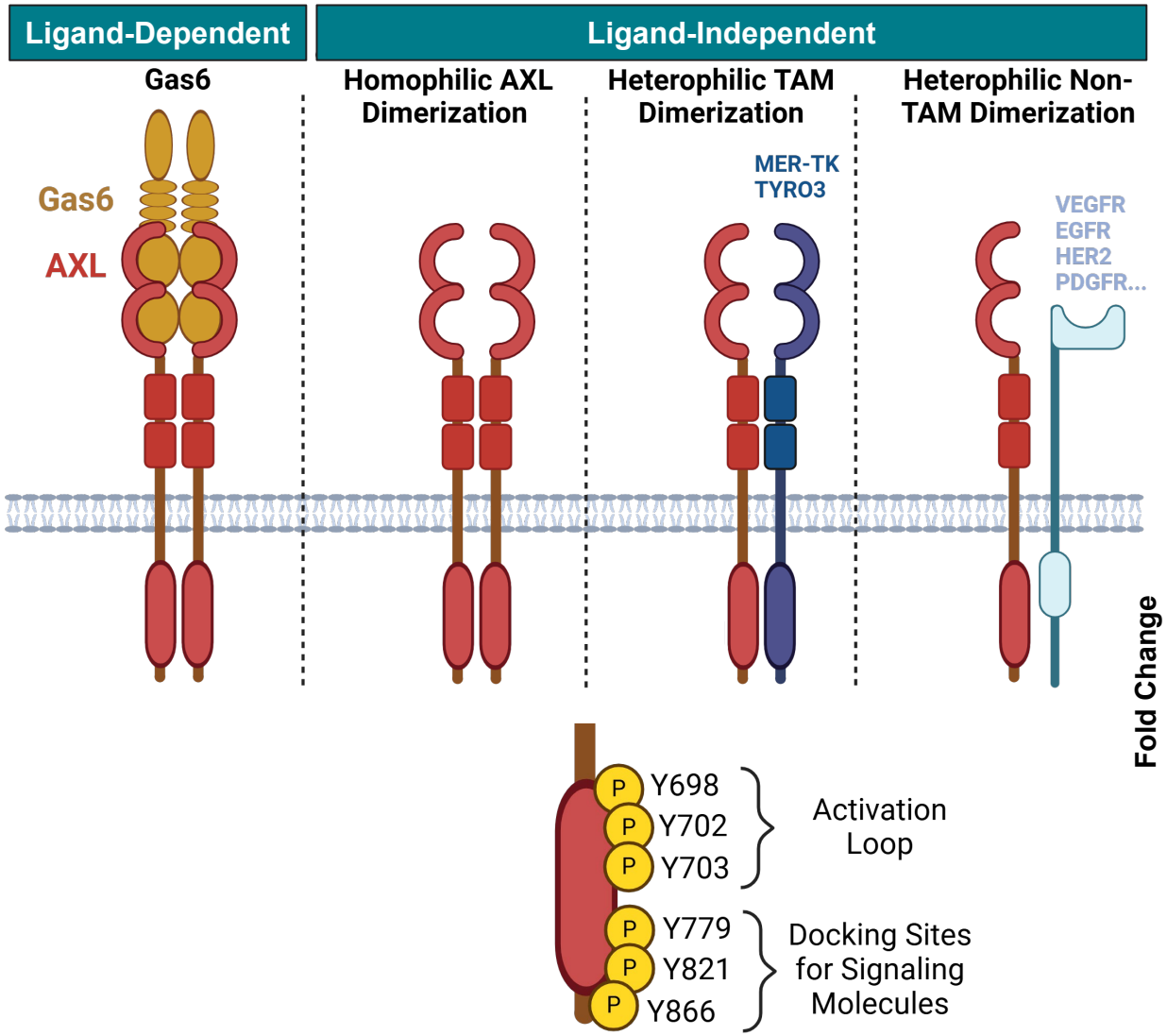
***In vitro* kinase inhibition profile of Cabozantinib**

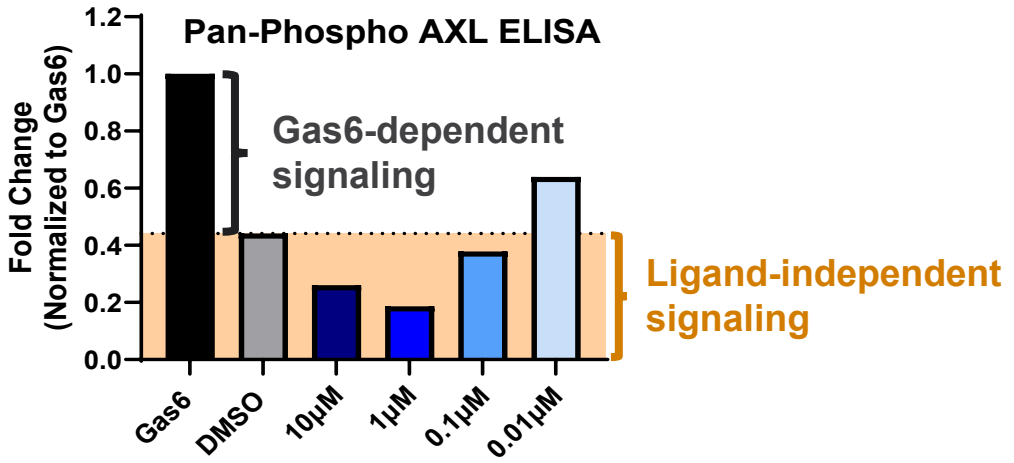
Kinase	$IC_{50} \pm SD$,[a] nmol/L
VEGFR2	0.035 ± 0.01
MET	1.3 ± 1.2
MET (Y1248H)	3.8
MET (D1246N)	11.8
MET (K1262R)	14.6
RET	5.2 ± 4.3
TIE2	14.3 ± 1.1
AXL	7
FLT3	11.3 ± 1.8
KIT	4.6 ± 0.5
RON	124 ± 1.2

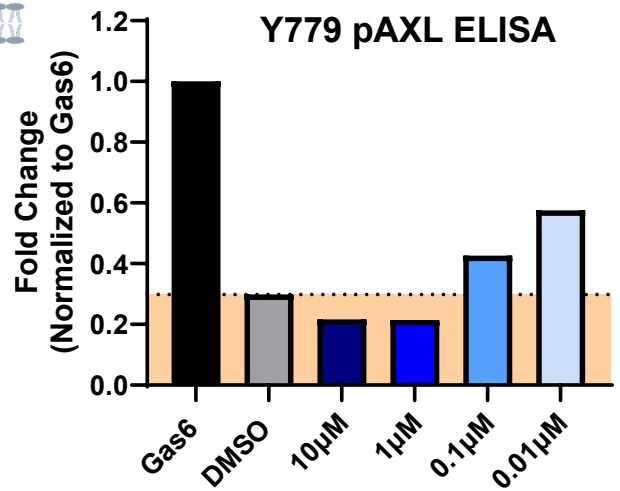
Osanto, et al. Ther Adv Urol. 2018

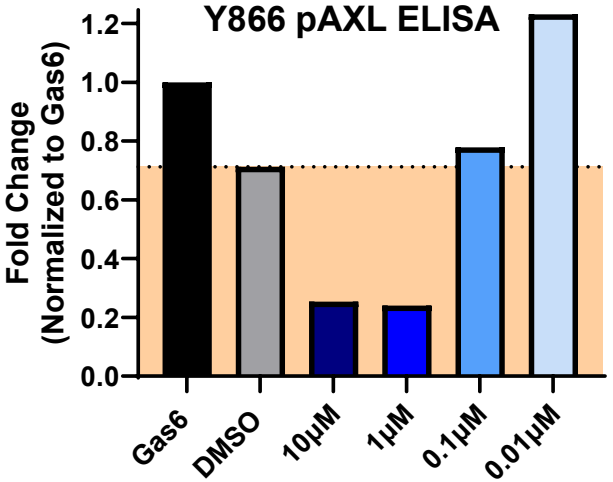
Ghoreschi, et al. Nature Immunology. 2009

AB801 Inhibits Both Ligand-Dependent and Ligand-Independent AXL Signaling









Arcus has developed custom antibodies for pAXL sites that are directly involved in AXL signaling

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AB801 RESTORES SENSITIVITY TO TARGETED THERAPIES

EGFR-mutant NSCLC

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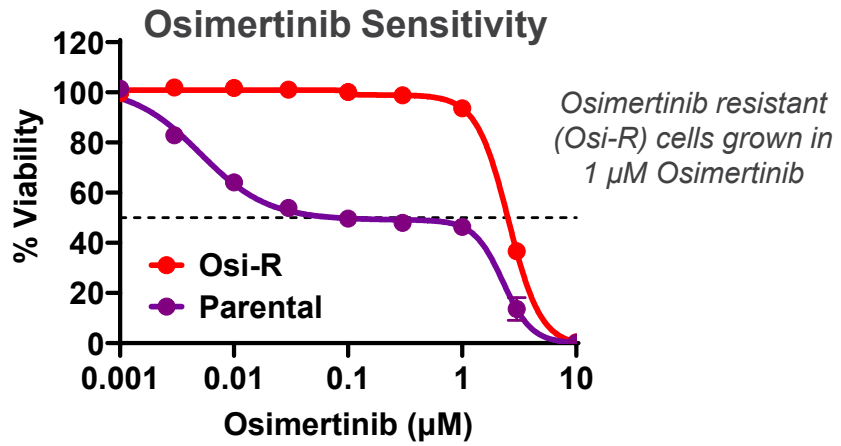
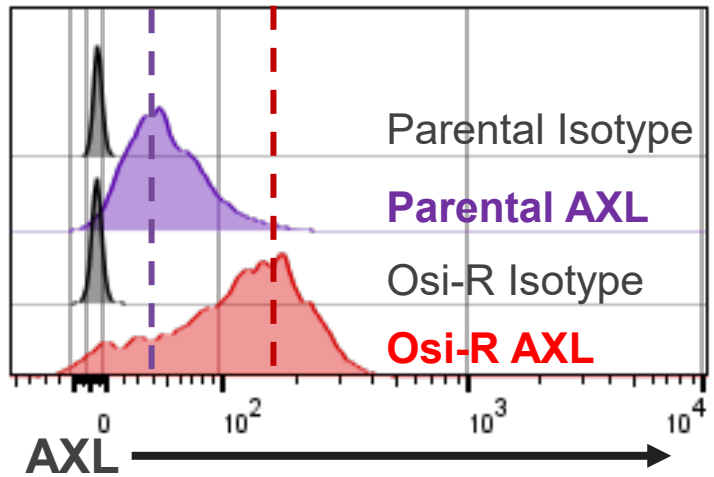
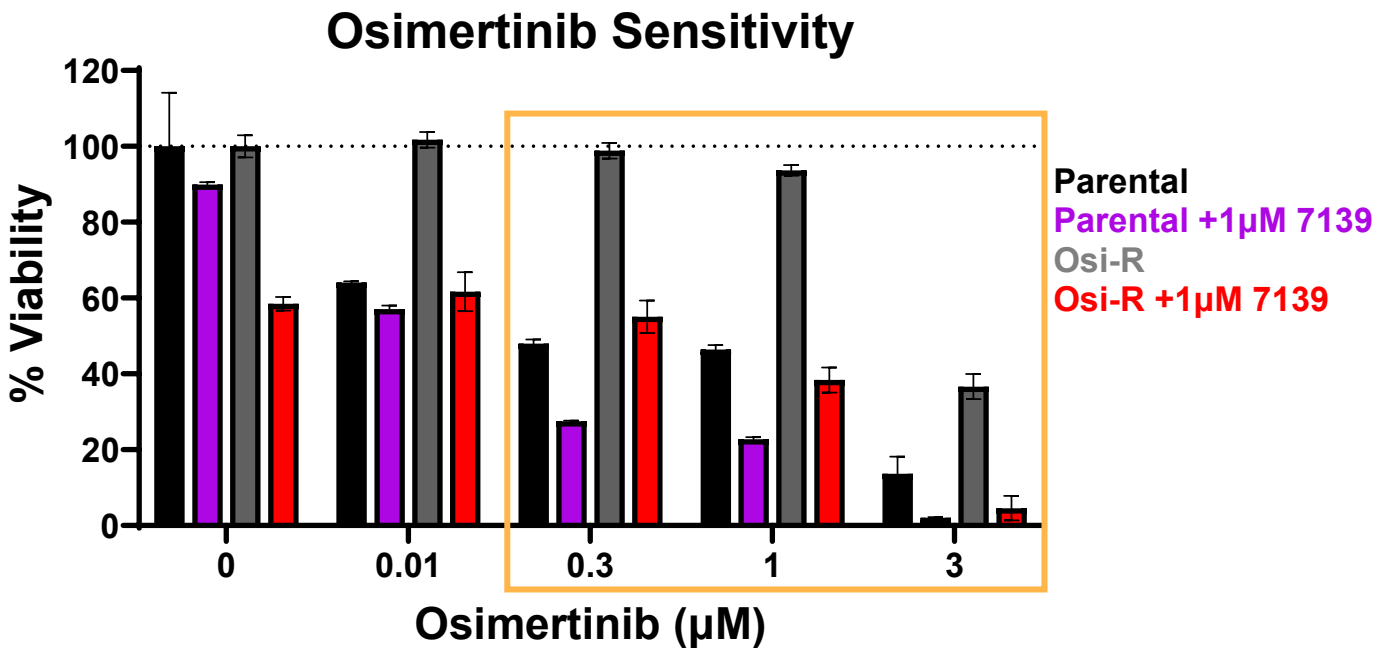
AXL Expression Increases in Osimertinib-Resistant PC9 Cells: AXL Inhibition Restores Sensitivity

AXL is Upregulated in Osimertinib-Resistant PC9 Cells





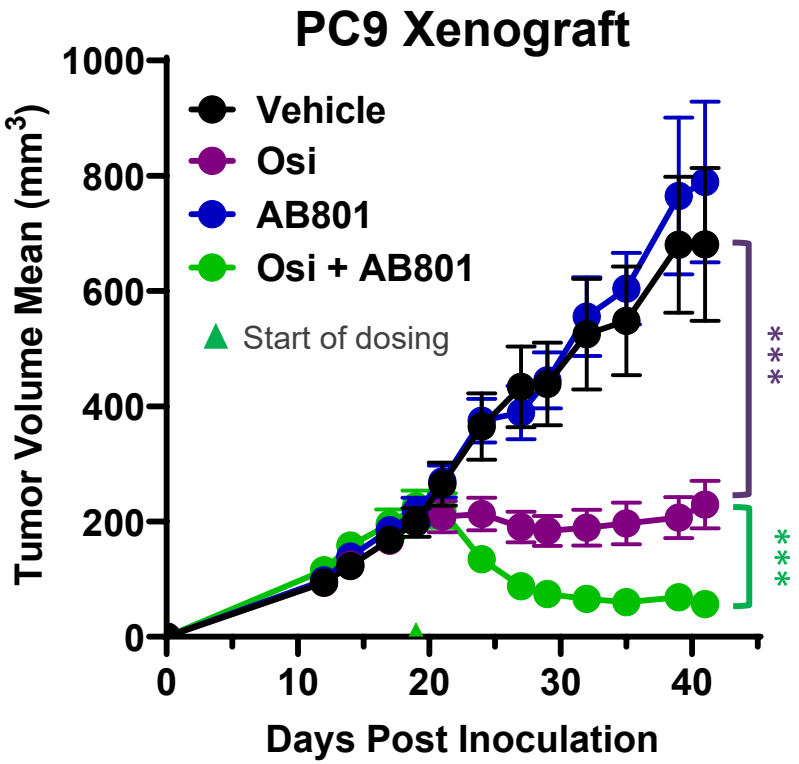
AXL Inhibition Enhances Responses to Osimertinib



7139 is an Arcus AXL inhibitor tool compound

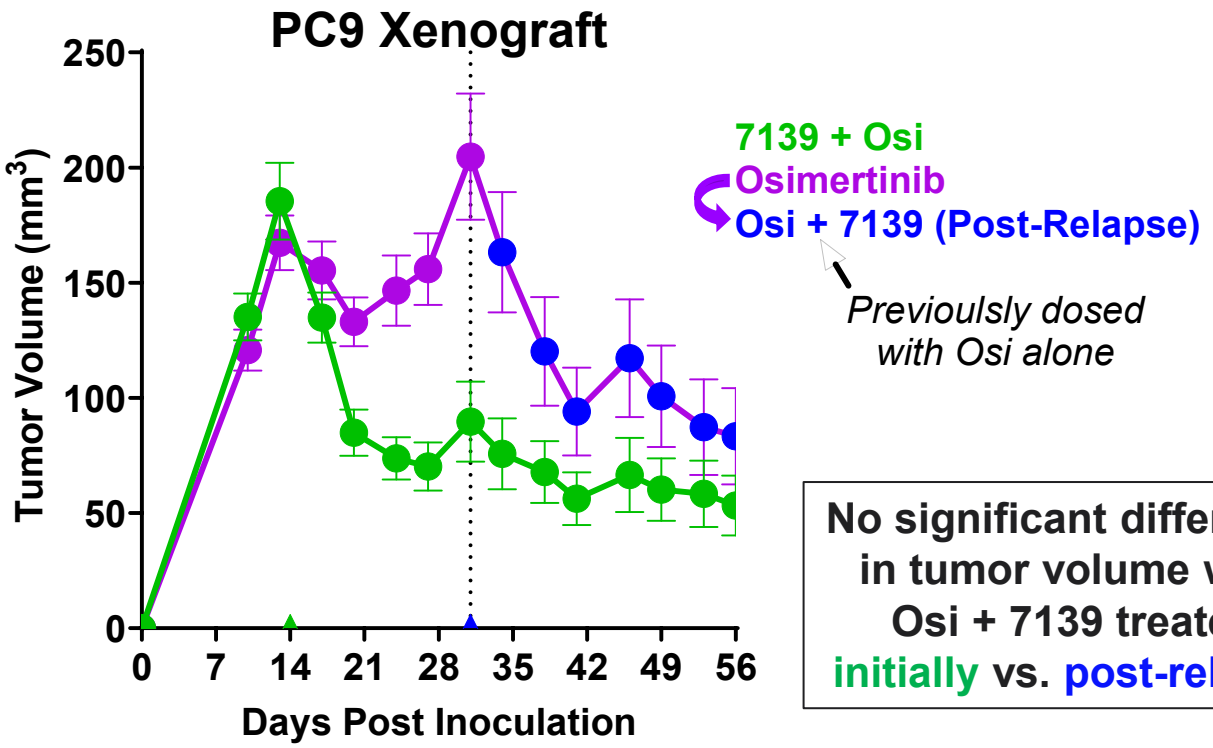
Significant Efficacy Is Observed with AXL Inhibition in Combination with Osimertinib Initially & Post-Relapse

AB801 in Combination With Osimertinib Drives Tumor Regressions



AB801: 30 mg/kg BID
Osimertinib ("Osi"): 2.5 mg/kg QD

AXL Inhibition Reverses Relapse to Osimertinib Treatment



7139: 100 mg/kg BID
Osimertinib ("Osi"): 2.5mg/kg QD

No significant difference in tumor volume with Osi + 7139 treated initially vs. post-relapse

AB801 RESTORES SENSITIVITY TO CHEMOTHERAPIES

Taxanes and Platinum Therapies

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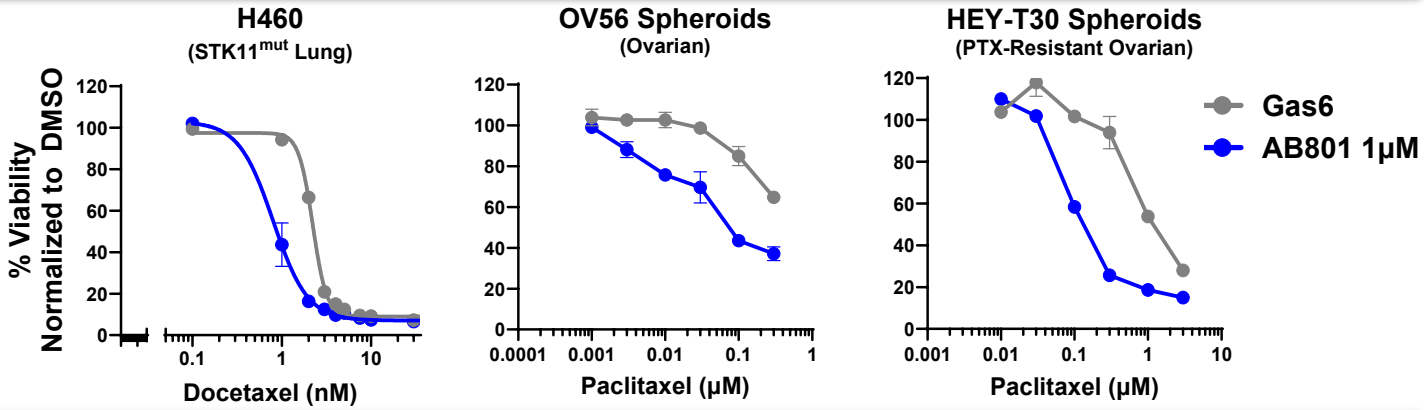
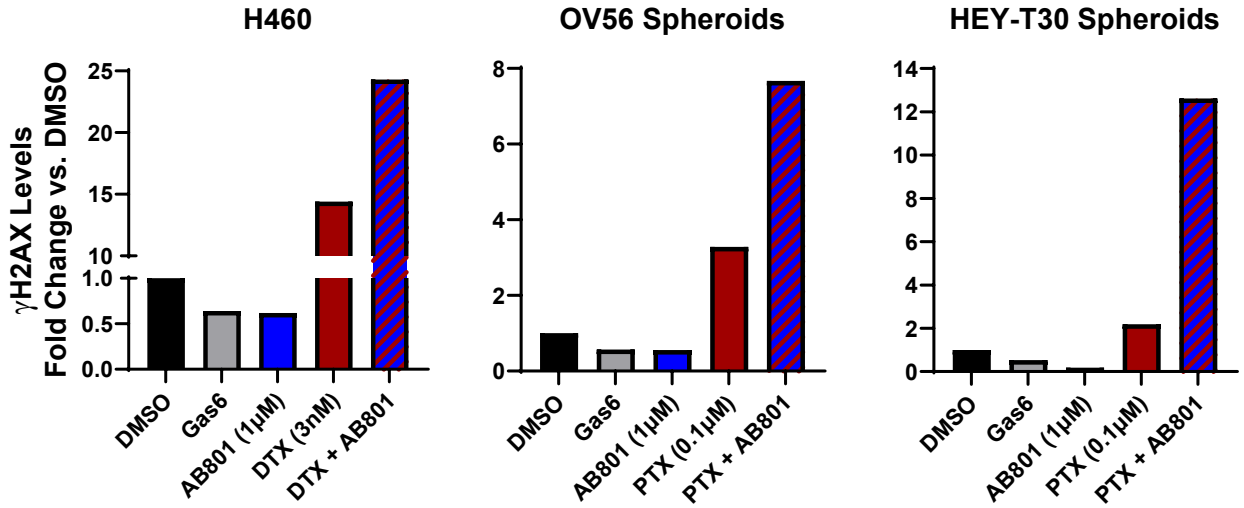
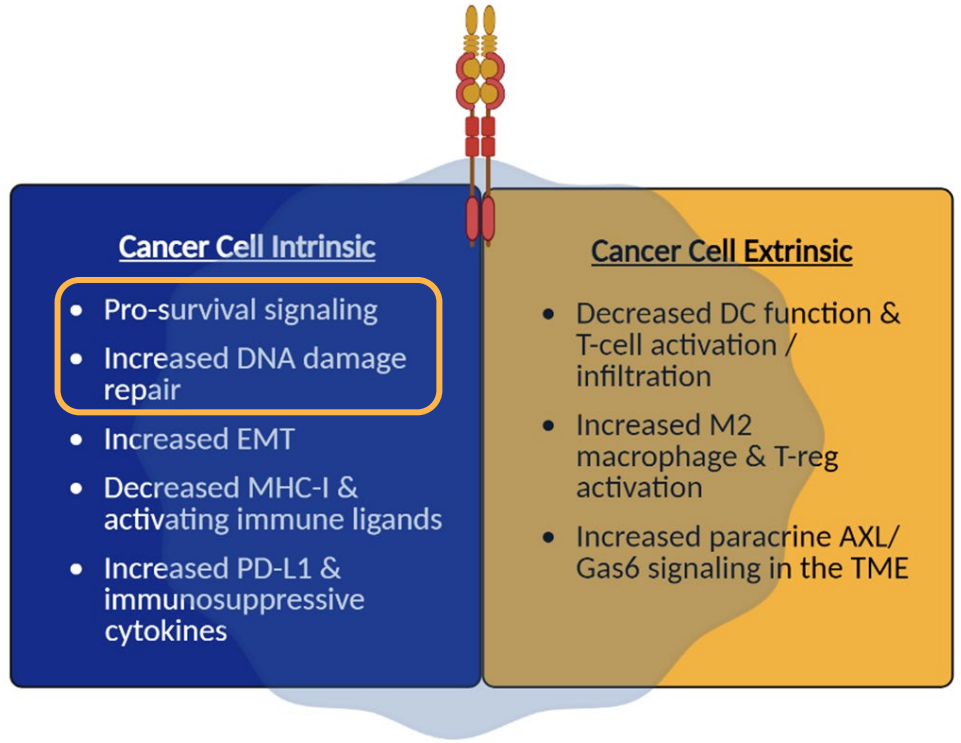
AB801 Increases DNA Damage Leading to Cell Death In Combination With Chemotherapy

AB801 Increases Chemosensitivity

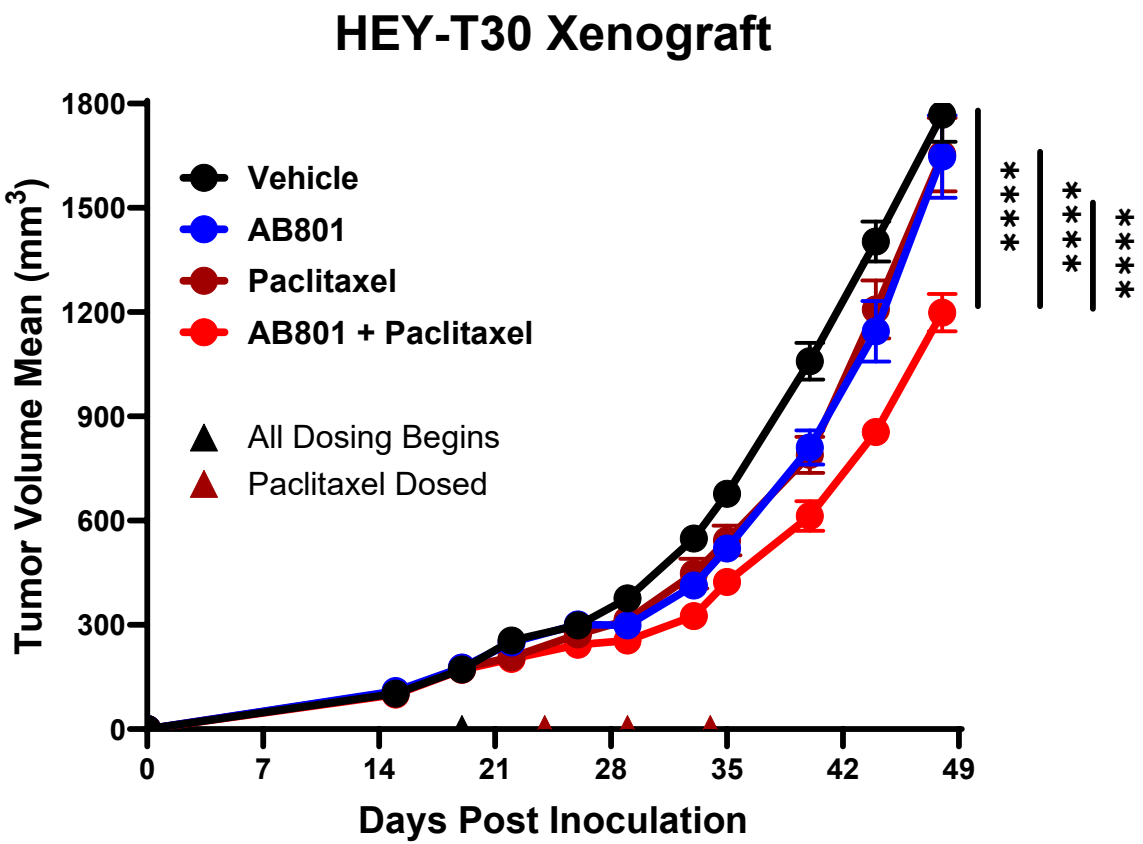


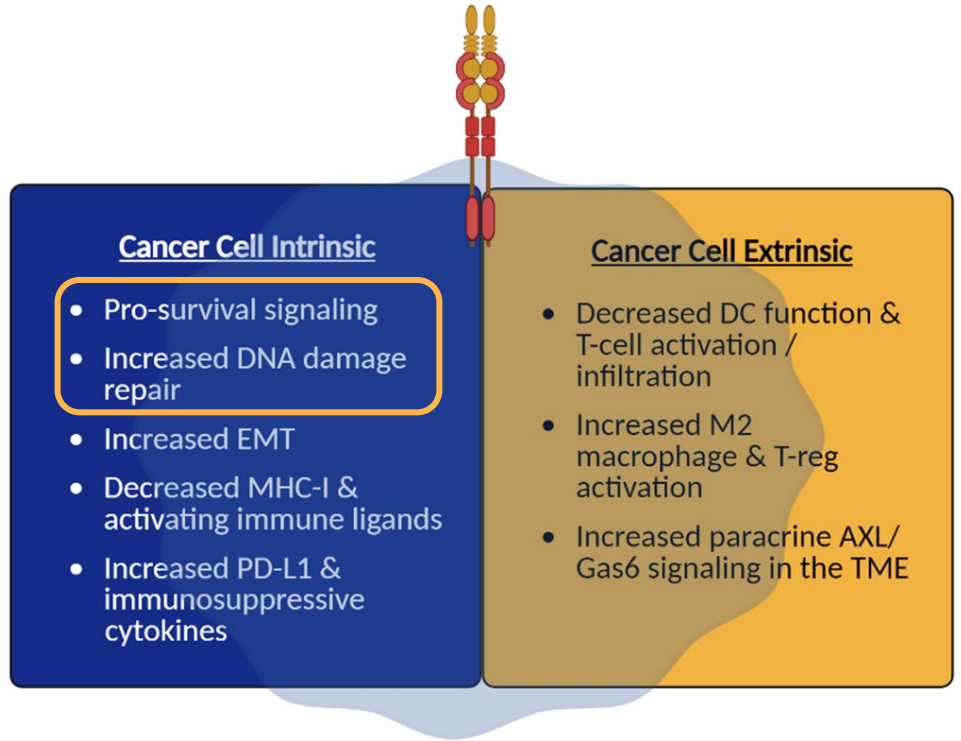
AB801 Increases γH2AX In Combination with Chemotherapy



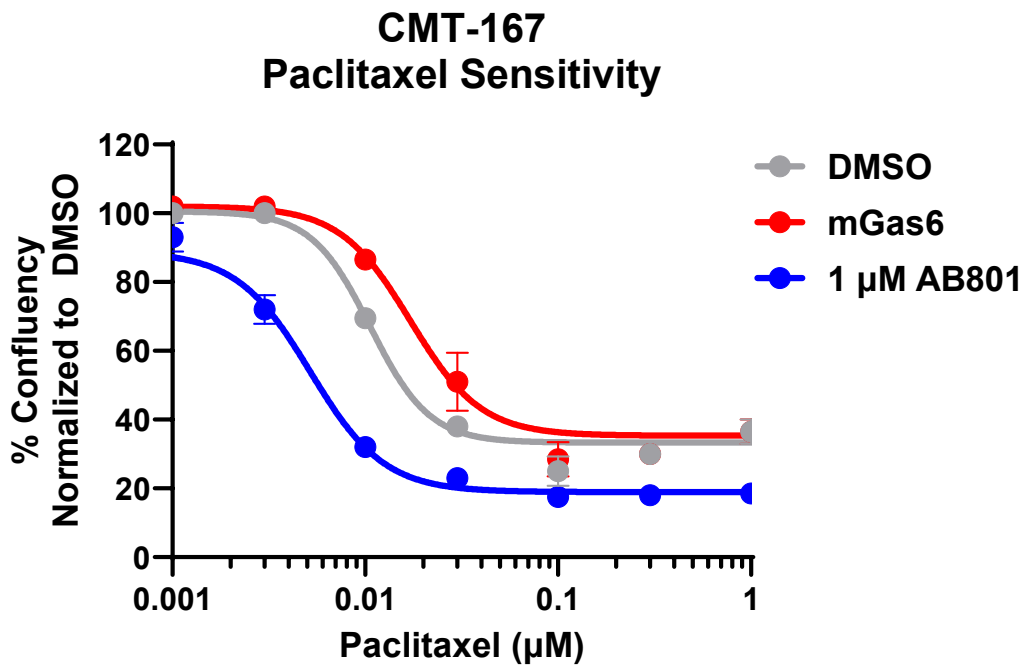


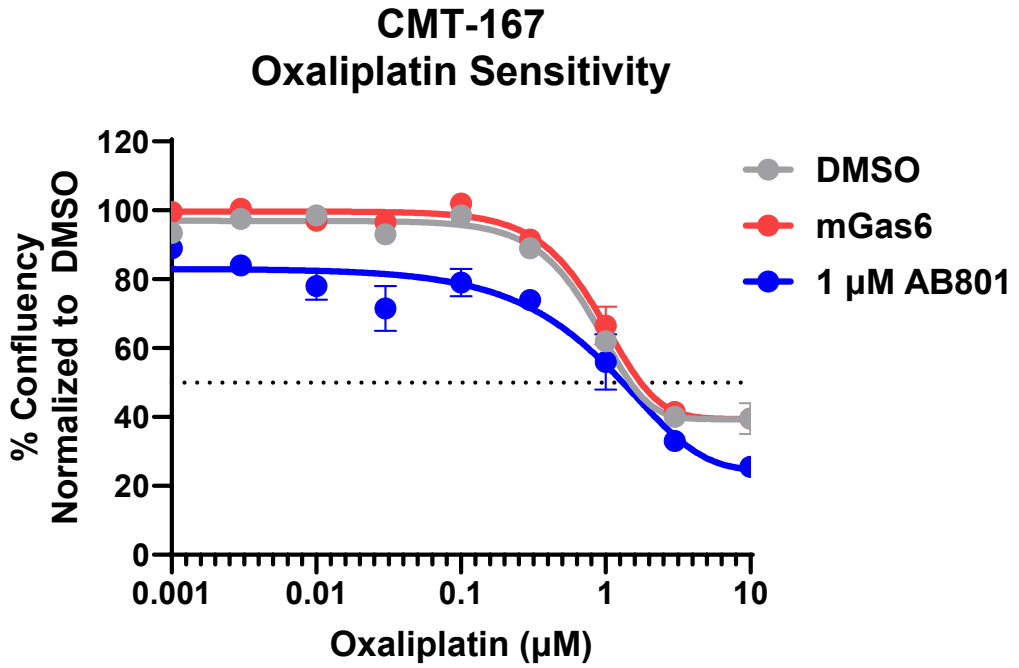
AB801 Combined with Paclitaxel Demonstrates Anti-Tumor Activity in Paclitaxel-Resistant HEY-T30 Xenografts



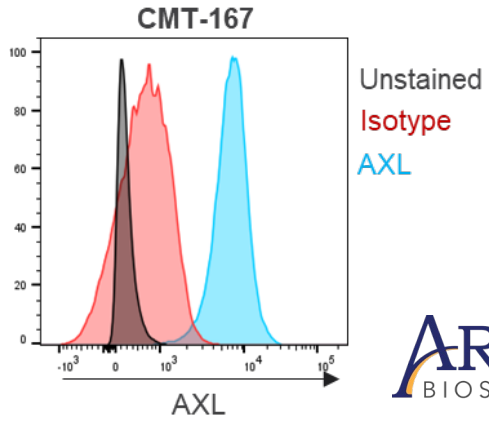


AB801 Increases Sensitivity to Chemotherapy in CMT-167 Murine Lung Cancer Cells *In Vitro*



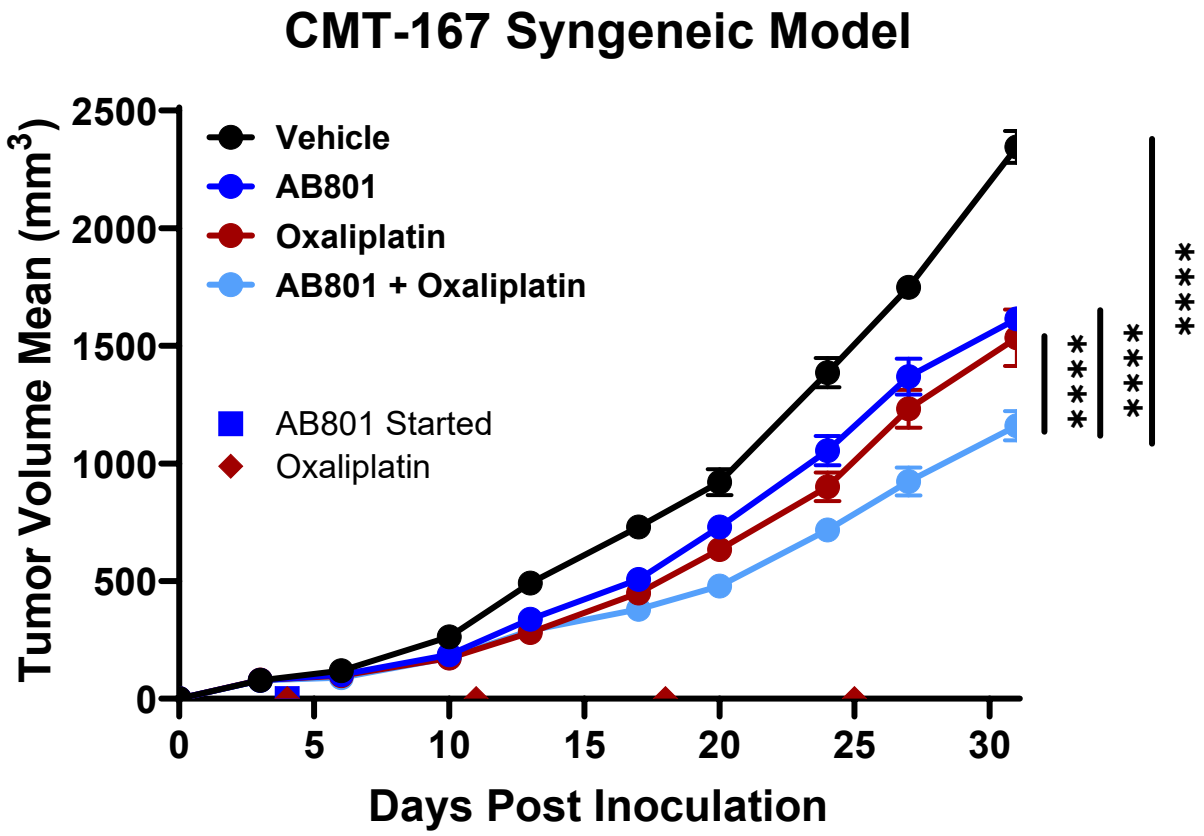


- Express high levels of AXL and very low levels of MHC-I
- Respond poorly to chemotherapy and αPD-1 therapy
- Immunosuppressive TME *in vivo*

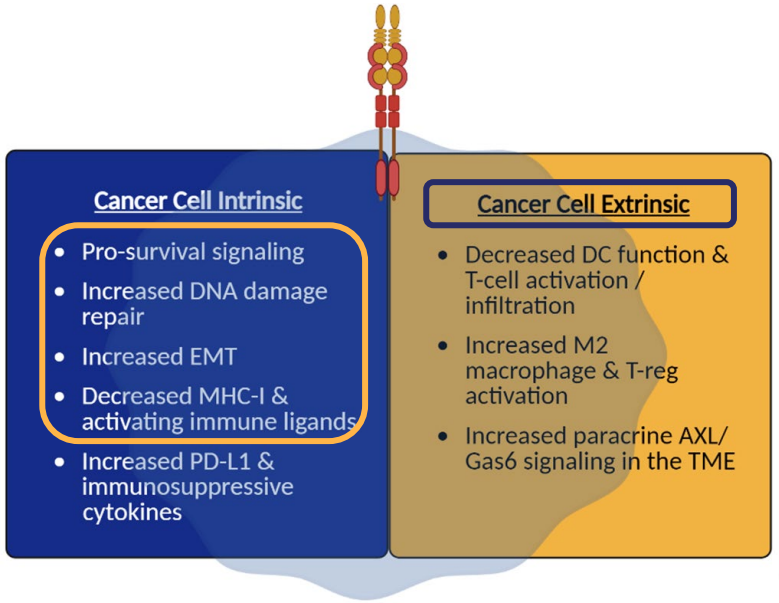


AB801 treatments are all in the presence of Gas6

AB801 in Combination with Oxaliplatin Demonstrates Significant Anti-Tumor Efficacy in CMT-167 Lung Syngeneic Model



- Single-agent activity of AB801 is observed
- AB801 + Oxaliplatin doublet shows significant anti-tumor efficacy vs. AB801 or Oxaliplatin single agent



AB801 ENHANCES RESPONSES TO IMMUNO CHEMOTHERAPIES

Combination with αPD1 and chemotherapies

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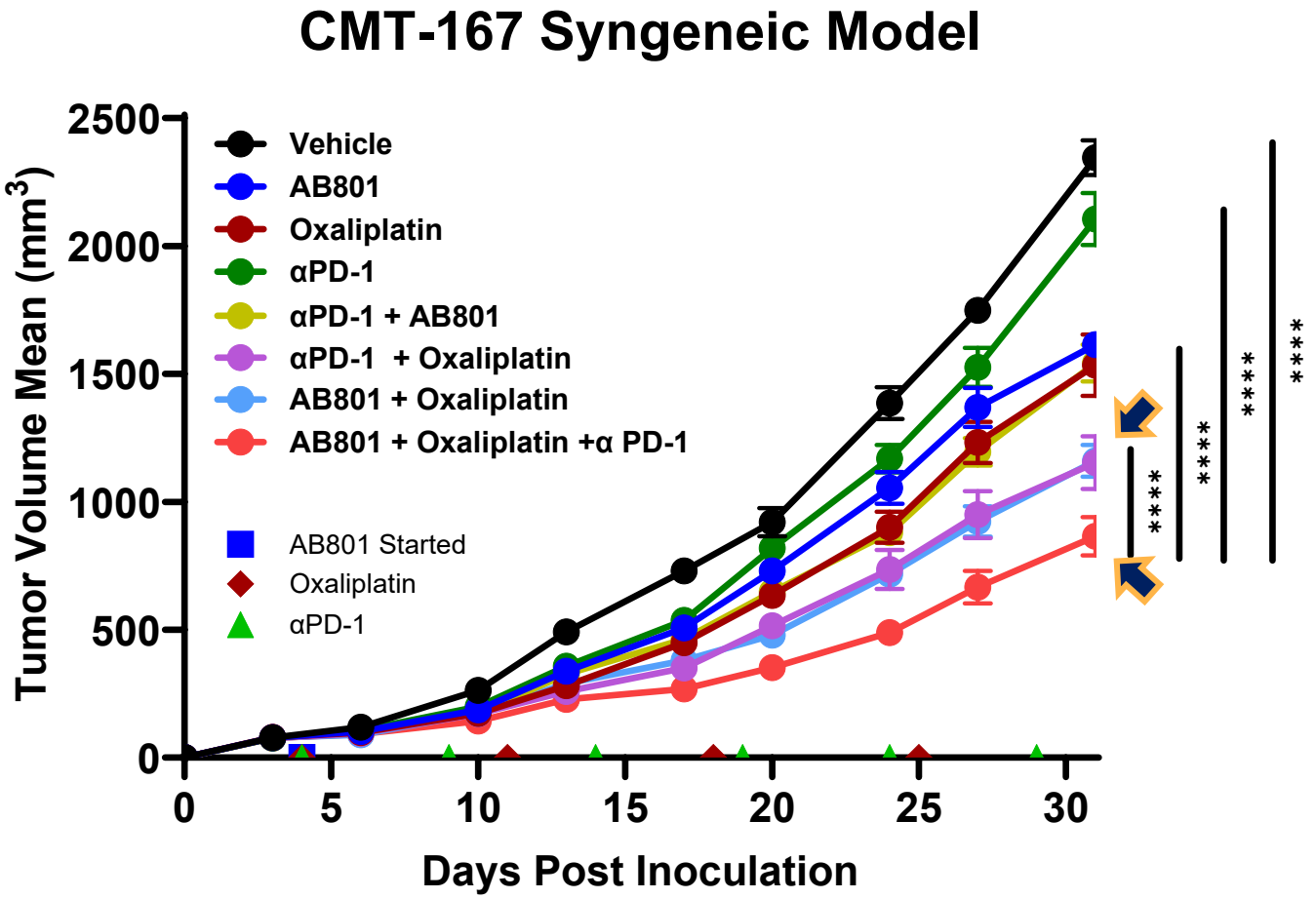
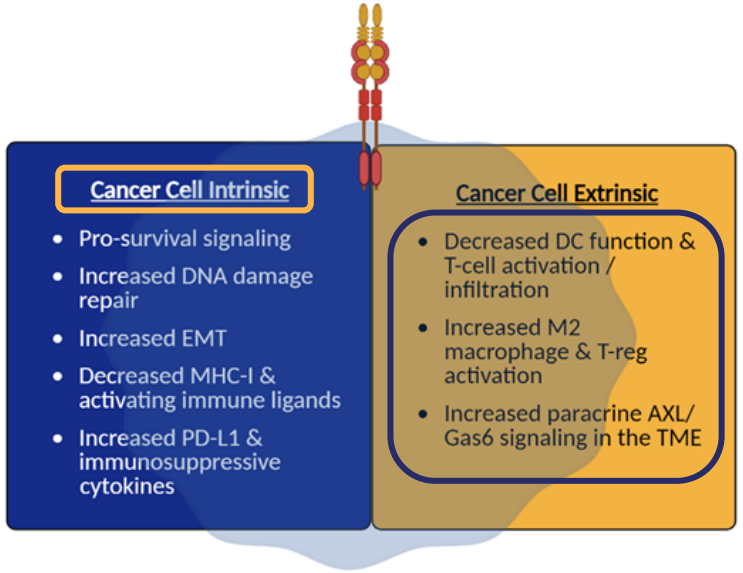
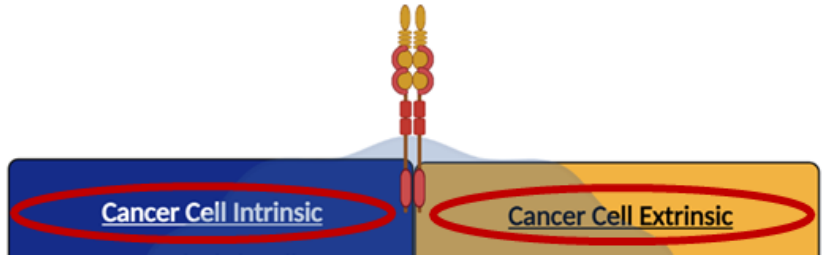
AB801 in Combination with Oxaliplatin and αPD1 Demonstrates Significant Efficacy in CMT-167 Lung Syngeneic Model



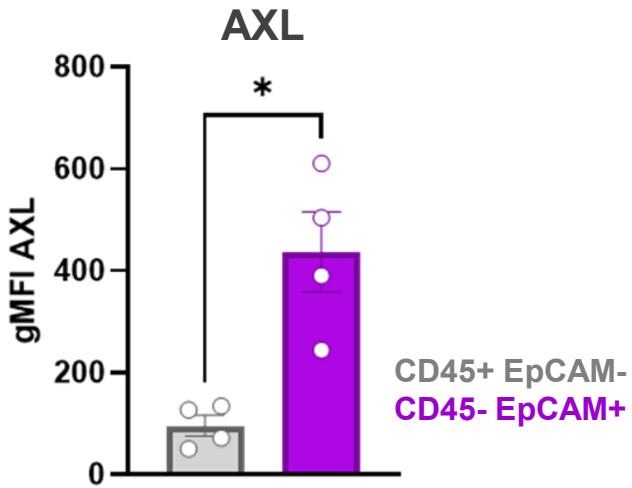
- Comparable efficacy between AB801 + Oxaliplatin and PD-1 + Oxaliplatin doublets
- AB801 + αPD-1 + Oxaliplatin triplet shows significant anti-tumor efficacy vs. doublet or single-agent therapies



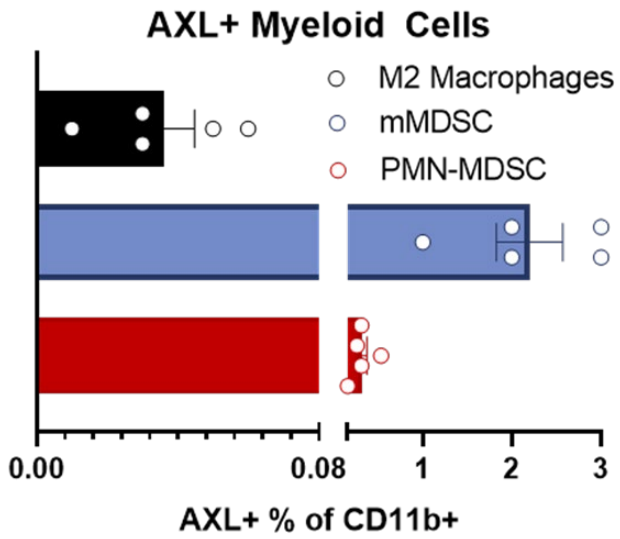
AXL Is Expressed In Both Tumor and Immune Cells in MC38 Tumors



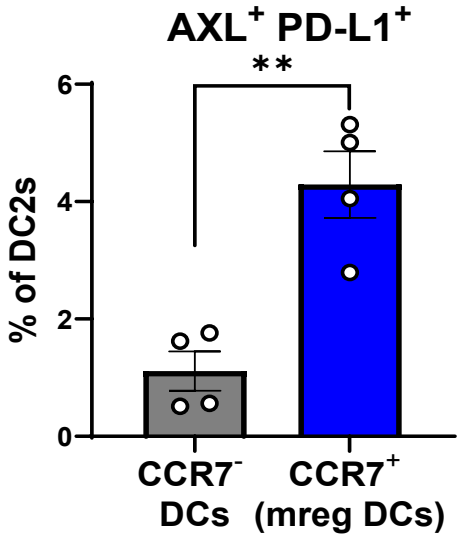
MC38 Tumor Cells Express AXL



Myeloid Cells Express AXL



mregDC's Co-Express Significantly Higher Levels of AXL & PD-L1

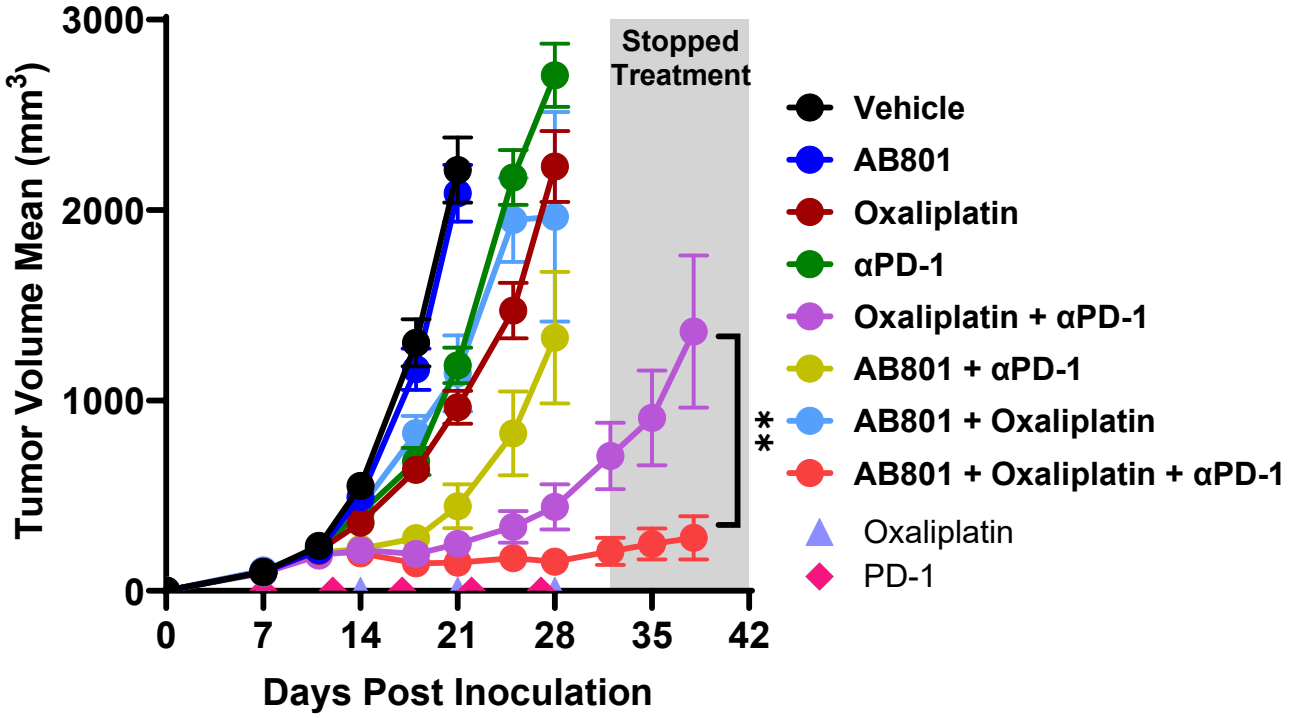


AXL signaling dampens immunostimulatory functions of select immune cells

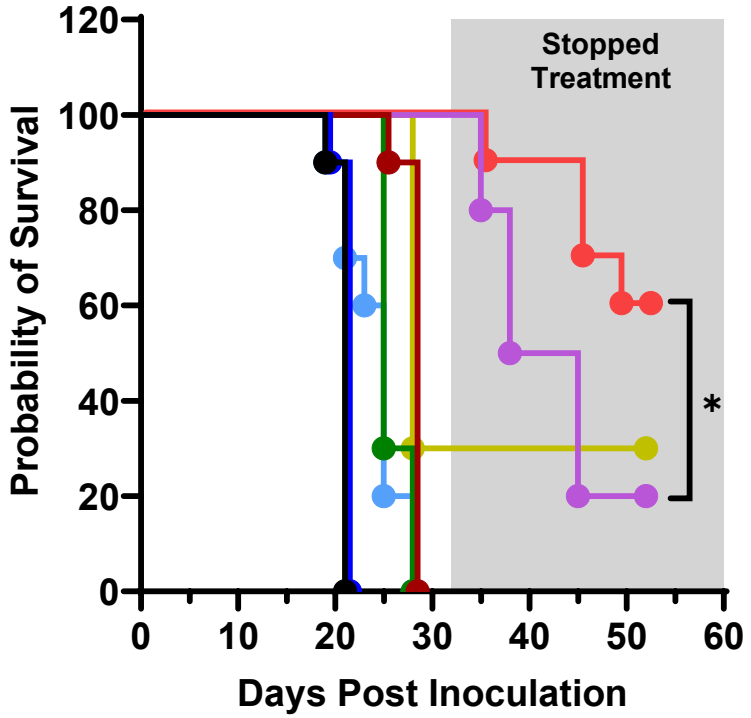
AB801 in Combination with Oxaliplatin and αPD-1 Significantly Enhances Efficacy & Survival in αPD-1 Unresponsive Tumors

MC38 Syngeneic Model

Efficacy

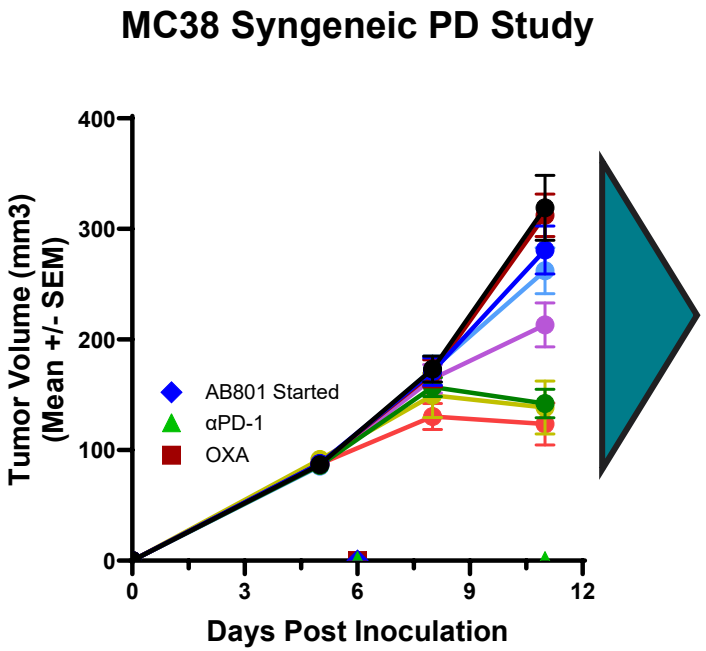


Survival



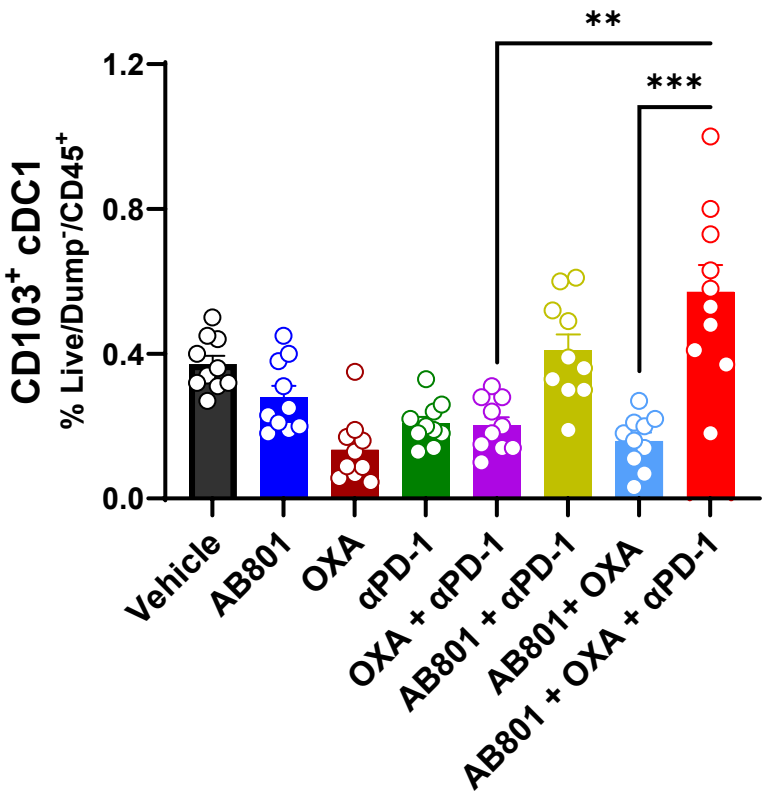
Larger MC38 tumors do not respond well to αPD-1

AB801 in Combination with Oxaliplatin and αPD-1 Generates a Pro-Inflammatory Immune Response

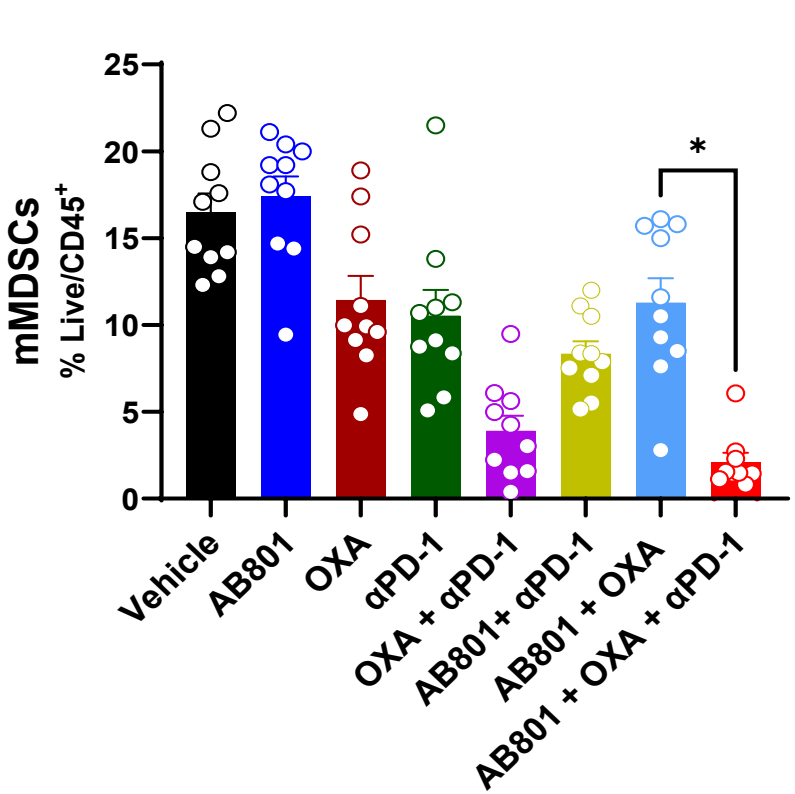


Single agent efficacy of αPD-1 was observed, in contrast to efficacy study

cDC1's



mMDSC's



AB801 in combination with Oxaliplatin & αPD-1:

- **Increases pro-inflammatory cDC1's**
- **Decreases immunosuppressive mMDSC's**

Summary:
AXL Inhibition Will Overcome Therapeutic Resistance

- **AXL is a bypass survival pathway that mediates resistance to several therapeutic modalities**
- **AB801 inhibits both ligand-dependent & ligand-independent AXL signaling**
- **AB801 reverses therapeutic resistance through both tumor intrinsic and extrinsic mechanisms**
  - AB801 sensitizes tumor cells to chemotherapy by increasing DNA damage
  - AB801 enhances immunostimulatory DC's and reduces suppressive MDSC's *in vivo*
- **AB801 restores responses to targeted therapy and chemotherapy in human xenograft models**
- **Combination treatment of AB801, Oxaliplatin & αPD-1 increases anti-tumor efficacy and prolongs survival in several murine models**

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AB801 CLINICAL DEVELOPMENT

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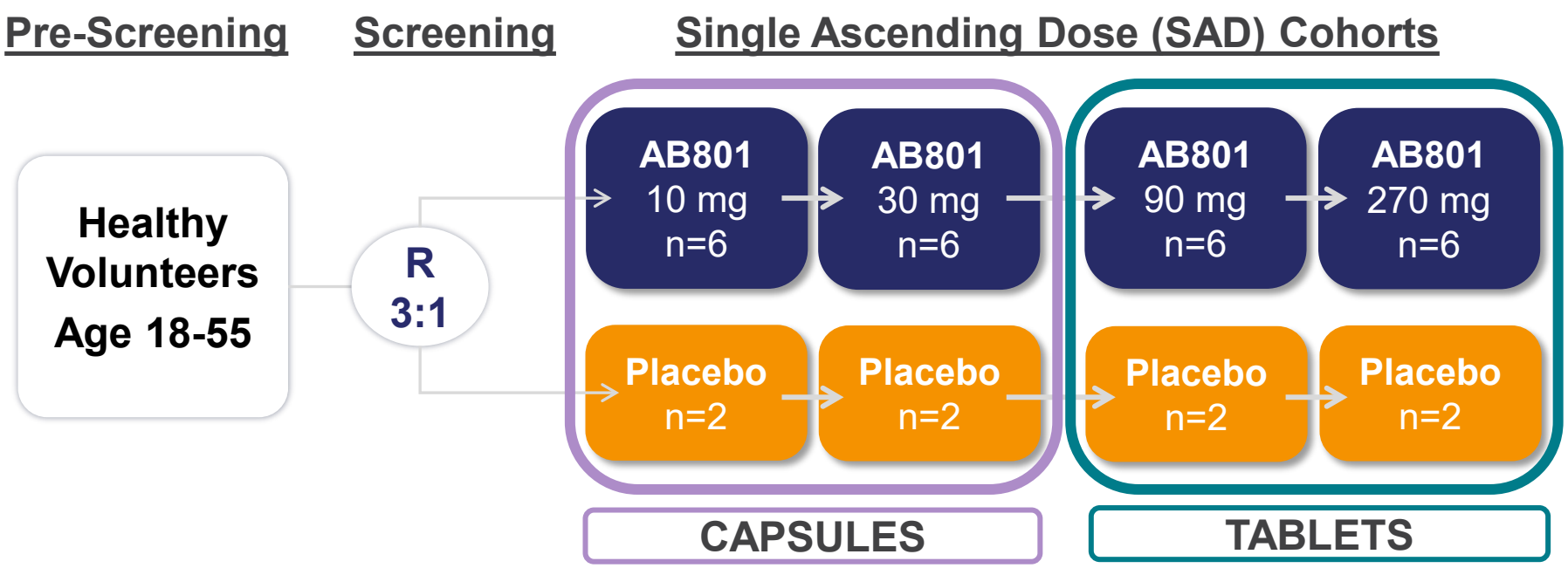
ARC-26: Phase 1 Healthy Volunteer Single Ascending Dose Study for AB801 Has Been Completed



PRIMARY ENDPOINT
- Safety

SECONDARY ENDPOINT
- PK

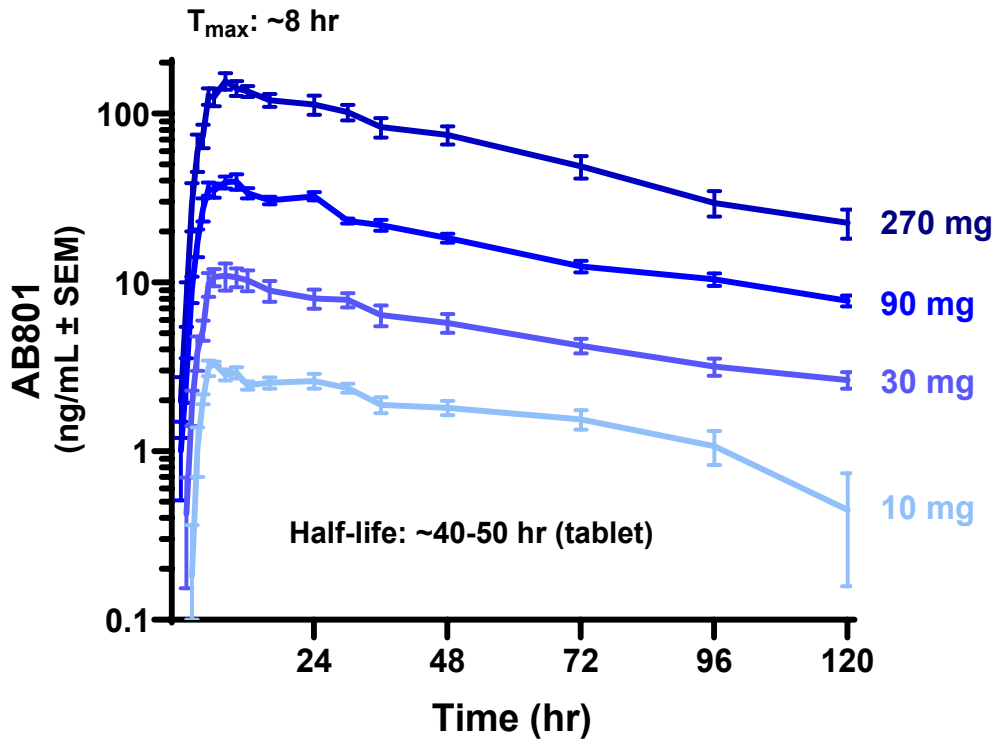
EXPLORATORY ENDPOINTS
- Biomarkers
- Holter ECG monitor readings

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

ARC-26

AB801 Pharmacokinetics and Safety Observed in ARC-26 Supports the Planned AB801 Doses for the ARC-27 Patient Study

AB801 Exposure Increases Dose-Proportionally with a Single Oral Dose (n=6)



ARC-27

- **Dose escalation in advanced solid tumors**
  - NSCLC, CRC, Breast, RCC, Ovarian, HNSCC, Bladder
  - Evaluate AB801 single agent tolerability and activity to inform dose in expansion stage
- **Expansion cohort with AB801 + Docetaxel in 2L+ non-squamous NSCLC**
  - Safety, PK, and activity (ORR) to support POC Phase 2 study

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Conclusions

- Data supports the therapeutic hypothesis that AXL signaling is a mechanism of therapeutic resistance to several therapies
- This therapeutic hypothesis has not yet been fully tested in the clinic due to the lack of potent and selective AXL inhibitors (or the use of molecules that block only ligand-dependent AXL signaling)
- AB801 is a highly potent and selective AXL inhibitor
- No safety signals with AB801 were observed in a healthy volunteer study, supporting dose escalation in cancer patients and dose expansion of AB801 combined with docetaxel


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