



Preclinical characterization of ARRY-575

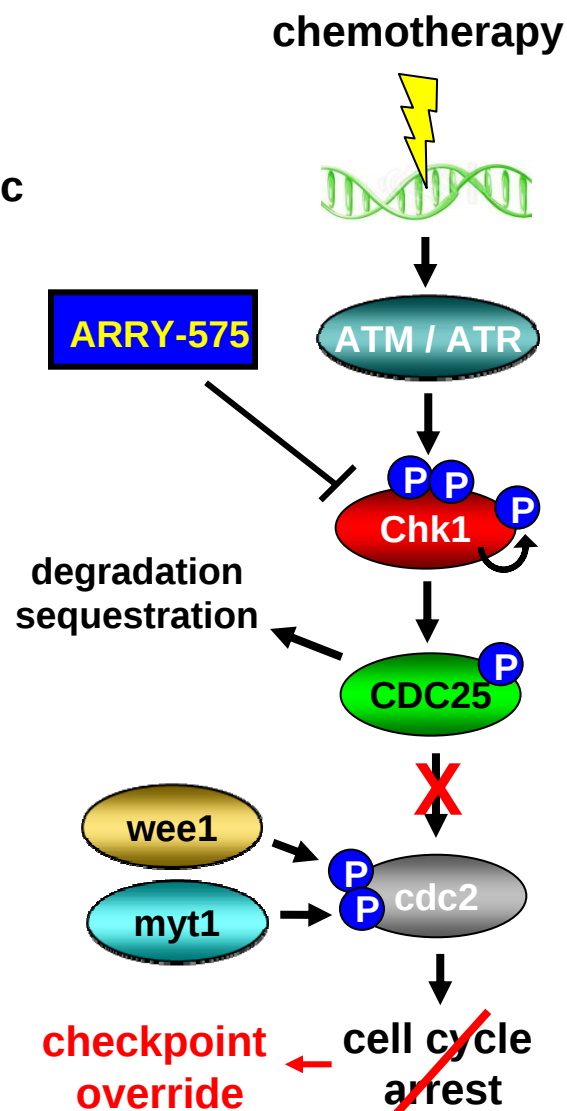
A potent, selective, and orally bio-available small molecule inhibitor of Chk1

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The opportunity for Chk1 inhibitors: chemo-potential

- Chemotherapeutics induce DNA damage and activate the DNA damage response (DDR)
- The DDR is a key mechanism of chemotherapeutic resistance
- Chk1 inhibitor/chemotherapy combination:
 - Inhibit DNA repair
 - Induce checkpoint override
 - Drive mitotic catastrophe and apoptotic cell death
 - Potentiate the cell killing effect of chemotherapy

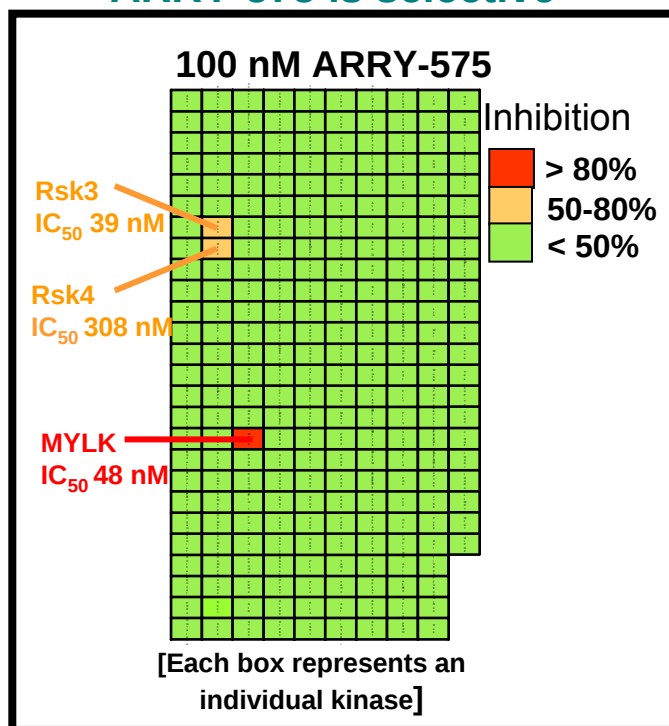


ARRY-575: *in vitro* profile

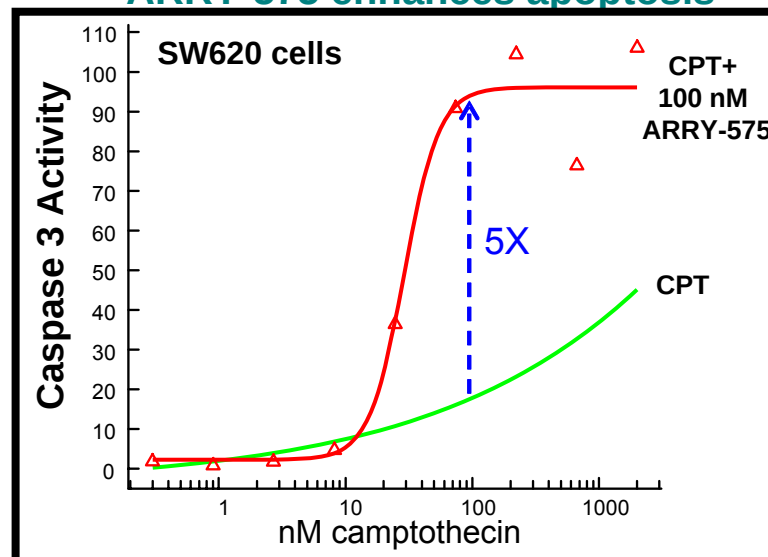
ARRY-575 is potent

Chk1 Enzyme Assay	IC ₅₀ (nM)
ARRY-575	2

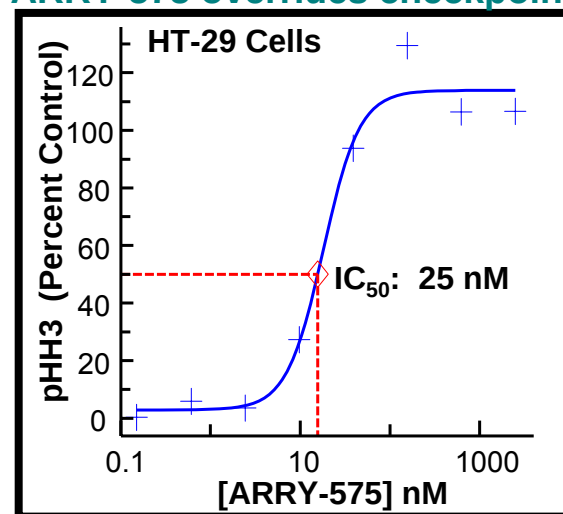
ARRY-575 is selective



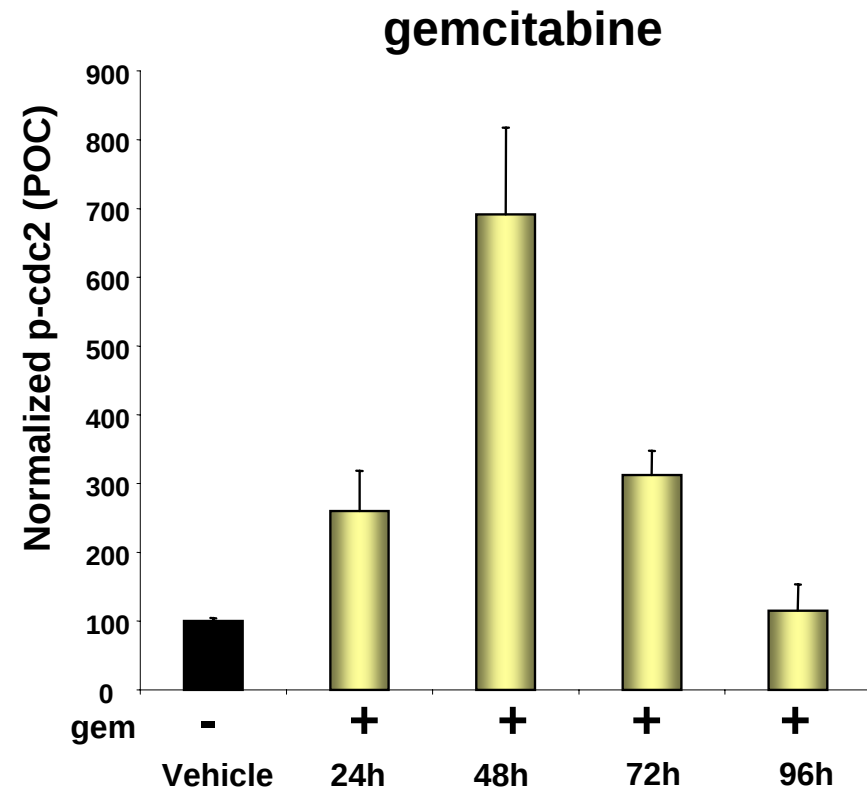
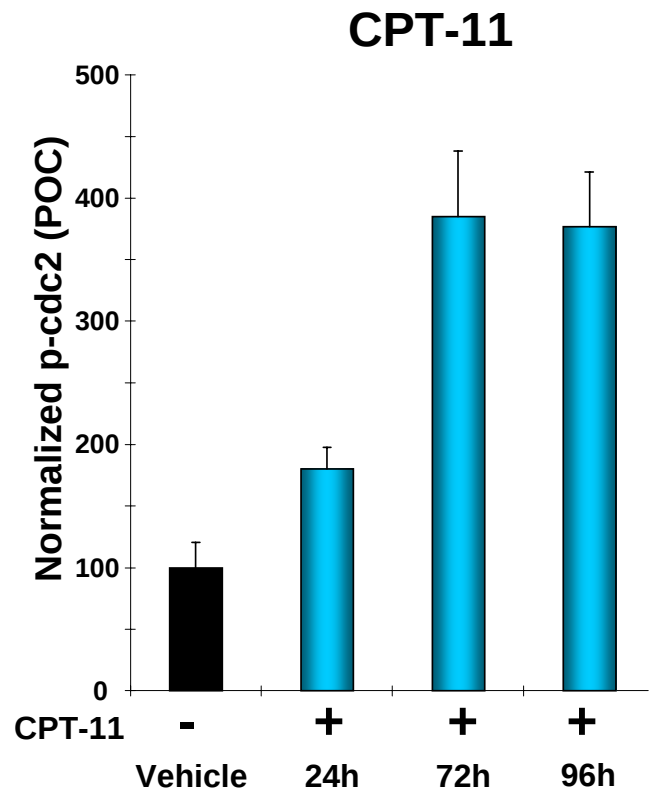
ARRY-575 enhances apoptosis



ARRY-575 overrides checkpoints

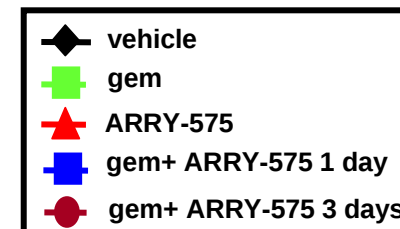
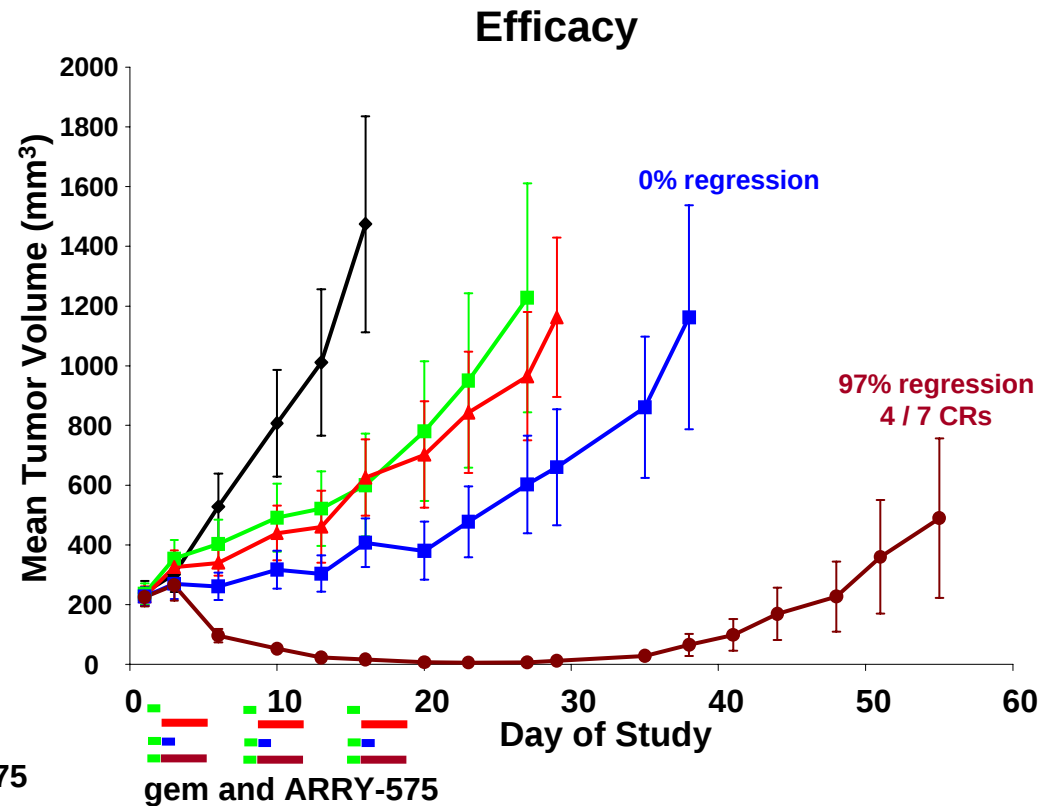
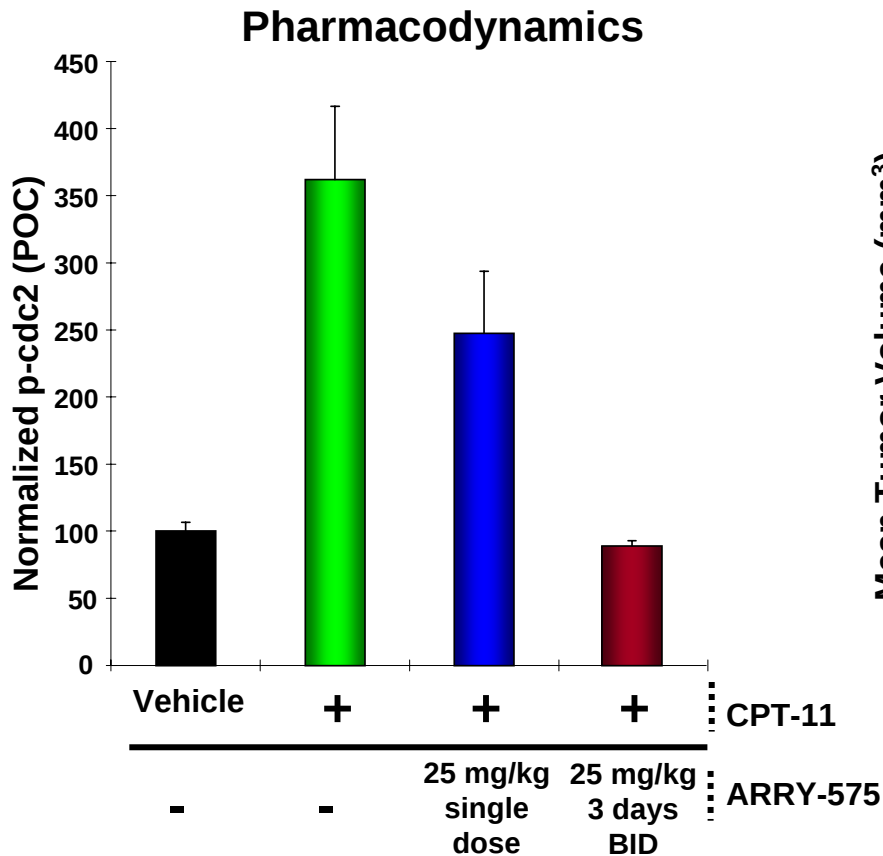


Checkpoint activation is protracted *in vivo*



- Chemotherapeutics that target replication induce sustained checkpoint activation

Prolonged Chk1 inhibition is required for maximal checkpoint override



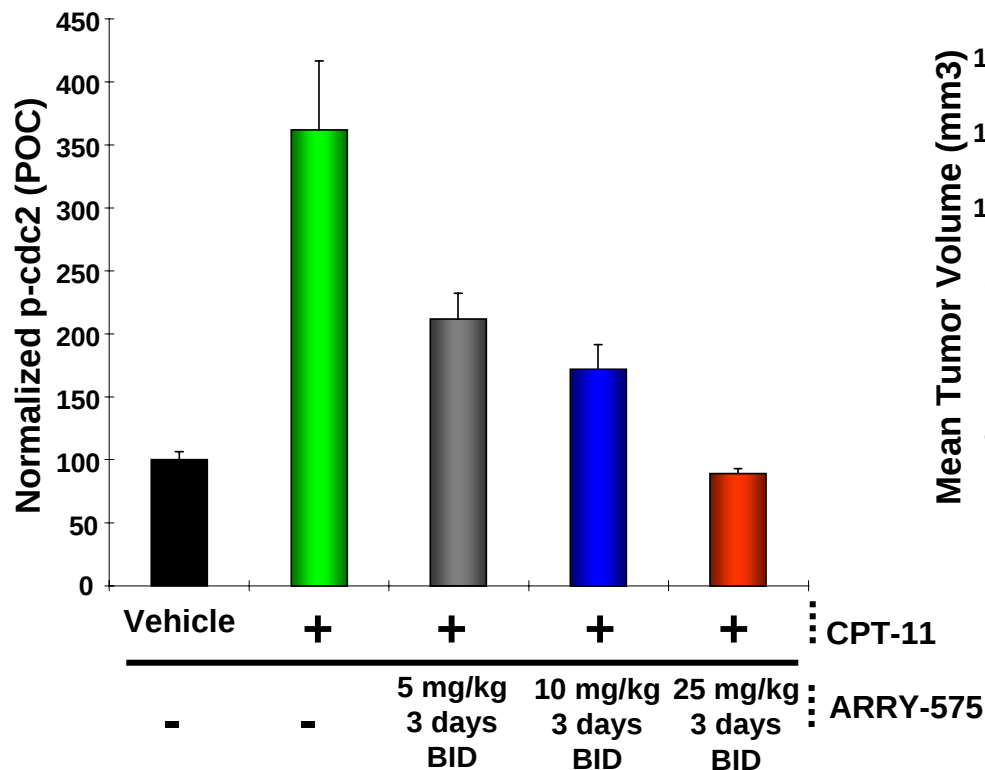
gem: 120 mg/kg (IP)
ARRY-575: 25 mg/kg BID (PO)
3 cycles of dosing

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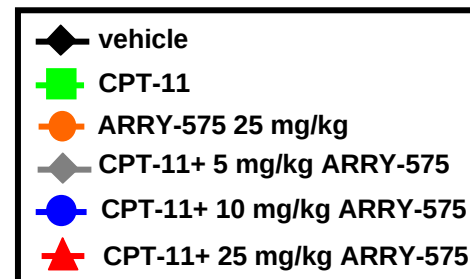
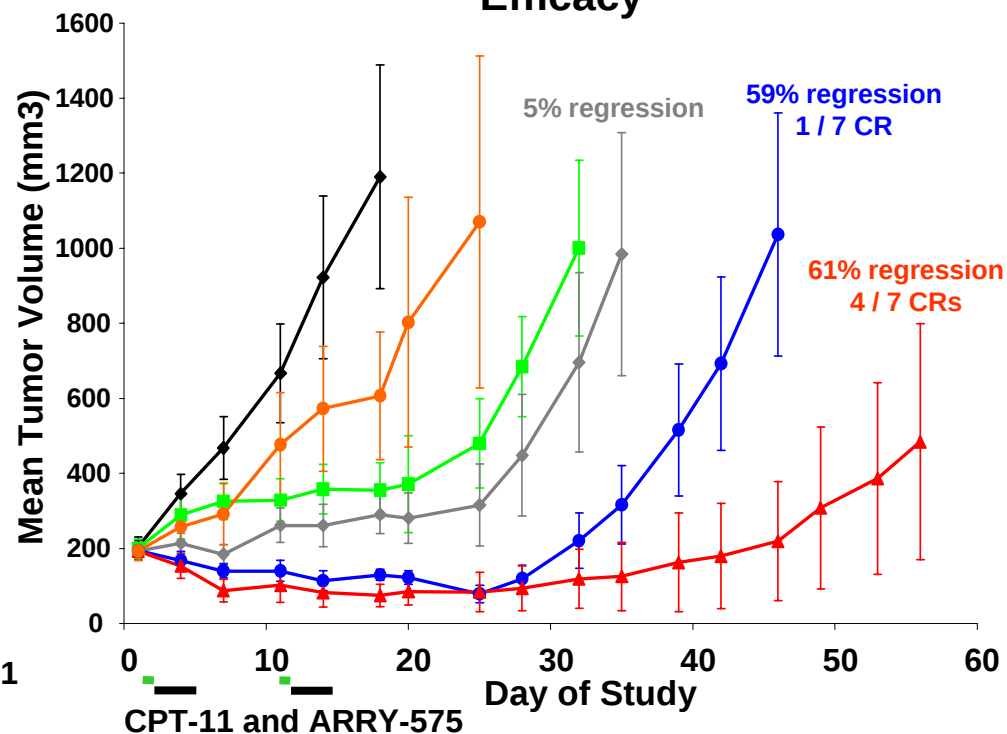
- Oral delivery provides flexibility for multi-day dosing

Checkpoint override correlates with efficacy

Pharmacodynamics



Efficacy

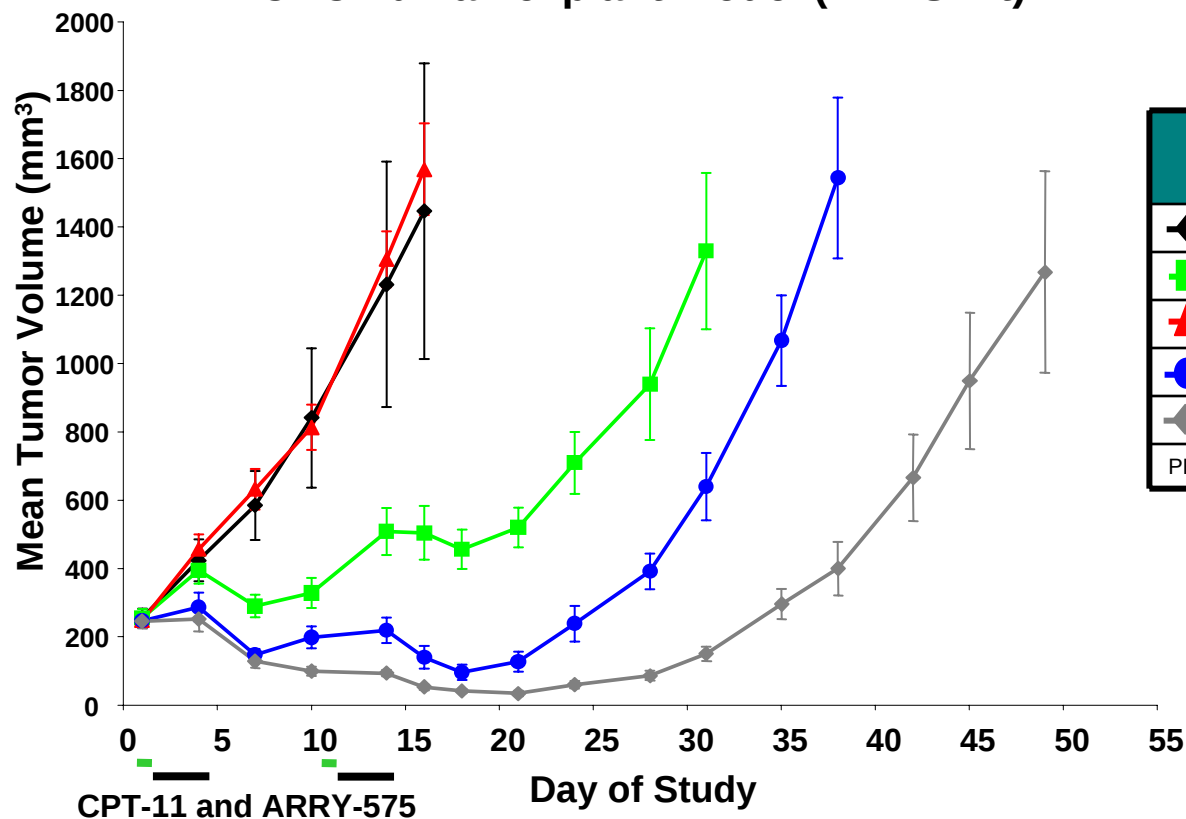


CPT-11: 100 mg/kg (IP)
 ARRY-575: PO, BID for 3 days
 2 cycles of dosing



ARRY-575 potentiates CPT-11 in patient derived explants

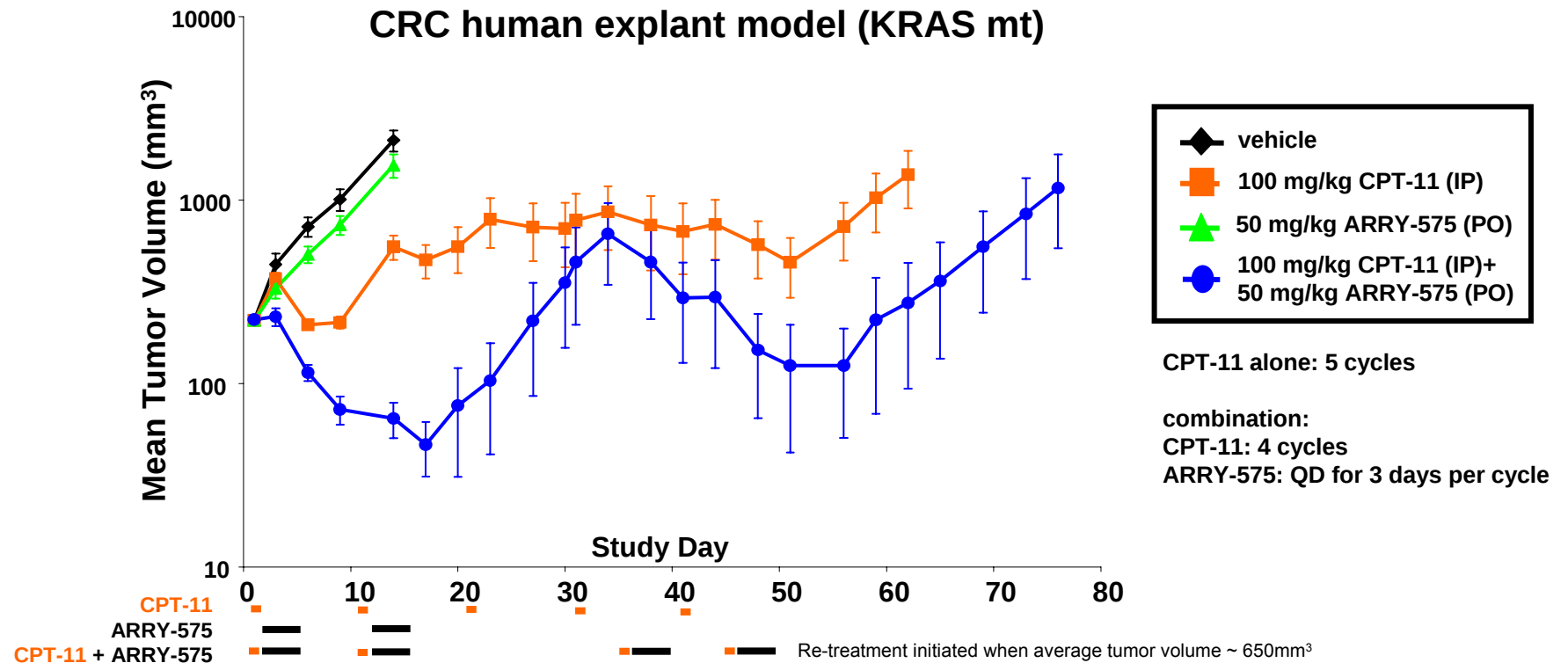
CRC human explant model (KRAS mt)



Treatment groups (N=8/group)		Growth delay (days)	PR
	Vehicle	N/A	-
	CPT-11	16.2	0/7
	25 mg/kg ARRY-575	0	0/7
	CPT-11+ 10 mg/kg ARRY-575	21.7	7/8
	CPT-11+ 25 mg/kg ARRY-575	34.1	8/8
PR: Partial response, ≥ 50% regression of an individual tumor			

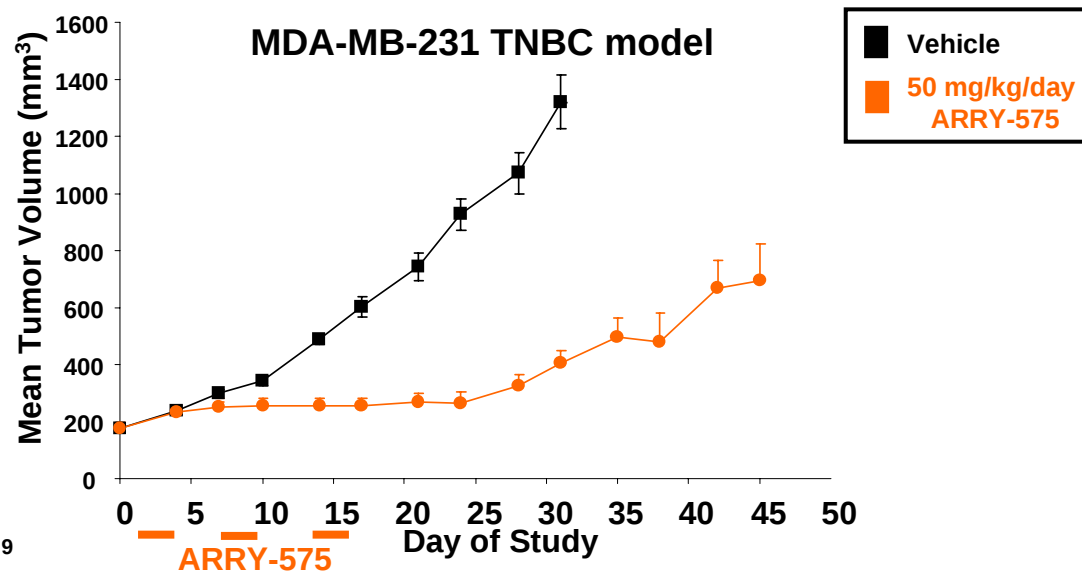
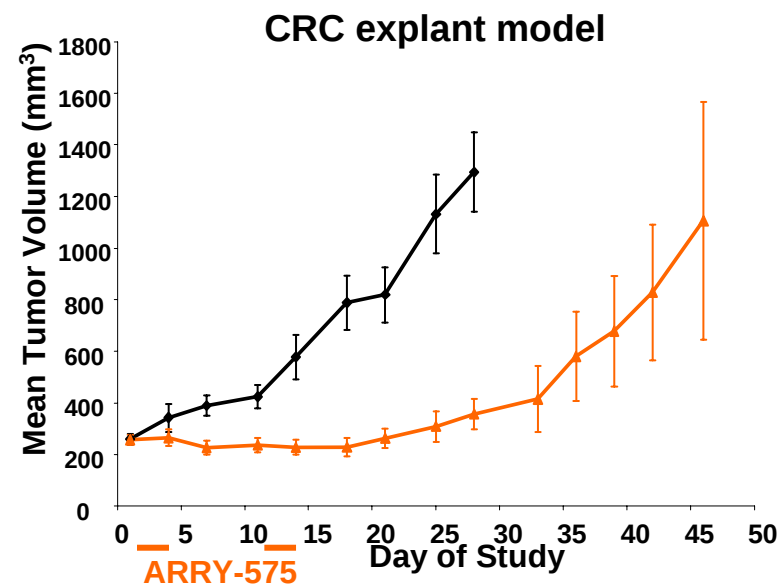
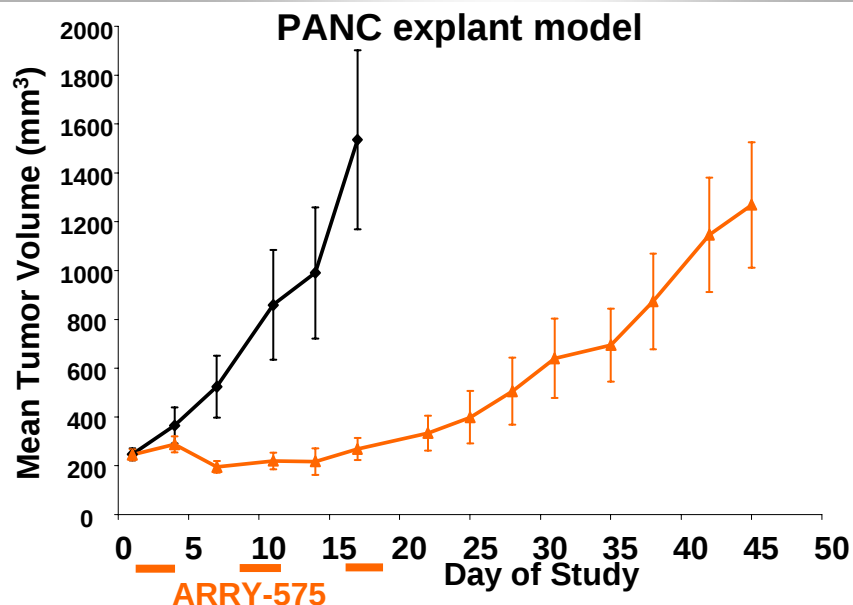
CPT-11: 100 mg/kg (IP)
ARRY-575: PO, BID for 3 days
2 cycles of dosing

ARRY-575 combination therapy is active following tumor re-growth



Treatment	Initial Treatment		Re-growth Treatment	
	% Mean Tumor Regression	PR	% Mean Tumor Regression	PR
CPT-11	5	1 / 8	N/A	N/A
CPT-11 + ARRY-575	79	8 / 8	81	7 / 8

ARRY-575 mono-therapy



- ARRY-575 displays anti-tumor activity on intermittent dose schedules
- Work is ongoing to understand the underlying determinant of sensitivity

ARRY-575: oral Chk1 inhibitor delivers superior efficacy

- **Chk1 inhibition provides a mechanism to potentiate chemotherapy**
 - Prolonged Chk1 inhibition maximizes efficacy and biomarker inhibition
 - Checkpoint override correlates with efficacy
 - Oral inhibitor allows for flexible and prolonged multi-day targeting of Chk1
- **ARRY-575 is highly potent, selective, orally bioavailable Chk1 inhibitor**
 - Potentiates clinically important cytotoxics
 - Potentiates irinotecan in clinically relevant patient derived tumor models
 - Exhibits single-agent activity in select tumor models
- **GLP safety studies complete**
- **IND slated for 3Q 2011**

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