

Prexasertib (LY2606368)

A CHK1 Inhibitor

Eli Lilly and Company
Pediatric ODAC Meeting
22 June 2017

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

Lilly Speakers

Introduction

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Prexasertib Development in
Adults & Pediatrics

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Research Advisor, Prexasertib

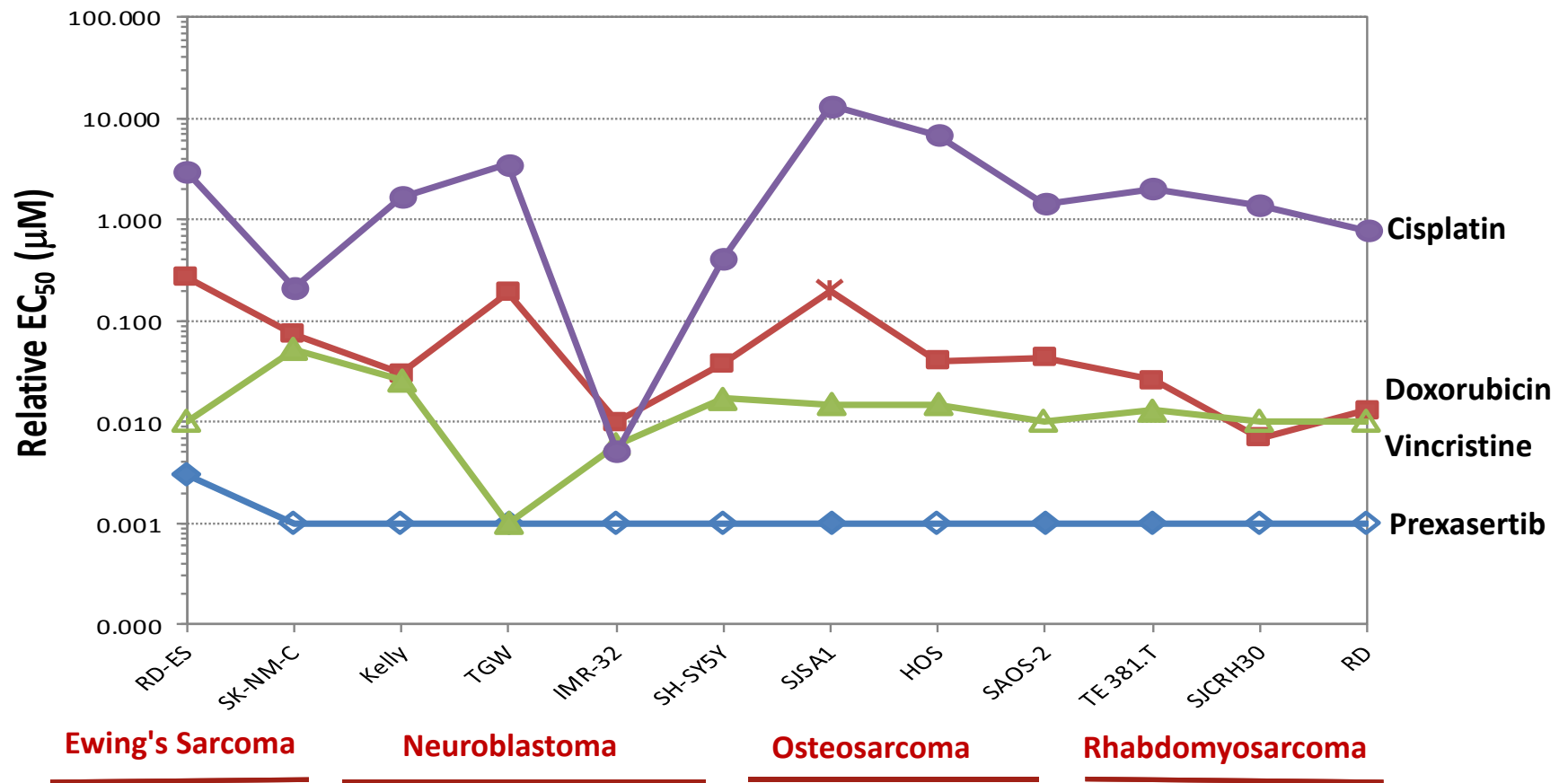
Lilly's Commitment to Pediatric Cancer Research

- Lilly's commitment to pediatric cancer research
 - Internal and collaborative development of nonclinical pediatric research capabilities
 - Early evaluation of Lilly's oncology drugs in these nonclinical models
 - Clinical evaluation of Lilly's oncology drugs when supported by nonclinical models
 - Support Innovative Medicines Initiative 2 partnership
 - Collaborative effort to develop comprehensive nonclinical proof of concept models to support clinical development in children with cancer
 - Find new approaches to solving the scientific and operational challenges of pediatric cancer drug development
- The goal is to improve treatment options for children with cancer
- Today we present our development plans in two drugs in children with cancer
 - LARTRUVO™ (olaratumab)
 - Prexasertib

Regulatory History

- Prexasertib is not approved for marketing in the United States or any other country worldwide
- Events:
 - 2010: The initial IND to support Study JTJA was in effect
 - 2015: The Office of Orphan Products Development of the FDA granted orphan drug designation status for the treatment of anal cancer
- Clinical Program:
 - 7 ongoing or completed Lilly sponsored clinical trials (Phase 1 or 2) in adults in the United States, Europe, Japan, and Asia
 - 4 ongoing exploratory investigator-sponsored studies in adults
 - 1 ongoing trial in pediatric patients sponsored by the Children's Oncology Group in the United States (NCT02808650)

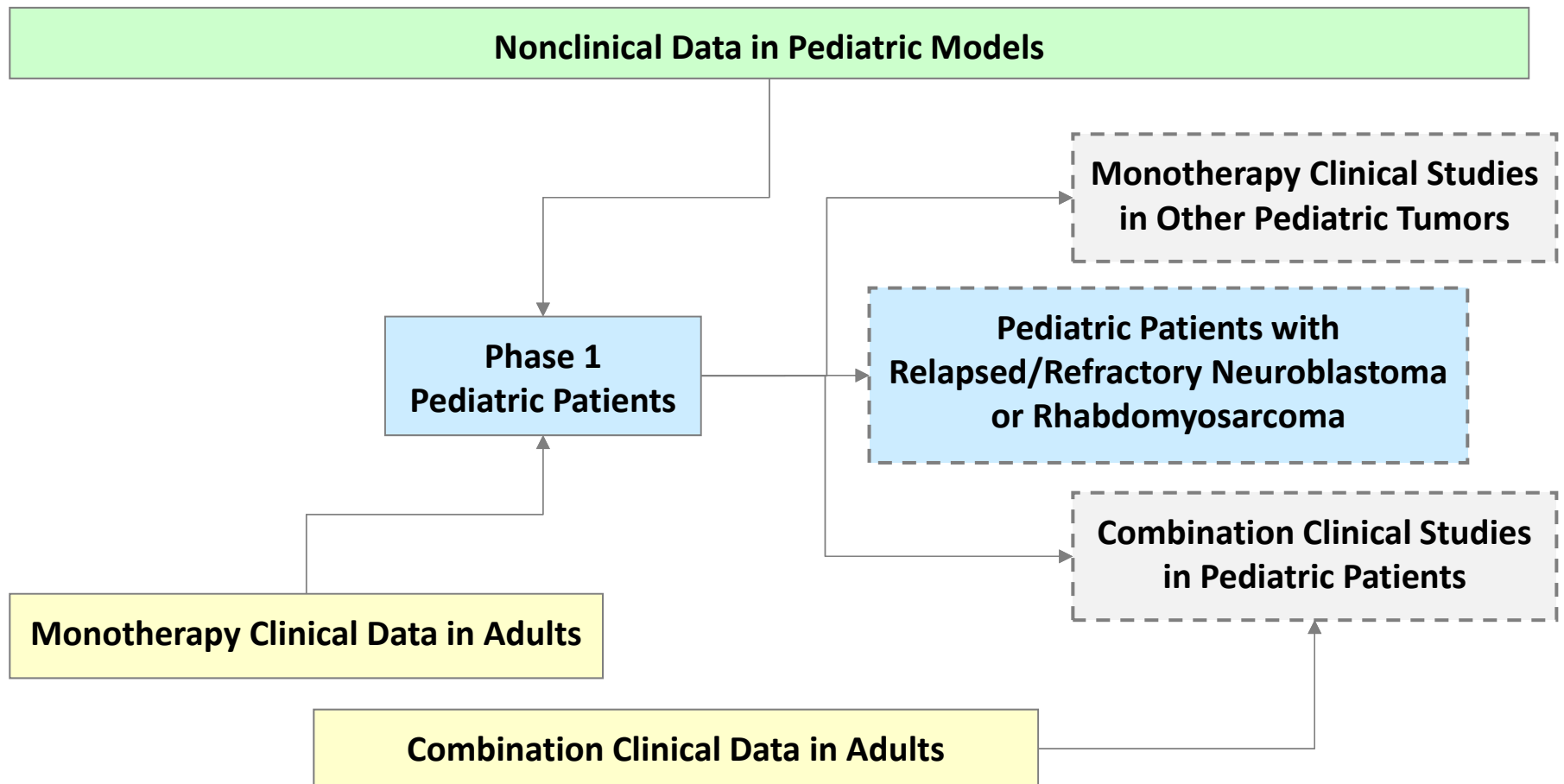
Prexasertib Is Superior to Standard of Care Agents in an In Vitro Assessment



Open symbols = value is less than lowest measured concentration

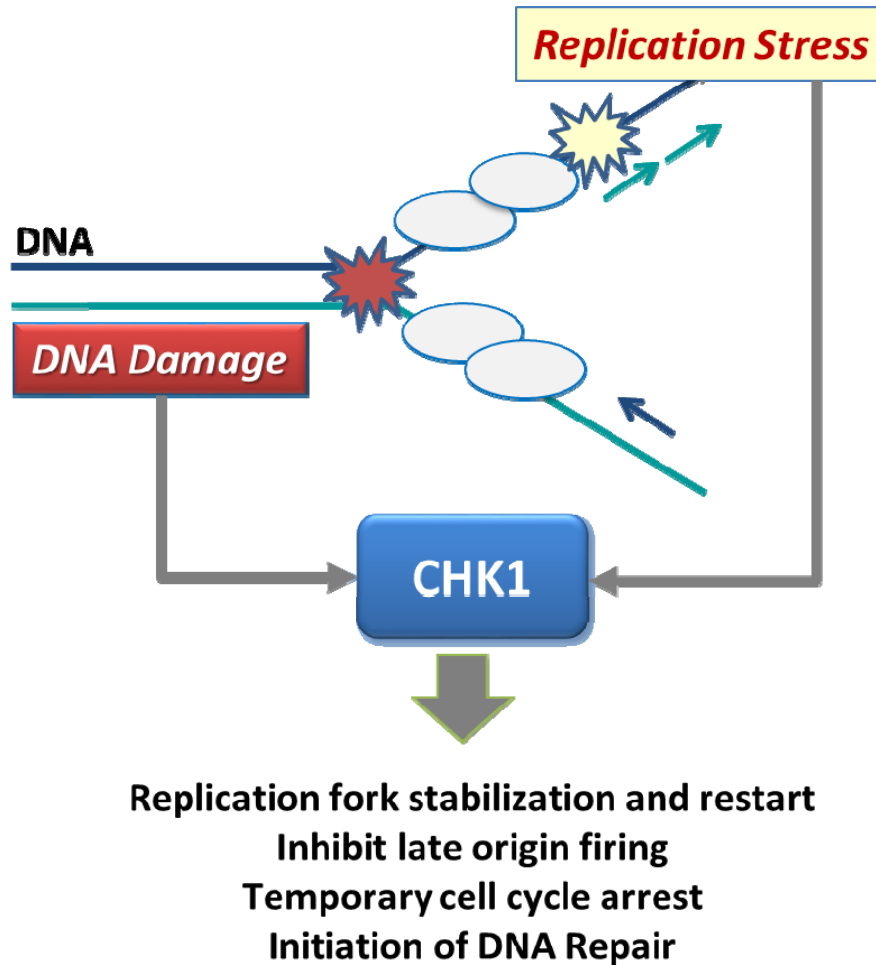
X symbols = value is greater than the highest measured concentration

Prexasertib Pediatric Development Plan



Yellow boxes represent adult clinical studies;
Blue boxes represent monotherapy in pediatric patients.

Checkpoint Kinase 1 (CHK1) Regulates Cell Cycle, DNA Replication, and DNA Damage Repair

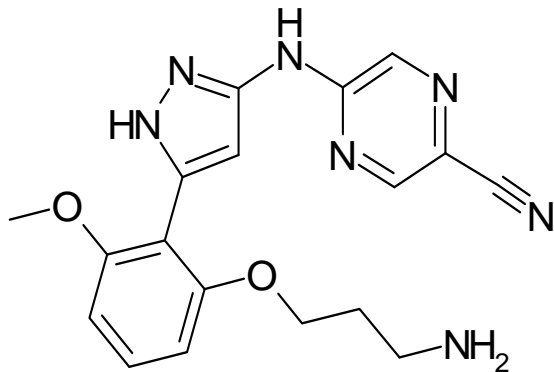


CHK1 is a master regulator of the cell cycle:

- Controls cell cycle checkpoints in response to DNA damage
- Essential for homologous recombination repair of DNA double strand breaks
- Controls DNA replication initiation and resolves replication stress

It is hypothesized that underlying alterations that increase replication stress or defects in DNA repair may lead to greater sensitivity to CHK1 inhibition

Prexasertib is a Potent ATP-Competitive Inhibitor of CHK1



Prexasertib (LY2606368)

Kinase	IC ₅₀ (nM)
CHK1	≤1nM
CHK2	8
RSK1	9
Other Targets	>35

King et al. *Mol Cancer Ther.* 2015; 14(9):2004-2013.

- Prexasertib inhibits the repair of DNA and disrupts replication, leading to replication/mitotic catastrophe and cell death
- Prexasertib inhibits growth of multiple xenografts as a monotherapy and in combination with chemotherapy, targeted agents, or radiation

Clinical Trial Experience in Adults

JTJA (First in Human Study) Established a Recommended Phase 2 Dose of Prexasertib

Dose Escalation



Part A

2 Schedules
d1-3 or d1 q14d

Dose Expansion Cohorts



Part B

- Cohort B1 - HNSCC
- Cohort B2 - SCC regardless of anatomical site



Part C

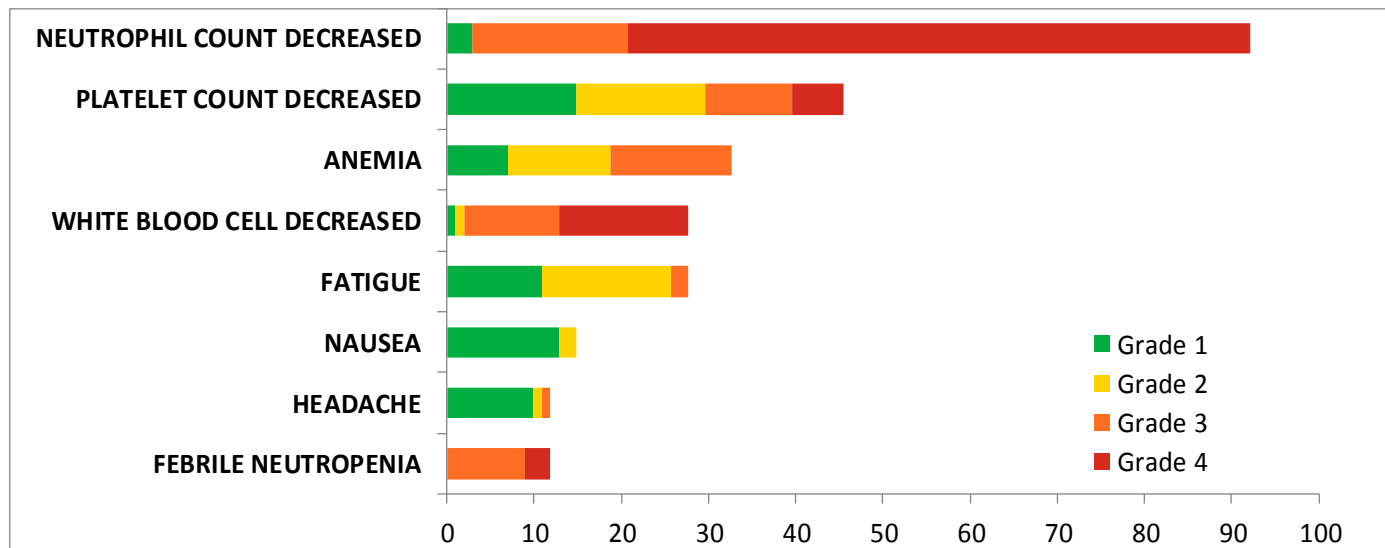
- Cohort C1 - HNSCC
- Cohort C2 - SCC NSCLC
- Cohort C3 - SCC of the anus

Summary:

- Durable objective responses observed
- PK characterized and systemic exposure aligned with the exposure predicted from nonclinical models to correlate with clinical efficacy
- Recommended Phase 2 dose (RP2D): 105 mg/m² IV every 14 days
 - Dose-limiting toxicities = neutropenia/leukopenia, febrile neutropenia, and thrombocytopenia

Transient Hematologic Toxicity Observed

Related AEs Occurring in >10% of Patients Treated at 105 mg/m² in Study JTJA



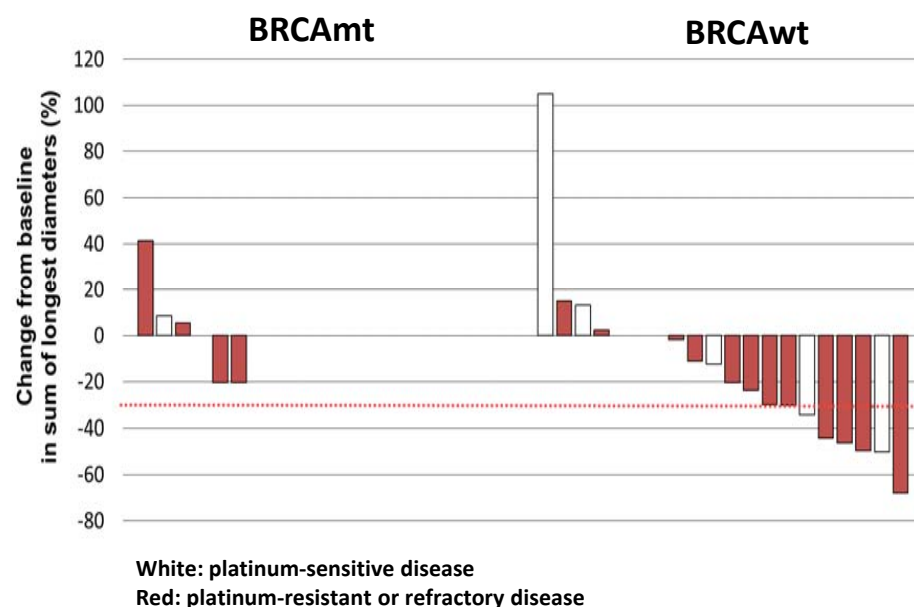
- Grade 4 neutropenia was transient, typically <5 days
 - Nadir occurs approximately 1 week after dosing
 - G-CSF may reduce extent and duration of neutropenia
- Non-hematologic toxicity was predominantly Grade 1 or Grade 2

NCI-Sponsored Phase 2 Study: Preliminary Data in Patients with Ovarian Cancer

Treatment Related Adverse Events Occurring in More Than 1 Patient

	Maximum Grade			Total (%; n=32)
	2 (%)	3 (%)	4 (%)	
Neutrophil count decreased	6	19	69	94
WBC decreased	9	44	25	78
Anemia	66	0	0	66
Platelet count decreased	13	9	13	34
Fatigue	9	0	0	9
Nausea	9	0	0	9
Vomiting	6	3	0	9
Diarrhea	3	6	0	9
Febrile neutropenia	0	6	0	6

Best Response for Target Lesions By Patient



35% of BRCAwt high-grade serous ovarian cancer patients achieved a partial response
Median duration of response was 6 months [range up to 13 months]

Clinical Studies with Prexasertib

Phase 1

JTJA: solid tumors and HNSCC, sqNSCLC, SCC Anus

JTJK: Japanese patients (solid tumors)

JTJG: 14C (solid tumors)

JTJF: With either cisplatin, cetuximab, pemetrexed, 5FU, or LY3023414 (PI3K/mTOR inhibitor) in solid tumors

JTJI: With either cisplatin/radiation or cetuximab/radiation (locally advanced HNSCC)

JTJL : With ralimetinib (solid tumors and KRAS/BRAF mut CRC or NSCLC)

MD Anderson-Sponsored: With cytarabine/ fludarabine in AML and HRMDS

Dana Farber Cancer Institute-Sponsored: With olaparib (solid tumors)

Children's Oncology Group-Sponsored: Pediatric patients (solid tumors)

Phase 2

JTJH: Platinum-sensitive or Platinum-refractory SCLC

NCI-Sponsored
BRCAmut Ovarian or Breast Triple Negative Breast High Grade Serous Ovarian

Dana Farber Cancer Institute-Sponsored:
Molecular basket trial: markers of replication stress or DNA damage repair defects

Completed

Ongoing

The background is a solid red color with several large, overlapping, curved shapes in a lighter shade of red, creating a dynamic, abstract pattern. The shapes are primarily on the right side and bottom, with some extending towards the center.

Nonclinical Data Supporting Pediatric Clinical Studies

Prexasertib Shows Activity in In Vivo Models of Pediatric Cancer

Lilly Pediatric Models

Subtype	Response to Prexasertib
Neuroblastoma	2/3 CR 1/3 SD
Alveolar rhabdomyosarcoma	2/3 CR 1/3 PR
Embryonal rhabdomyosarcoma	1/5 CR 2/5 SD
Desmoplastic small round cell tumor	1/1 CR
Ewing's sarcoma	1/4 SD
Osteosarcoma	1/4 SD

No response in single models of hepatoblastoma, retinoblastoma, or rhabdoid tumor

Pediatric Preclinical Testing Consortium (PPTC) Pediatric Models

Subtype	Response to Prexasertib
Neuroblastoma	2/6 CR 4/6 PR
Rhabdomyosarcoma	1/2 PR
Rhabdoid	1/1 CR

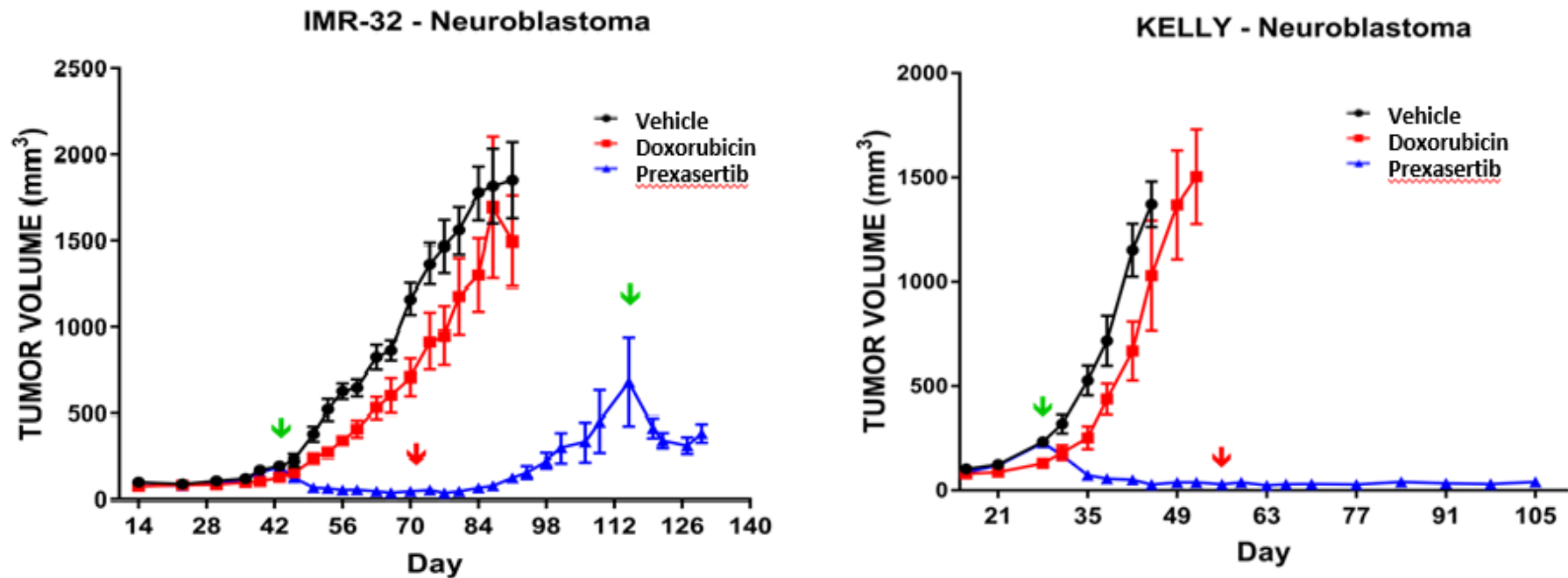
No response in a single model of Ewing's sarcoma and 2 models of osteosarcoma

- 9/9 neuroblastoma and 7/10 rhabdomyosarcoma models were sensitive to prexasertib
- Combination approaches with cytotoxic and targeted agents also are being evaluated

Lowery et al. *Clin Cancer Res.* 2017; published online; DOI: 10.1158/1078-0432.CCR-16-2876.

Prexasertib administered subcutaneously at 10 mg/kg BID x 3 for 3 weeks; Models included patient-derived and cell-derived xenografts

Prexasertib Results in Tumor Regression in Models of Pediatric Neuroblastoma



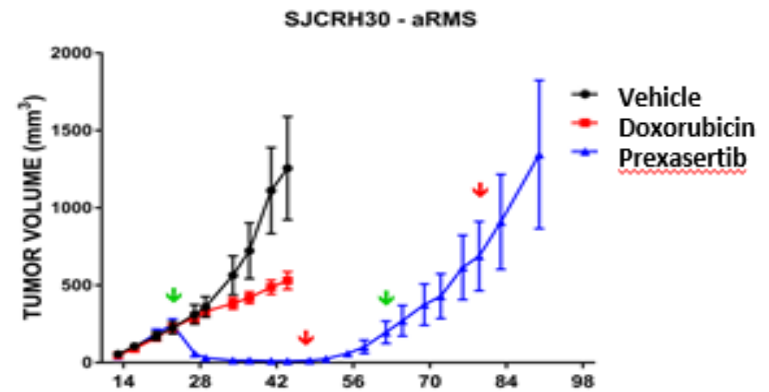
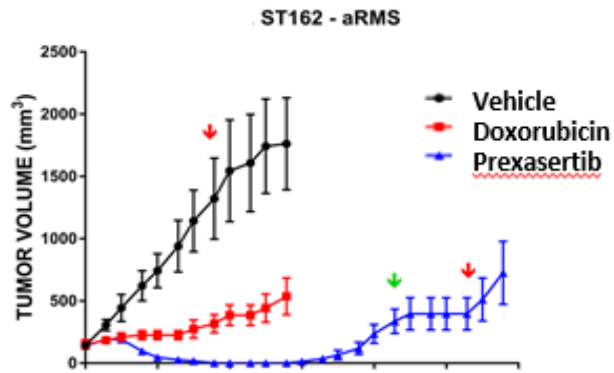
Green and red arrows represent the start and stop of a treatment, respectively

Regression was observed in neuroblastoma models when treated with 4 weekly cycles of 10 mg/kg prexasertib BID for 3 consecutive days

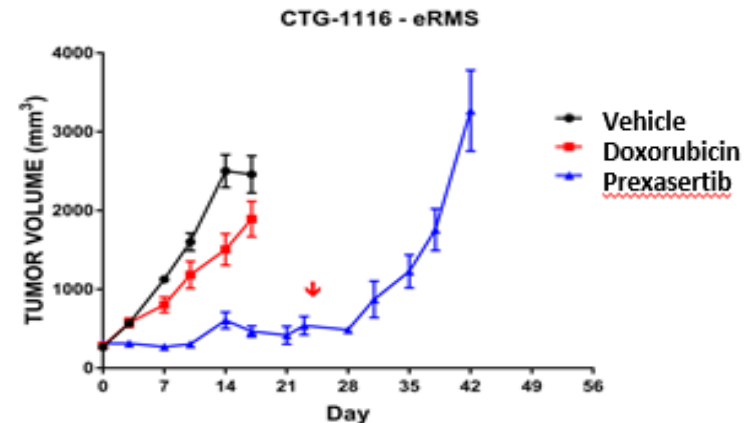
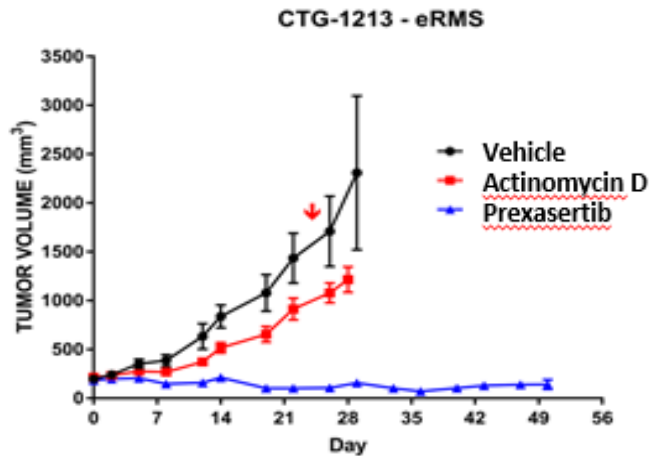
Prexasertib Results in Tumor Regression in Models of Pediatric Rhabdomyosarcoma

Unless otherwise indicated by a green arrow, treatment started on Day 0; a red arrow marks the end treatment

Alveolar
RMS Models



Embryonal
RMS Models



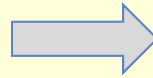
Regression was observed in rhabdomyosarcoma models when treated with 4 weekly cycles of 10 mg/kg prexasertib BID for 3 consecutive days

Ongoing Clinical Trial in Pediatric Patients

Children's Oncology Group Phase 1 Study in Pediatric Patients

Pediatric patients (1-21 years) :

- Recurrent or refractory solid tumors, including CNS tumors
- No known curative therapy or therapy proven to prolong survival with an acceptable quality of life.



**Estimate the MTD of prexasertib
(1-hour infusion once every 14 days)**

Objectives:

- Estimate MTD and/or RP2D
- Characterize toxicities, pharmacokinetics, and antitumor activity
- Examine biomarkers
 - Tissue: Archival tumor tissue is requested from all patients
 - Peripheral Blood Mononuclear Cells

Enrollment opened in March 2017

Pediatric Dose Selection Strategy

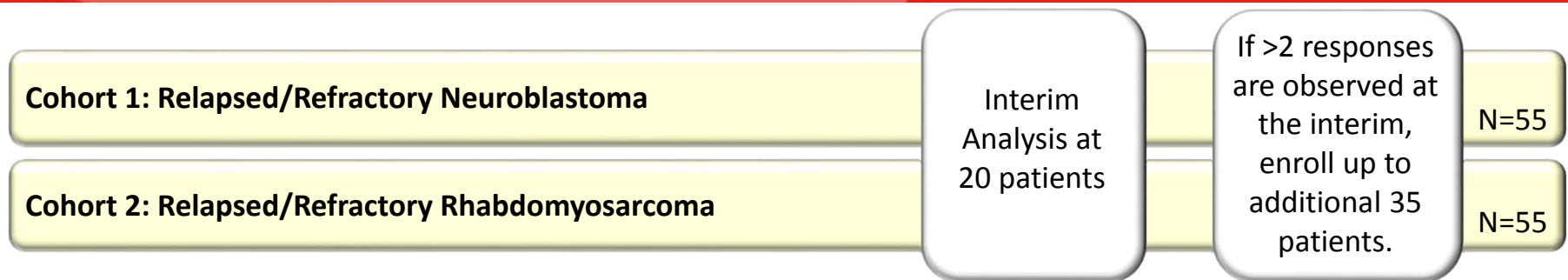
- Exposure and safety data from the Phase 1 COG study, human ¹⁴C data and PK/PD modeling will inform final dose selection
- Dosing is not planned in patients < 1 year of age
- Predicted pediatric doses to achieve equivalent systemic exposure to the adult RP2D:

Dose (mg/m ²)	BSA Range (m ²)	Approximate Age (years)
90	0.50 to <0.60	1-2
95	0.60 to <1.2	3-11
105	≥1.2	>11

- The pediatric RP2D may be different than the adult RP2D

Proposed Clinical Trial in Pediatric Patients

Potential Next Study in Pediatric Patients



Key Entry Criteria:

- ≥ 1 year and ≤ 21 years
- Not be an appropriate candidate for surgery, radiotherapy, or other conventional systemic therapy
- No more than 2 prior therapies for relapsed/refractory disease

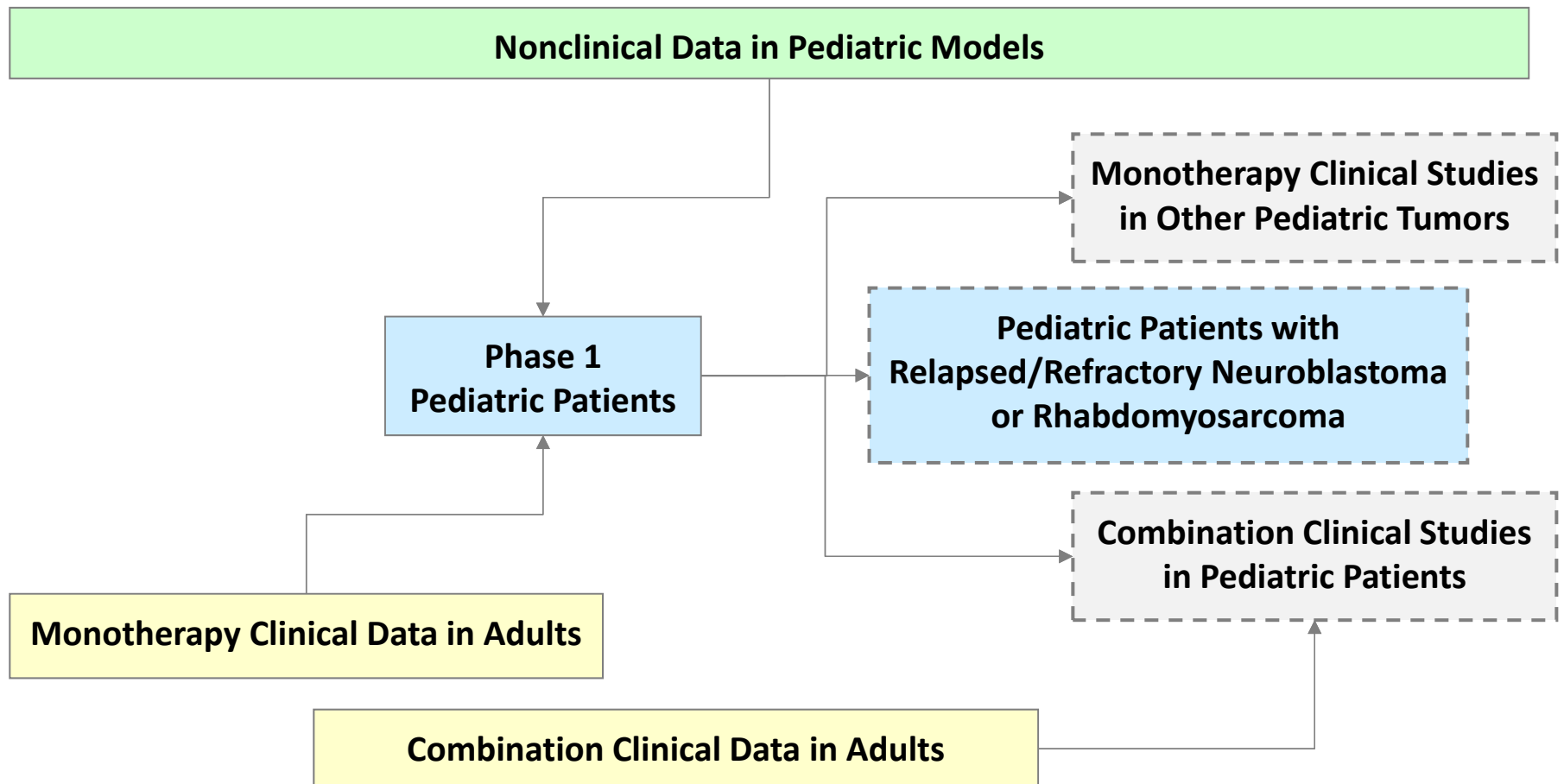
Primary Objective:

- Overall response rate (ORR)
- If the lower bound of a 95% CI is $>15\%$, then prexasertib is considered to have superior ORR compared with historical controls for that cohort

Secondary/Exploratory Objectives:

- Safety and toxicity profile, PK parameters, secondary efficacy measures (e.g. centrally assessed ORR, duration of response or stable disease, event-free survival, overall survival), biomarker assessments, and patient-focused outcomes

Prexasertib Pediatric Development Plan



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