Preclinical characterization of ARRY-575

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

Mike Humphries, Ph.D.
Senior Research Scientist
Pharmacology
Array BioPharma

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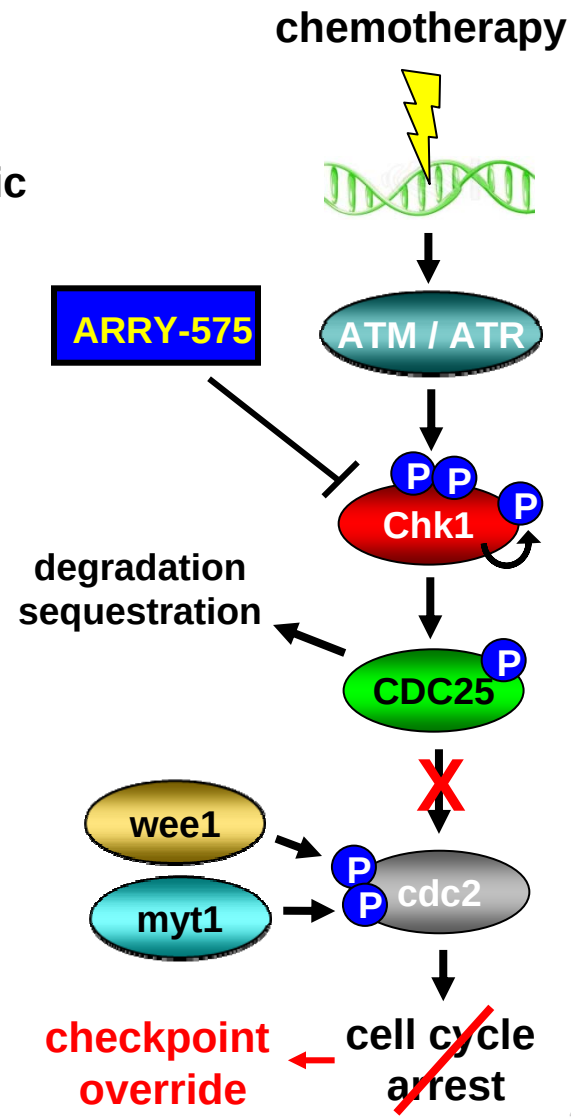
The opportunity for Chk1 inhibitors: chemo-potentiation

- **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

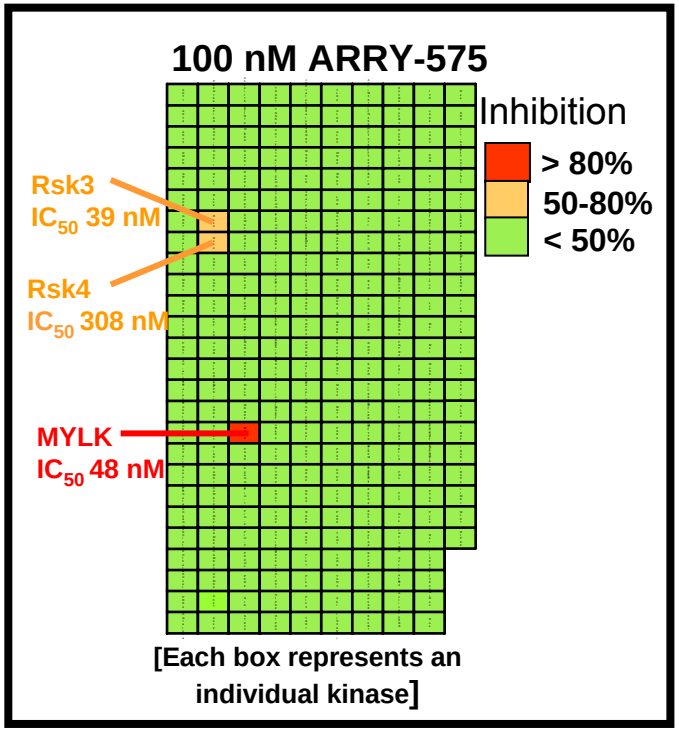


ARRY-575: *in vitro* profile

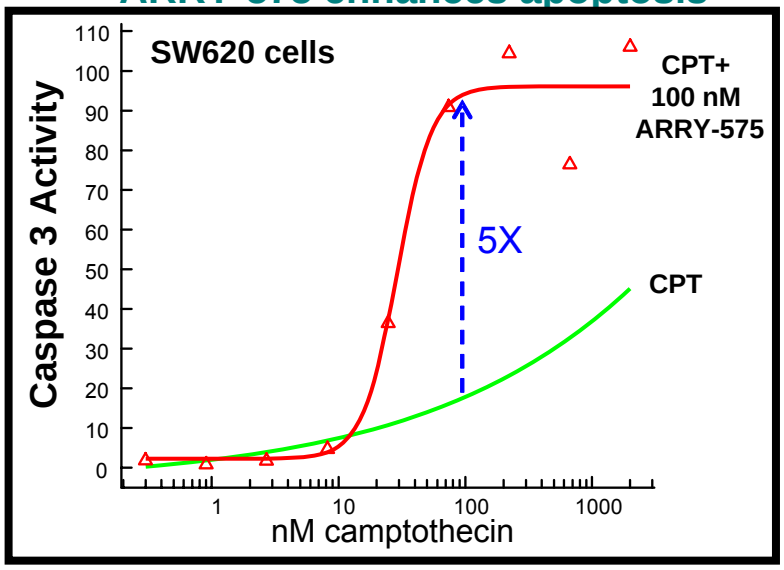
ARRY-575 is potent

Chk1 Enzyme Assay	IC_{50} (nM)
ARRY-575	2

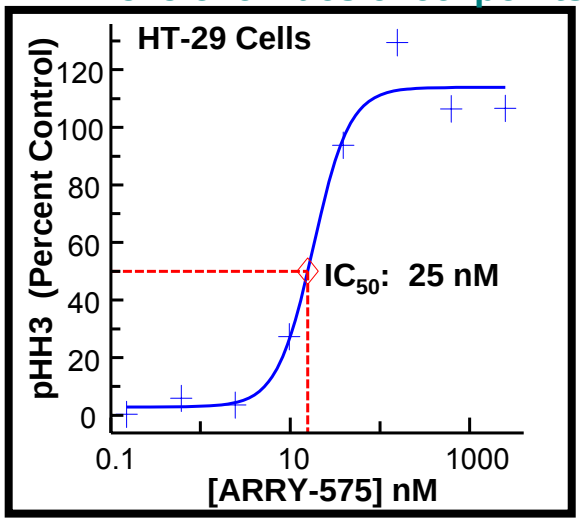
ARRY-575 is selective



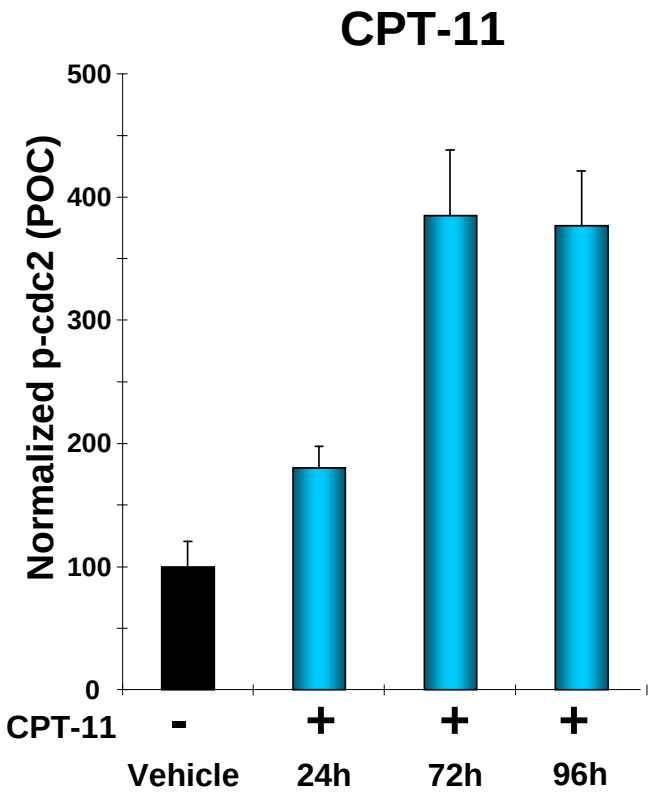
ARRY-575 enhances apoptosis

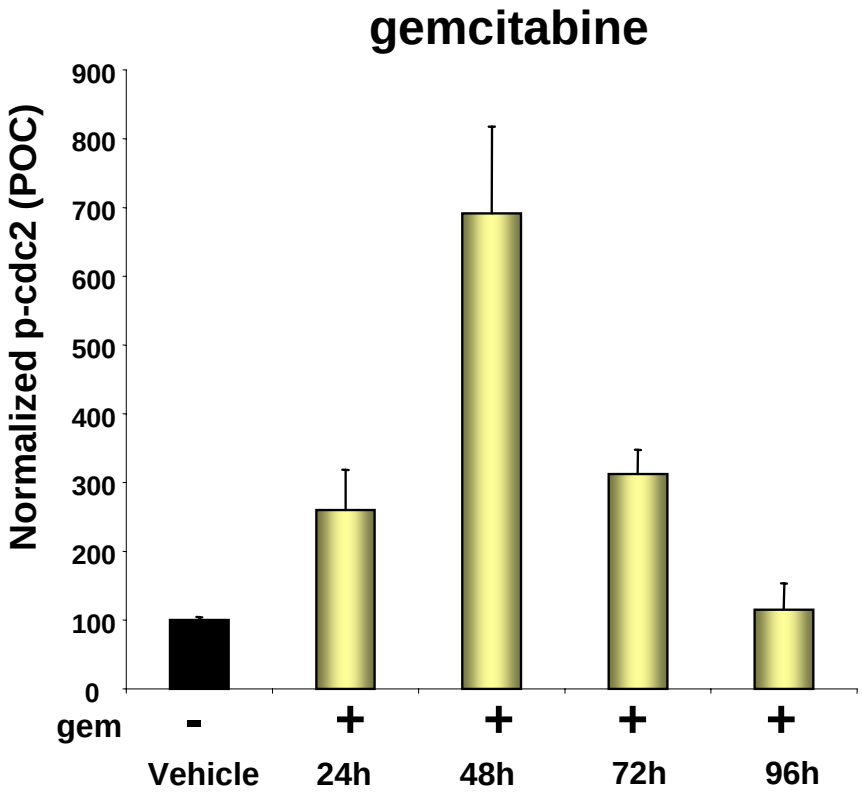


ARRY-575 overrides checkpoints



Checkpoint activation is protracted *in vivo*

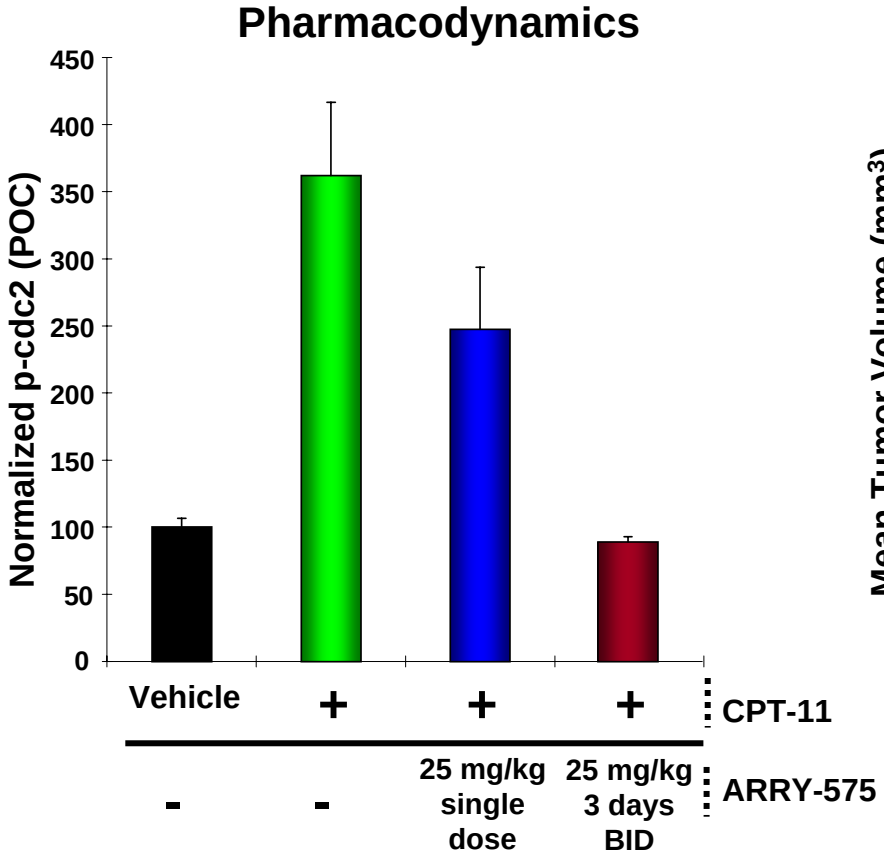


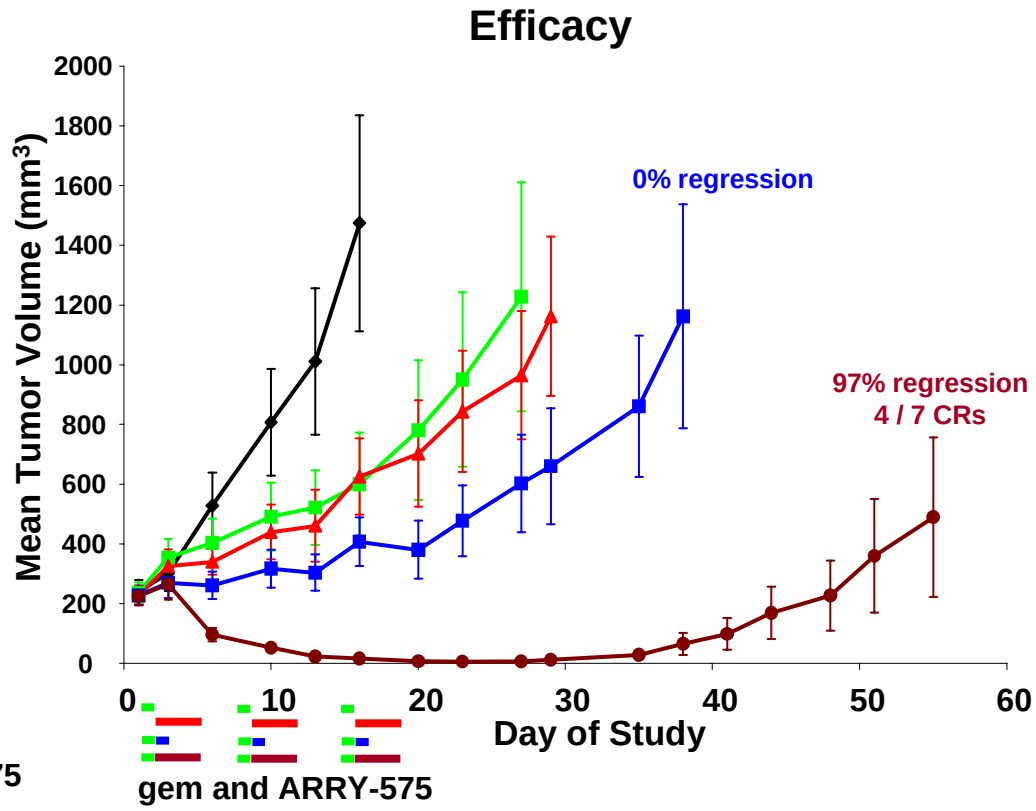


- **Chemotherapeutics that target replication induce sustained checkpoint activation**

HT-29 tumors

Prolonged Chk1 inhibition is required for maximal checkpoint override



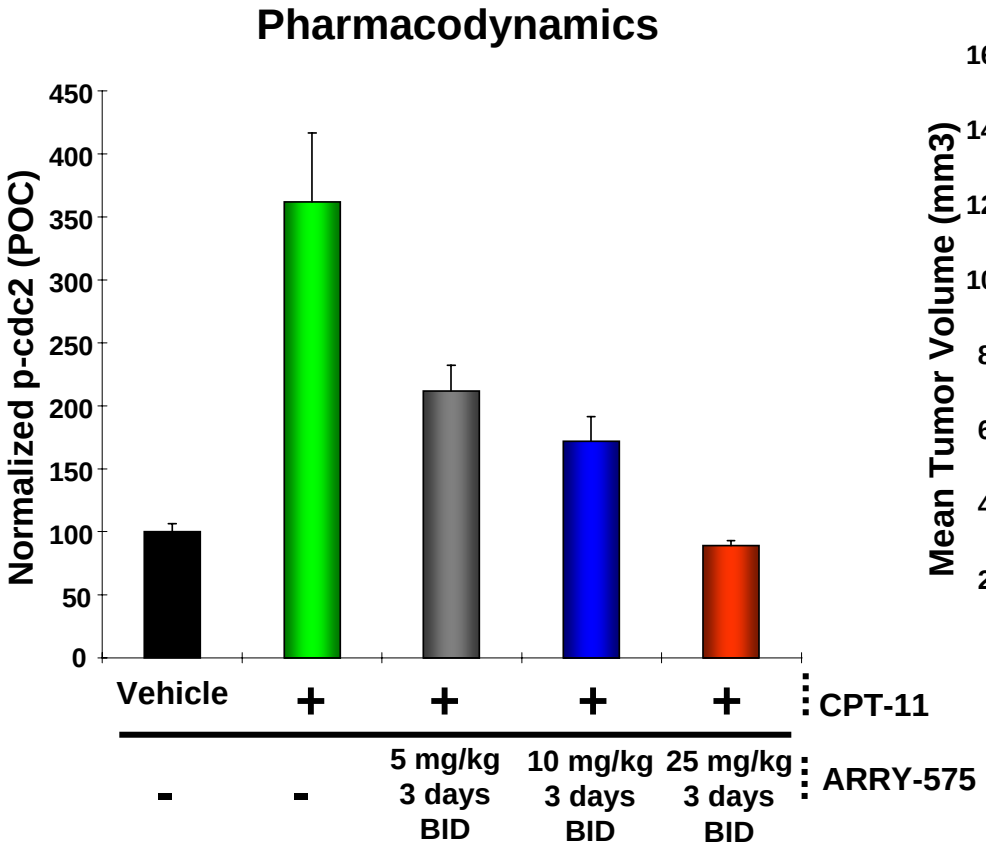


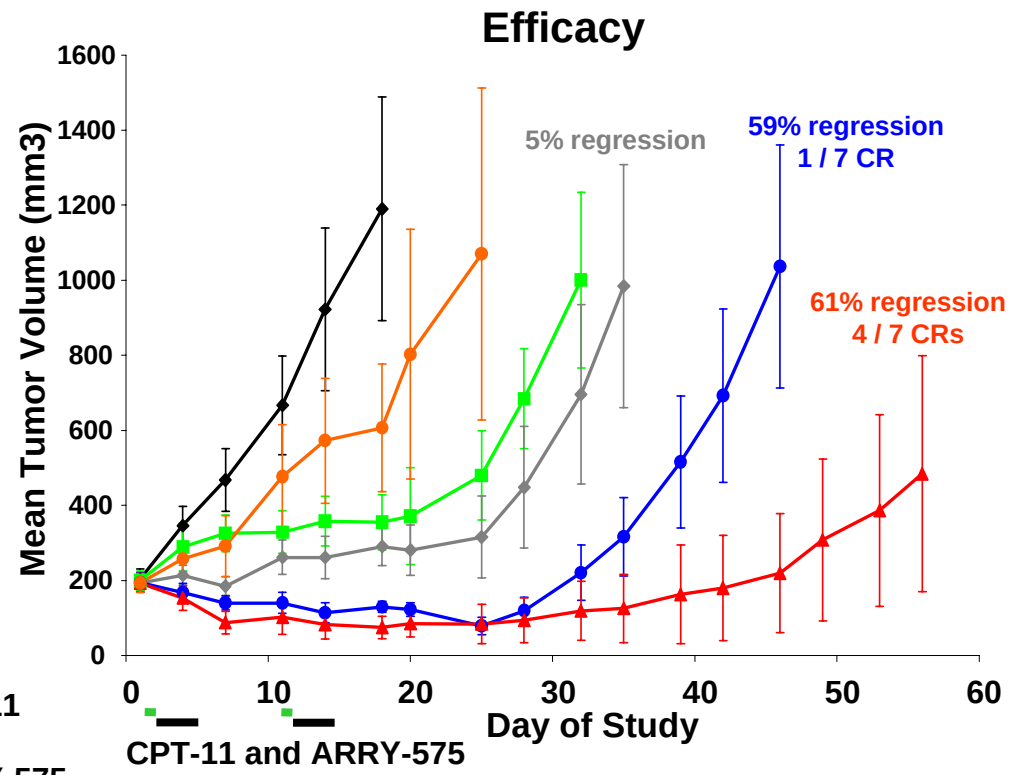
- **Oral delivery provides flexibility for multi-day dosing**

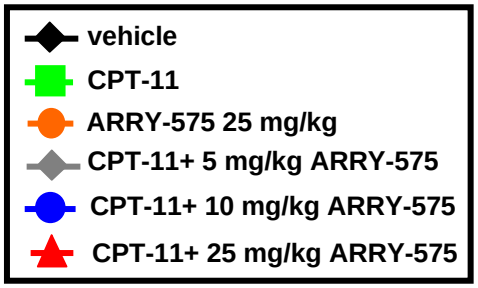
gem: 120 mg/kg (IP)
ARRY-575: 25 mg/kg BID (PO)
3 cycles of dosing

HT-29 tumors

Checkpoint override correlates with efficacy



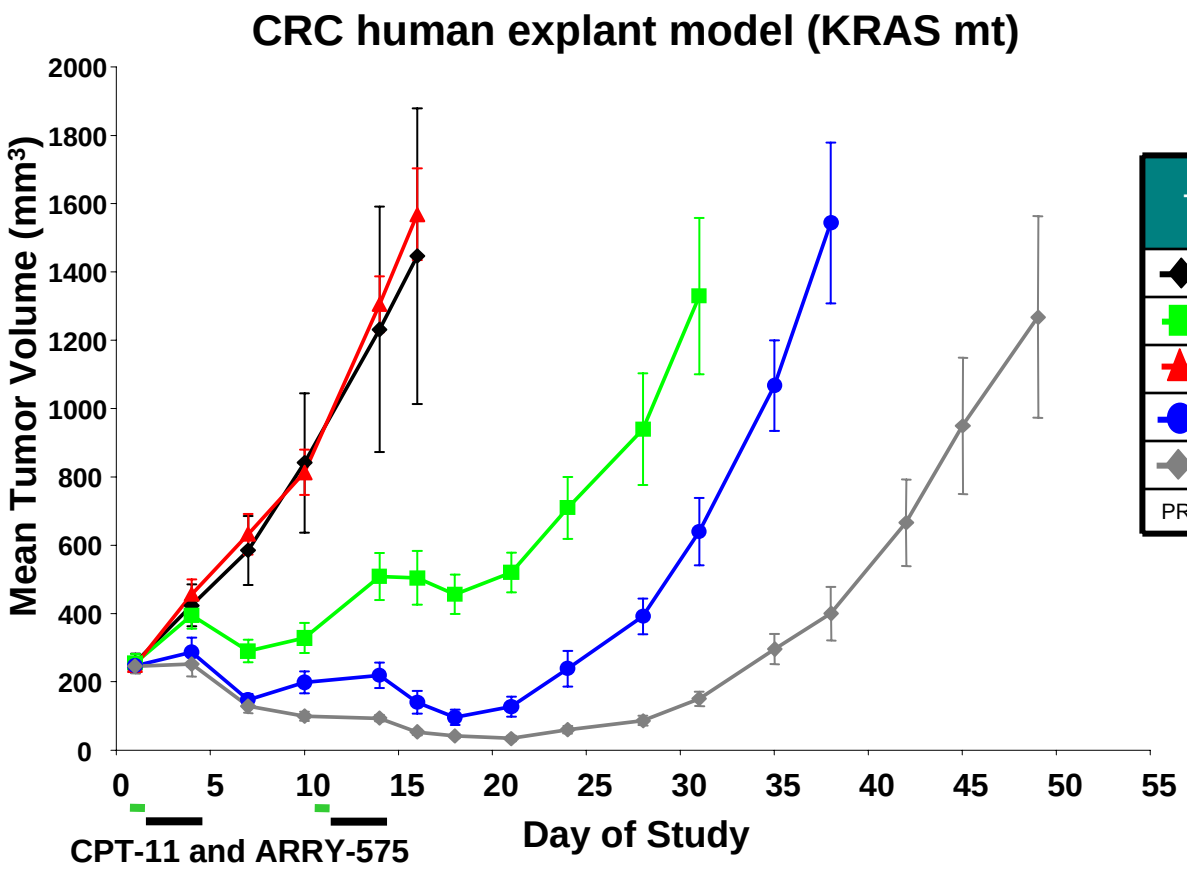




CPT-11: 100 mg/kg (IP)
ARRY-575: PO, BID for 3 days
2 cycles of dosing

HT-29 tumors

ARRY-575 potentiates CPT-11 in patient derived explants



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

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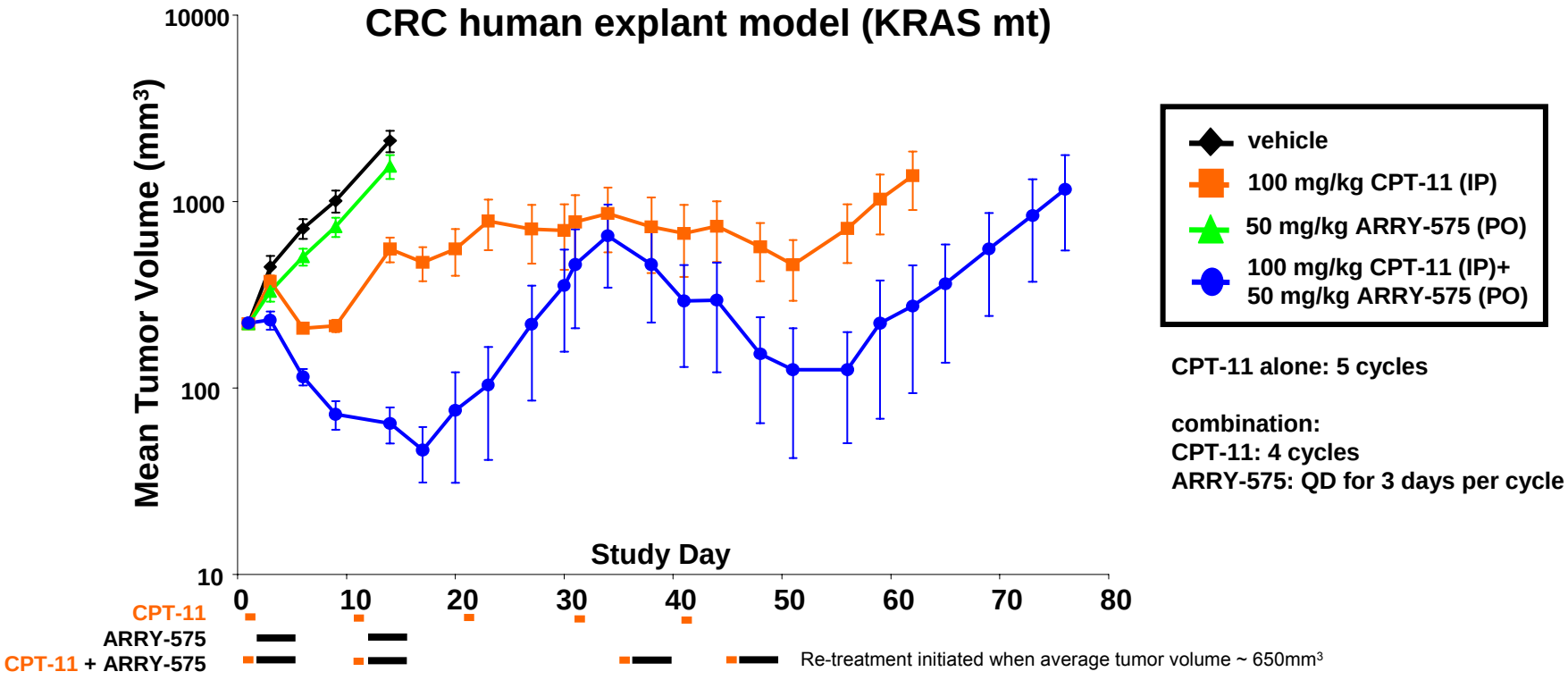
ARRY-575 combination therapy is active following tumor re-growth

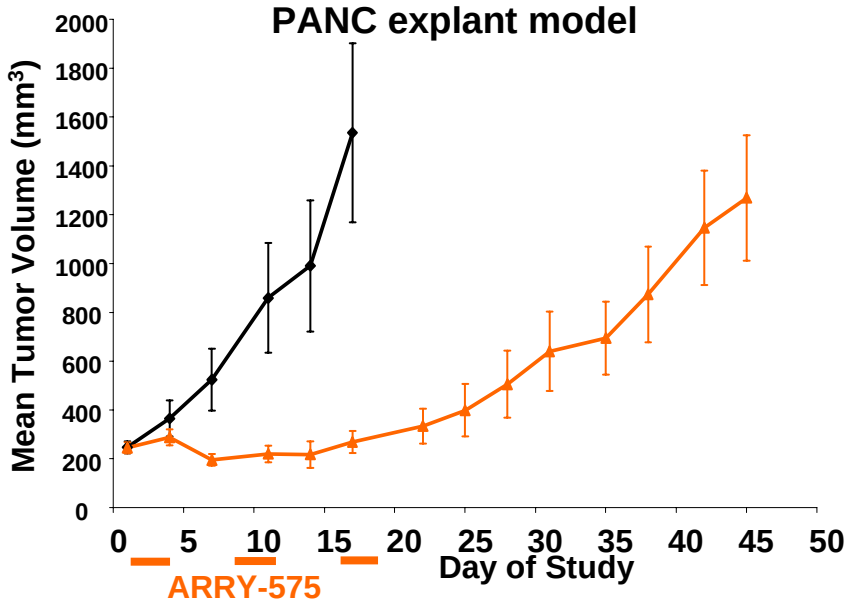


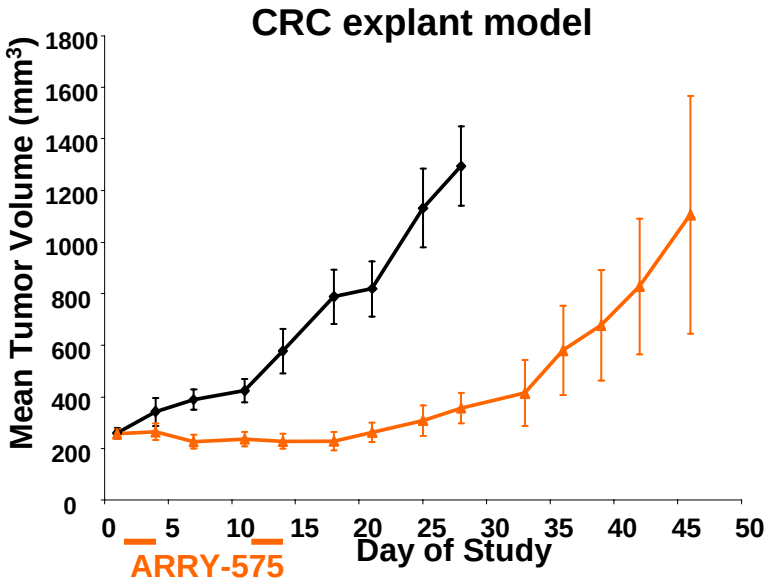
CPT-11 alone: 5 cycles

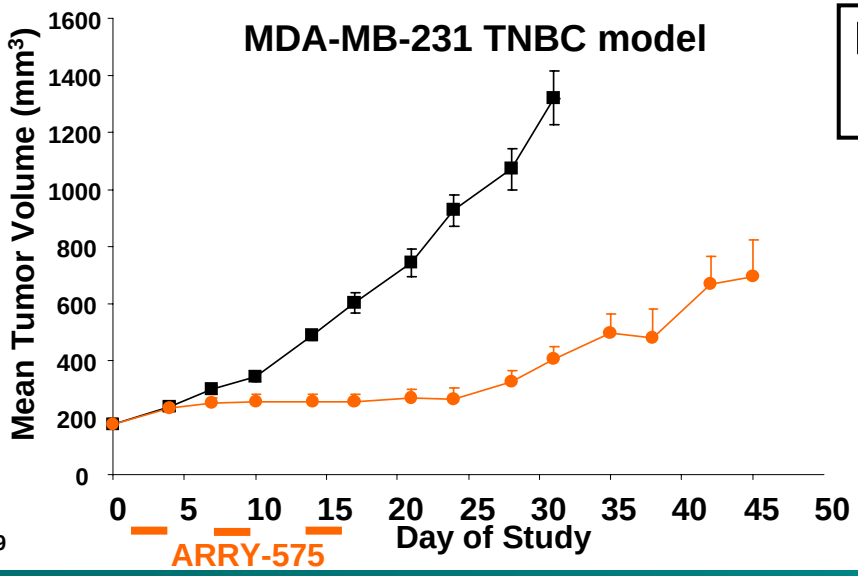
combination:
CPT-11: 4 cycles
ARRY-575: QD for 3 days per cycle

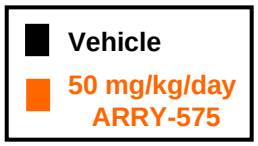
Treatment	Initial Treatment		Re-growth Treatment	
	% Mean Tumor Regression	PR	% Mean Tumor Regression	PR
CPT-11	5	1 / 8	N/A	N/A
CPT-11 + ARRY-575	79	8 / 8	81	7 / 8

ARRY-575 mono-therapy









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

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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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