

LARTRUVO™
(olaratumab) in Advanced Soft
Tissue Sarcoma

Eli Lilly and Company
Pediatric ODAC Meeting
22 June 2017

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Lilly Speakers

Introduction

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Olaratumab
Development in Adults &
Pediatrics

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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

Challenges to Pediatric Development

- ◆ Enrollment of rare tumor types
- ◆ Complexity of pediatric cancer regimens
- ◆ Translation of nonclinical data to clinical studies
- ◆ Risk-benefit in pediatric patients

Outline

- ◆ Executive Summary
- ◆ Compound Overview and Mechanism of Action
- ◆ Regulatory History
- ◆ Clinical Trial Experience in Adults
 - Olaratumab Clinical Development Program
 - Soft Tissue Sarcoma
- ◆ Pediatric Development
 - Nonclinical Studies
 - Clinical Studies
- ◆ Conclusions and Next Steps for Pediatric Development

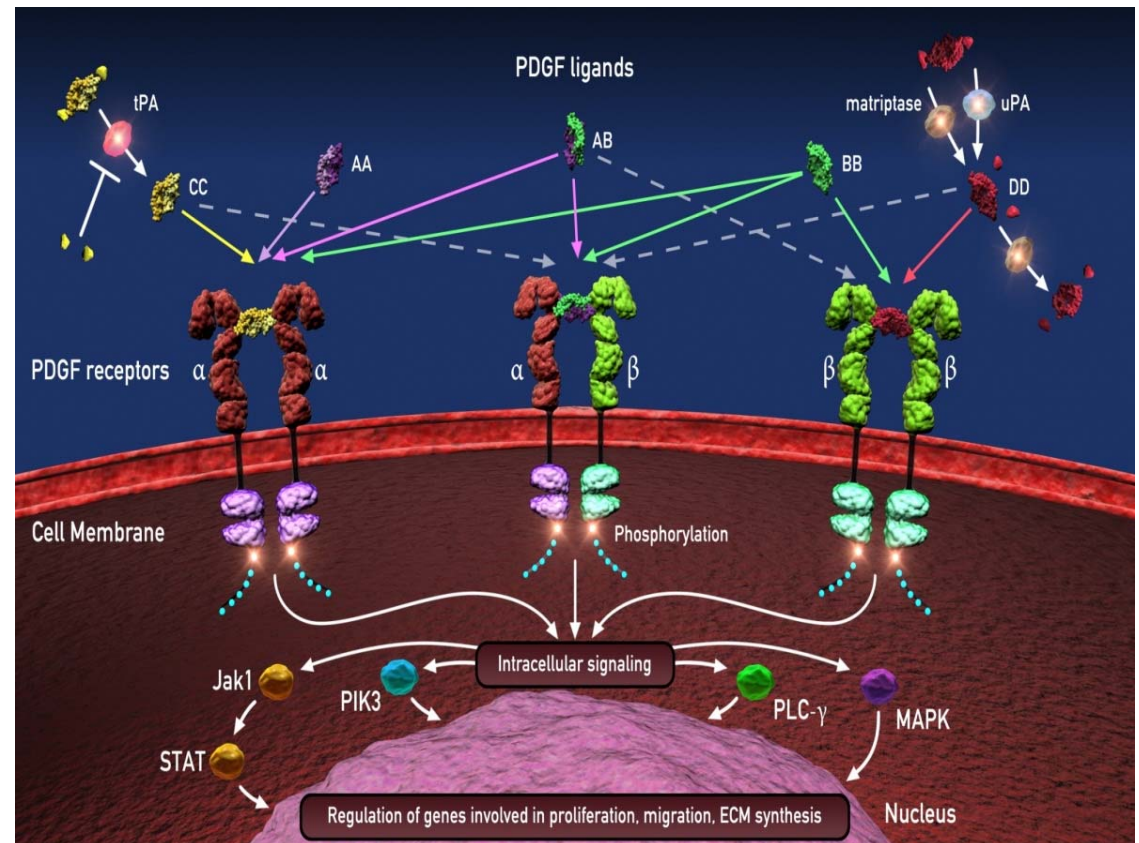
Executive Summary

- ◆ Efficacy results represent substantial improvement over standard of care in adult patients with soft tissue sarcoma (STS) in study JGDG without a significant increase in serious toxicity
- ◆ Extensive regulatory interactions with the FDA leading to accelerated approval of olaratumab in combination with doxorubicin in adults with advanced STS
- ◆ Proactive and timely initiation of a pediatric development program in parallel with the adult STS registration, culminating in the initiation of the pediatric clinical study (study JGDN)
- ◆ Nonclinical and clinical data provide rationale for studying olaratumab in combination with standard of care treatment for childhood metastatic osteosarcoma or rhabdomyosarcoma

Compound Overview and Mechanism of Action

Platelet-Derived Growth Factor Receptors (PDGFR)

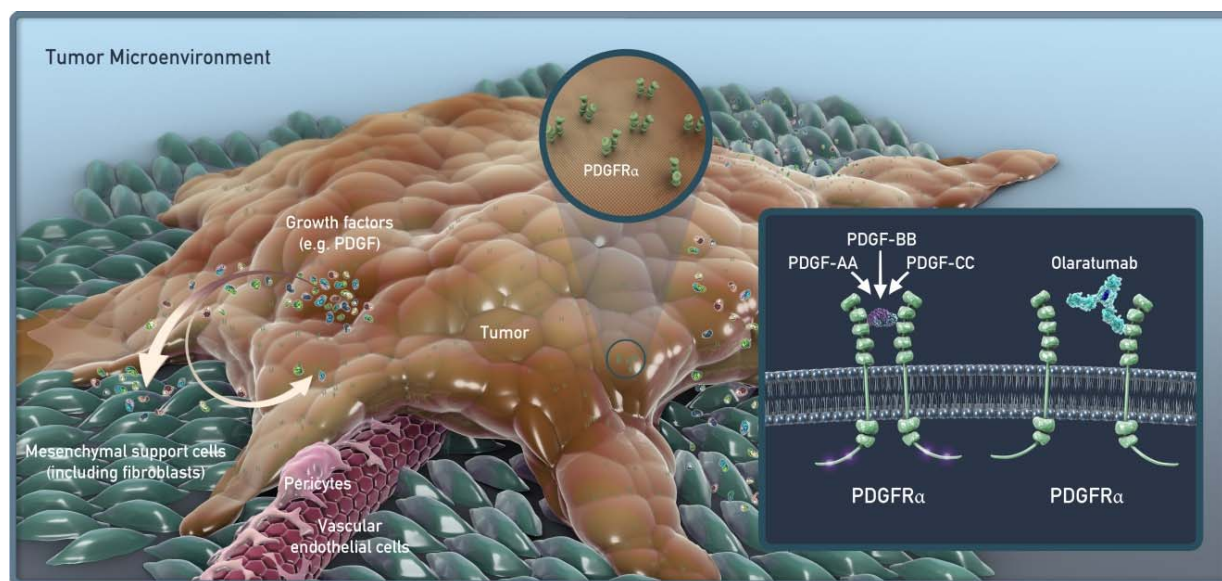
- ◆ Cell surface receptor tyrosine kinase (α,β) activated by the platelet-derived growth factor (PDGF A–D) family of ligands
- ◆ PDGF/PDGFR signaling plays a significant role in normal mesenchymal stem cell differentiation and growth and in angiogenesis and wound healing



PDGFR α : Role in Cancer

- ◆ Can be overexpressed in sarcomas
- ◆ Expression is associated with increased metastatic potential
- ◆ PDGFR α signaling on tumor stromal cells can enhance tumor growth and contribute to angiogenesis
- ◆ PDGFR α functions via autocrine and paracrine growth of tumor cells

Mechanism of Action of Olaratumab



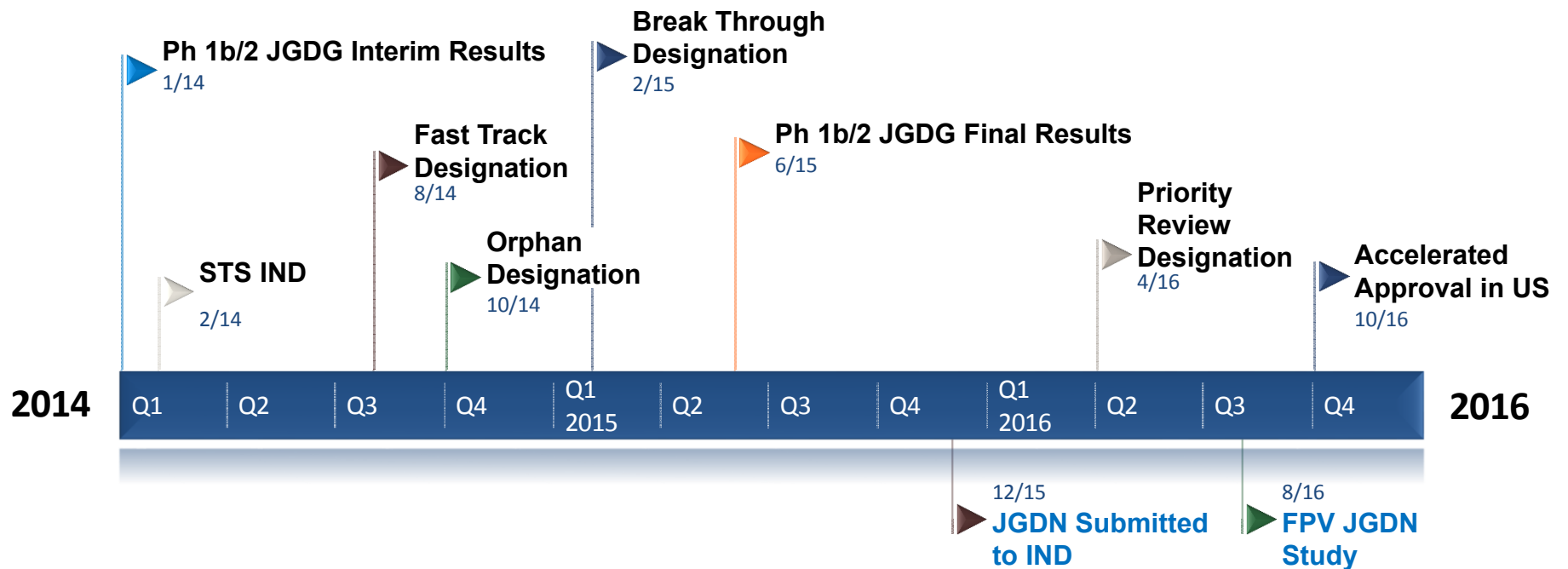
- ◆ Olaratumab is a fully human monoclonal antibody (mAb) of immunoglobulin G class 1 (IgG1) that binds PDGFR α and blocks PDGF-AA, -BB, and -CC, inhibiting ligand-induced receptor phosphorylation and downstream signaling

Regulatory History

LARTRUVO™ (olaratumab) has Accelerated Approval: Indication & Dose

- ◆ LARTRUVO™ is a platelet-derived growth factor receptor alpha (PDGFR- α) blocking antibody indicated, in combination with doxorubicin, for the treatment of adult patients with soft tissue sarcoma (STS) with a histologic subtype for which an anthracycline-containing regimen is appropriate and which is not amenable to curative treatment with radiotherapy or surgery
- ◆ Approved LARTRUVO™ Dose: 15 mg/kg as an intravenous infusion over 60 minutes on Days 1 & 8 of 21 day cycle

Extensive FDA Interactions Leading to Accelerated Approval



Clinical Trial Experience in Adults

Olaratumab Clinical Trial Development

- ◆ Phase 1 study results provided an acceptable safety profile and PK properties to proceed into Phase 2 clinical trials
 - JGDC – US study (N = 19)
 - 5 cohorts doses between 4 mg/kg qw and 20 mg/kg q2w
 - No DLTs observed in the trial, therefore the MTD was not reached
 - Most common AEs were fatigue, constipation, diarrhea, nausea, and pyrexia; all Grade 1-2
 - PK – Mean C_{max} and AUC increased in a greater than dose proportion, suggesting nonlinear PK.
 - Dose rationale for JGDG: olaratumab 15 mg/kg on Days 1 & 8 of 21-day cycle
 - Dose selected to achieve clinical trough serum levels of olaratumab consistent with those associated with anti-tumor activity in nonclinical models

- ◆ Completed or ongoing olaratumab trials in multiple combinations and tumor types - 14 Phase 1/2 trials and 1 Phase 3
 - 7 trials in soft tissue sarcoma (olaratumab + chemotherapy regimens)
 - 4 trials in ovarian, lung, pancreas or prostate cancer (olaratumab + chemotherapy regimens)
 - 4 trials in solid tumors, glioblastoma, or GIST (olaratumab monotherapy)

JGDG: Open-label, Multicenter, Phase 1b/2 Trial (led to accelerated approval)

Phase 1b

- Advanced STS, not amenable to surgery or radiotherapy
- Age ≥ 18 years; ECOG PS ≤ 2
- Any number of prior treatments; no doxorubicin

N=15;
21-day
cycles

Cycles 1-8: olaratumab 15 mg/kg D1,8 +
doxorubicin 75 mg/m² D1 for 8 cycles
Subsequent cycles: olaratumab monotherapy if
benefit

Primary endpoint: Safety

Phase 2

- New patients, same entry criteria as in Phase 1b
- Dynamic minimization used to balance arms with respect to PDGFR α , ECOG PS, line of treatment, and histology (LMS, synovial, other)

N=130;
21-day
cycles

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Olaratumab 15 mg/kg D1,8 +
doxorubicin 75 mg/m² D1
for 8 cycles

Olaratumab
monotherapy until
progression

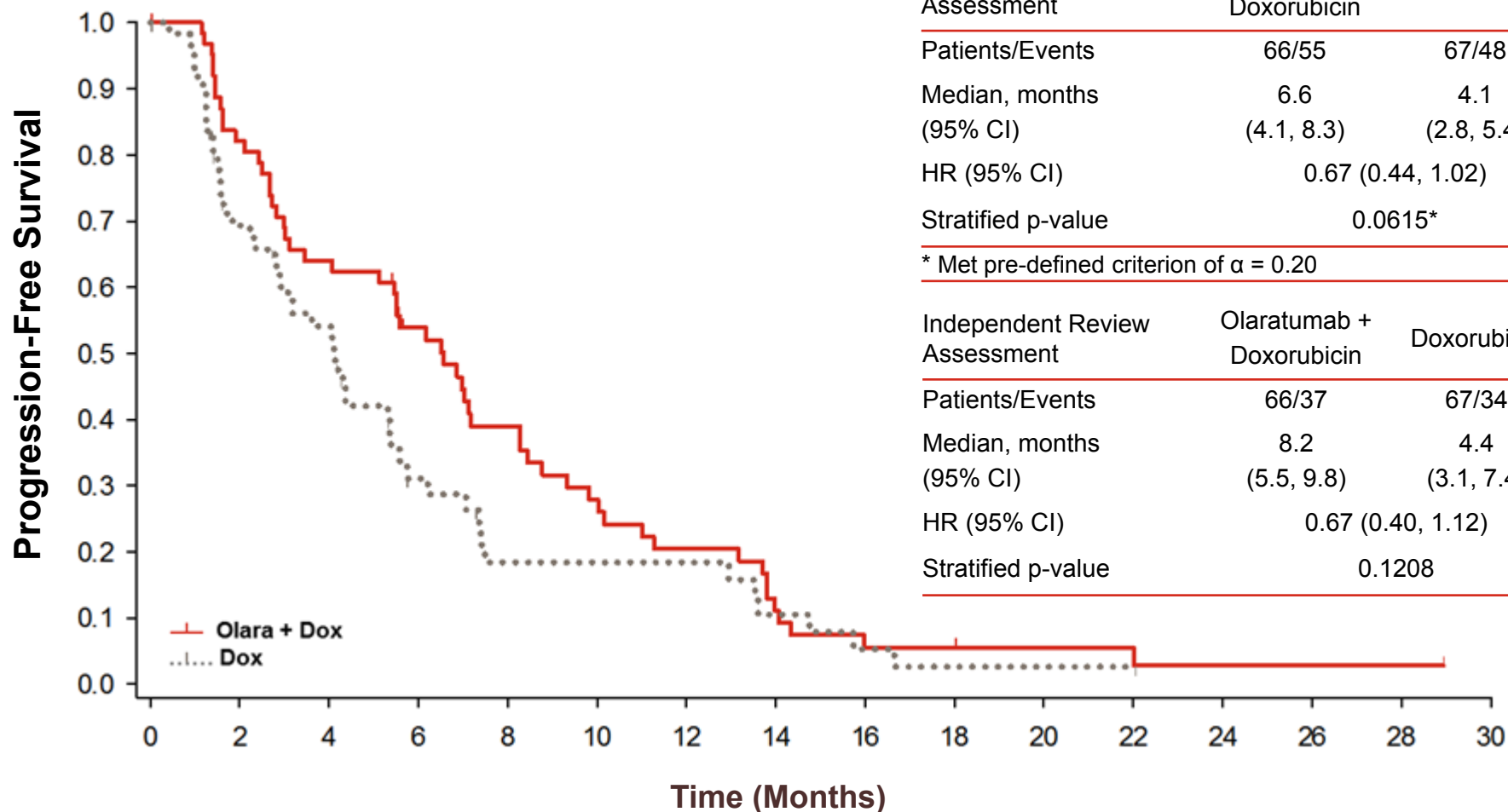
Doxorubicin 75 mg/m² D1
for 8 cycles

Option to receive
olaratumab
monotherapy
after progression

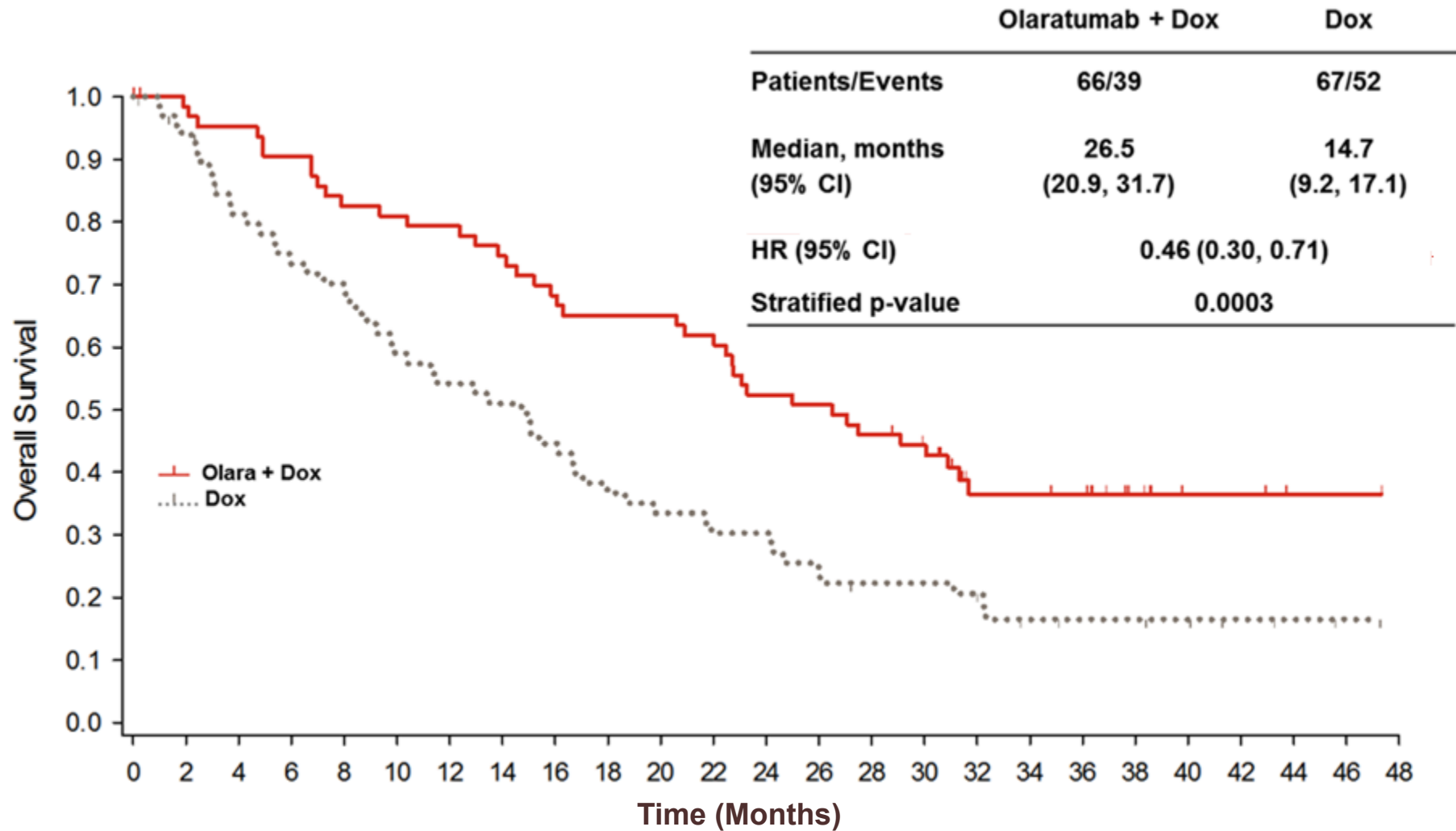
Primary endpoint: Progression-free survival

Key Secondary endpoints: Overall survival and safety

JGDG: Study Met Protocol-defined Significance Level for PFS per Investigator Assessment



JGDG: Statistically Significant Improvement in Overall Survival



JGDG: AEs >15% in Investigational Arm (%) Shows an Acceptable, Monitorable and Manageable Safety Profile

Adverse Event Term	Olaratumab + Doxorubicin ^a N = 64		Doxorubicin ^a N = 65	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Patients with any AE	98.4	79.7	98.5	69.3
Nausea	73.4	1.6	52.3	3.1
Fatigue	68.8	9.4	69.2	3.1
Musculoskeletal Pain	64.1	7.8	24.6	1.5
Neutropenia	59.4	54.7	38.5	33.8
Febrile Neutropenia	12.5	12.5	13.8	13.8
Mucositis	53.1	3.1	35.4	4.6
Alopecia	51.6	0	40.0	0
Vomiting	45.3	0	18.5	0
Infections and Infestations	42.2	7.8	41.5	10.8
Anemia	40.6	12.5	36.9	9.2
Constipation	34.4	0	32.3	1.5
Diarrhea	34.4	3.1	23.1	0
Decreased Appetite	31.3	1.6	20.0	0
Thrombocytopenia	25.0	10.9	21.5	7.7
Abdominal Pain	23.4	3.1	13.8	0
Pyrexia	23.4	0	18.5	0
Neuropathy	21.9	0	10.8	0
Cough	21.9	0	18.5	0
Headache	20.3	0	9.2	0
Dyspnea	17.2	0	18.5	1.5
Oedema Peripheral	15.6	0	10.8	0

^a The median number of doxorubicin infusions in the Investigational Arm (Olara + Dox) was 7 and 4 in the Control Arm (Dox).

JGDG: AE's of Special Interest as Expected for a mAb and No Increase in Cardiotoxicities

Adverse event (%)	Olaratumab + Doxorubicin (N=64)			Doxorubicin (N=65)		
	Any Grade	Grade 3	Grade ≥4	Any Grade	Grade 3	Grade ≥4
<i>Infusion-related reactions</i>	12.5	0	3.1	3.1	0	0
<i>Cardiac arrhythmias</i>	15.6	0	0	15.4	1.5	0
<i>Cardiac dysfunction</i>	7.8	1.6	0	6.2	0	0

Pharmacokinetics for Olaratumab in Adults is as Expected Given Monoclonal Antibody

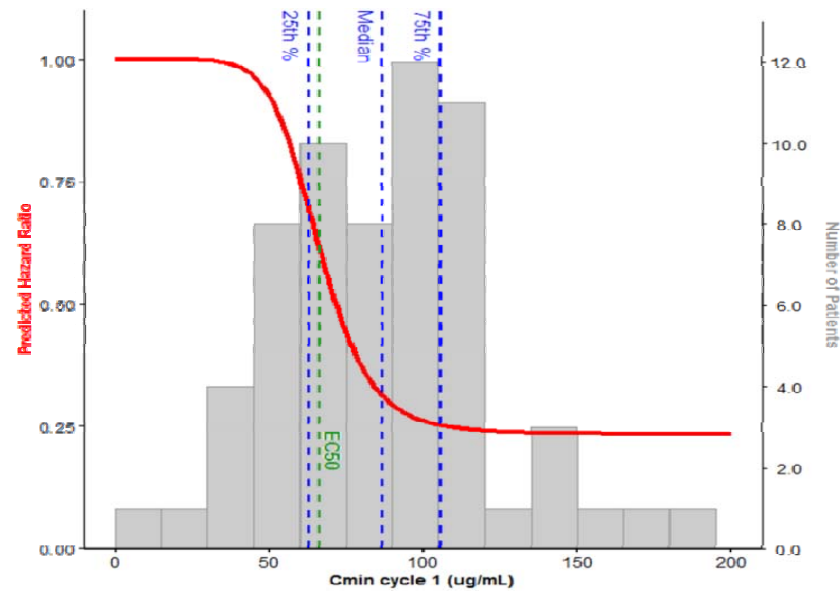
- ◆ PopPK model used a total of 1501 PK data obtained from 171 patients across 4 Phase 2 Studies (including JGDG)
- ◆ The PopPK model of olaratumab 15 mg/kg and 20 mg/kg doses is best described by a 2-compartment model with linear elimination

Clearance	Volume of Distribution (V_{ss})	Half-Life	Time to Steady State	Interpatient variability
0.0233L/h (0.56 L/day)	7.74L	11 days	50 days	15.6 - 33.3%

- ◆ Evaluated PK as a function of age, sex, body weight, race ethnicity, tumor size, tumor type, and renal & hepatic function, combination treatment
 - CL decreases with decreasing body weight in a less than directly proportional manner
 - Combination with chemotherapy did not affect olaratumab PK

Exposure-Response Relationship for Overall Survival

- ◆ A survival model estimated Olara EC_{min150}^* for overall survival at 66 ug/mL, which corresponds to the 25th percentile of C_{min1} in the study
- ◆ The maximum predicted improvement in the hazard ratio (E_{max}) for overall survival is approximately 75-77%, and was predicted to be achieved within the range of Olaratumab serum levels achieved in the study
- ◆ Significant covariates identified in the overall survival model were the ECOG prognosis score (0 vs. ≥ 1) and the number of lines of prior treatment.



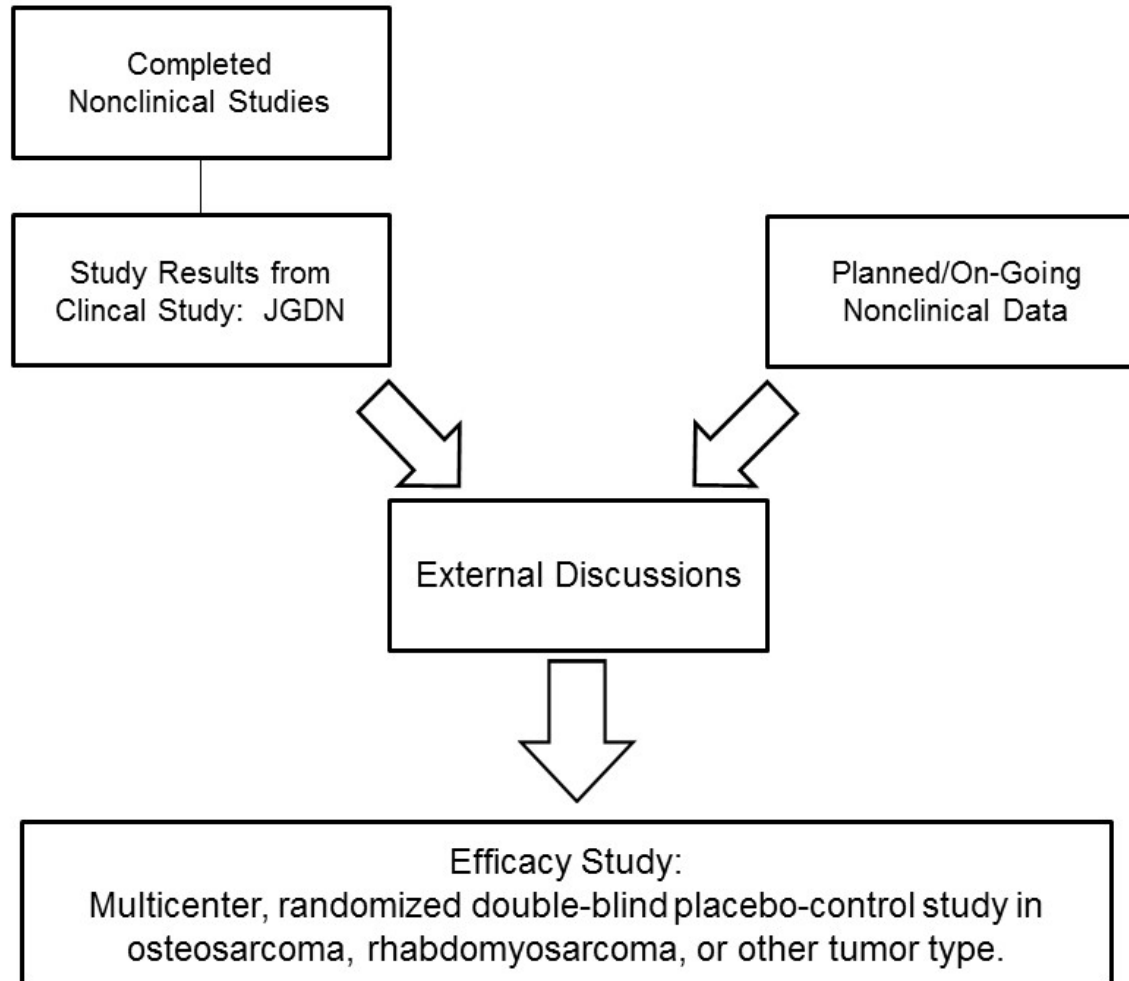
Benefit-Risk Conclusions for Study JGDG

- ◆ Efficacy results represent substantial improvement over the standard of care in the treatment of adult patients with advanced STS and led to accelerated approval
- ◆ The olaratumab plus doxorubicin combination has an acceptable, monitorable, and manageable safety profile.
- ◆ The improvement in median overall survival was achieved without an increase in serious toxicity
- ◆ PK/PD analysis supports olaratumab 15 mg/kg as the registered dose. A loading dose strategy of olaratumab 20 mg/kg in cycle 1 followed by 15 mg/kg thereafter is currently tested in adults to further optimize the benefit-risk in study JGDJ (ANNOUNCE)
- ◆ Randomized, double-blind, placebo controlled, global, multi-center Phase 3 confirmatory study JGDJ (ANNOUNCE) is fully enrolled. Started September 2015, expected completion 2020

Pediatric Development

Nonclinical Data and Supporting Studies

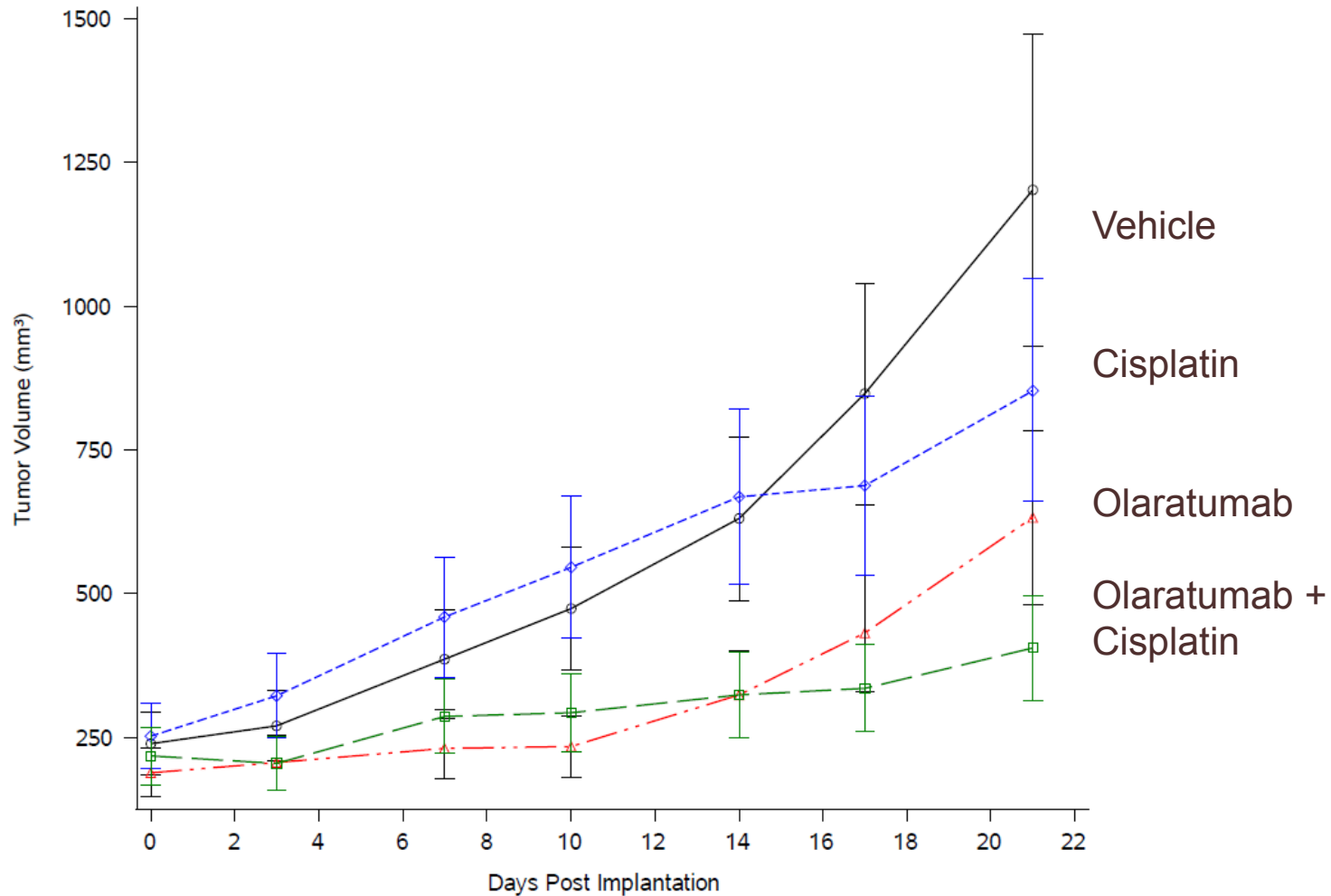
Overview of the Pediatric Development Program



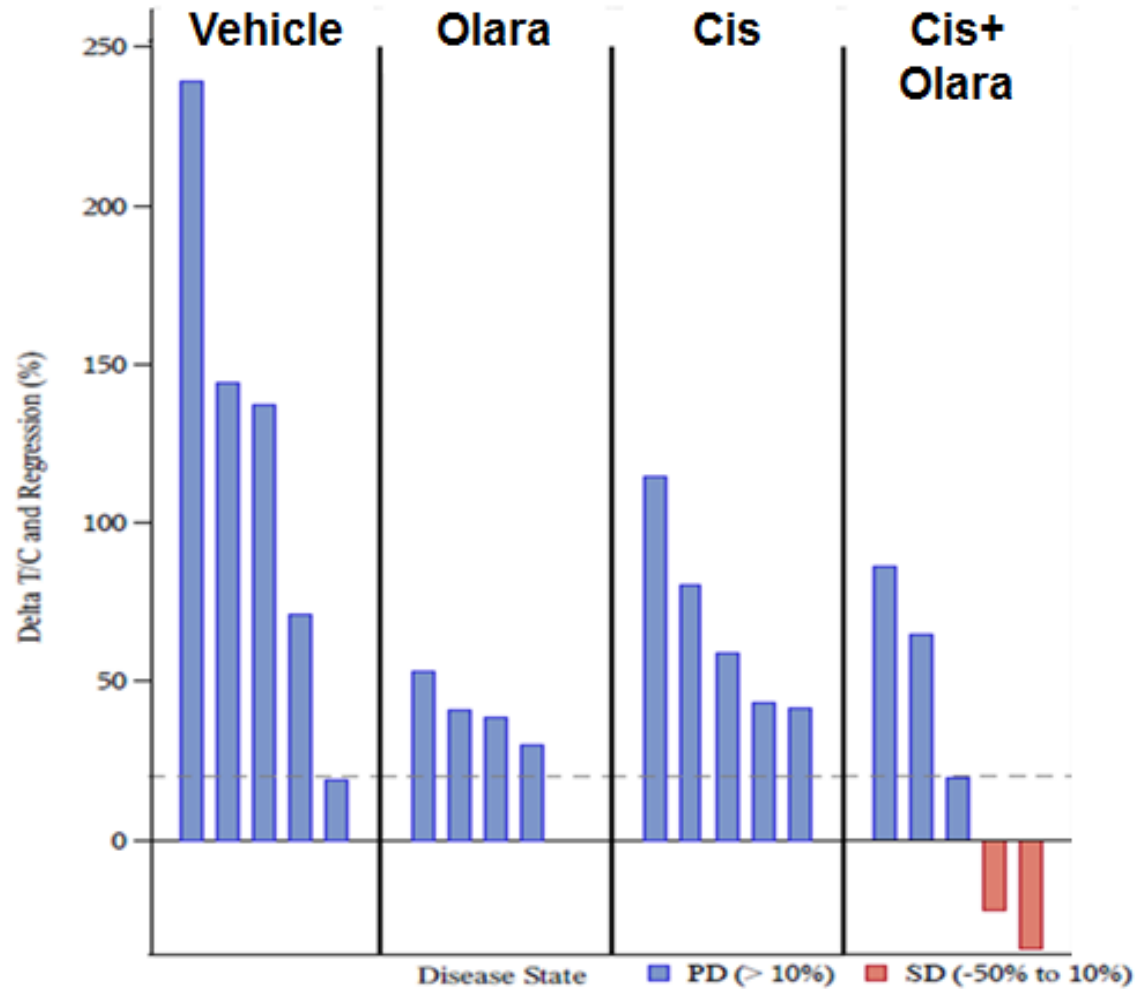
Nonclinical Data in Pediatric Models

- ◆ Olaratumab was evaluated in multiple pediatric cell lines with osteosarcoma and rhabdoid being the most significantly affected
- ◆ Olaratumab was evaluated in multiple mouse models of pediatric cancer:
 - Rhabdomyosarcoma (RMS)
 - Osteosarcoma
 - Synovial sarcoma
 - Rhabdoid tumor
- ◆ At present, osteosarcoma is one of the leading tumor types for further development

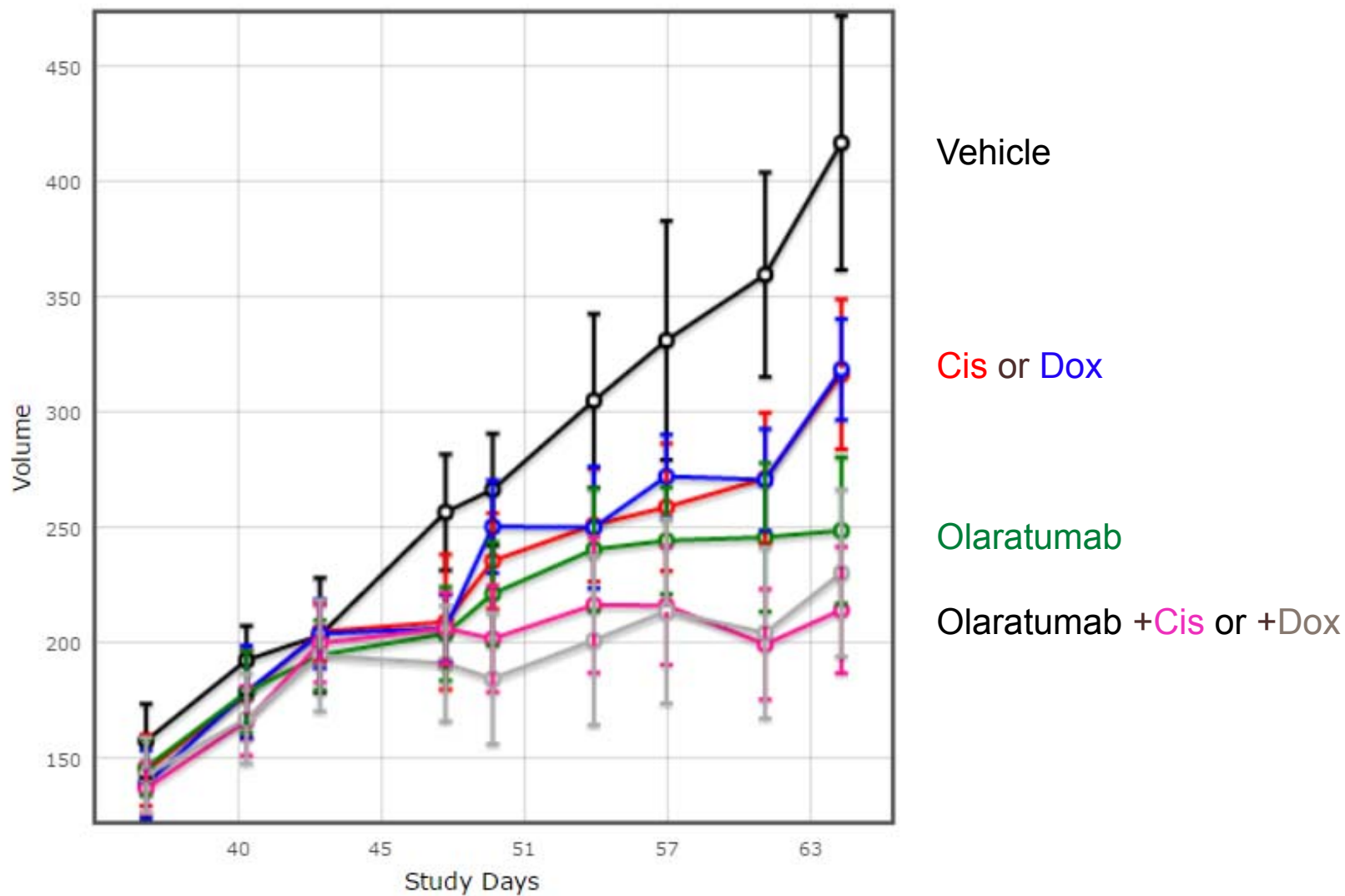
Olaratumab Demonstrated Efficacy in an Osteosarcoma Patient-derived Xenograft Model CTG-1095



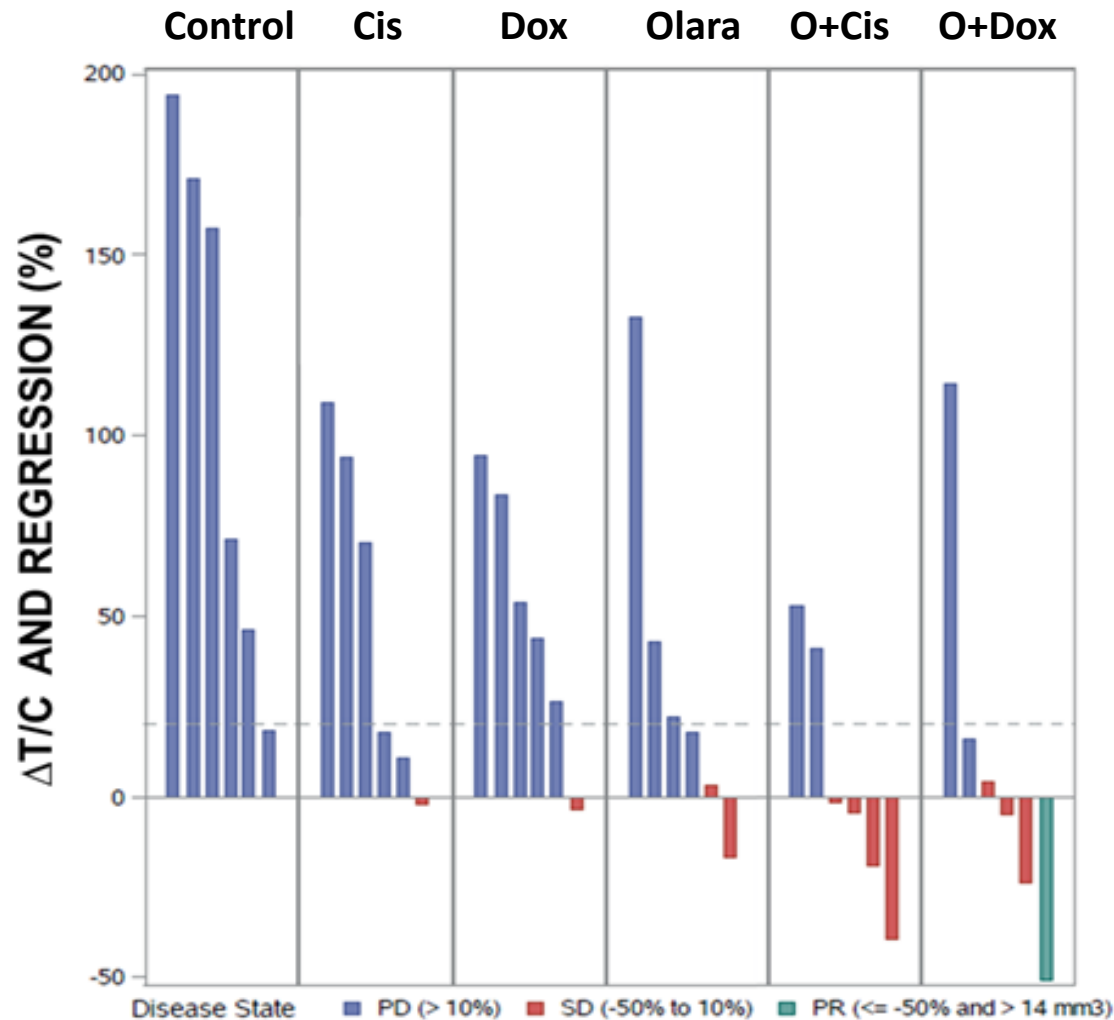
Waterfall Plot from a Osteosarcoma Patient-derived Xenograft Model CTG-1095 Showed Improved Response with Olaratumab Plus Cisplatin



Olaratumab is Efficacious in the HUO9 Osteosarcoma Xenograft Model



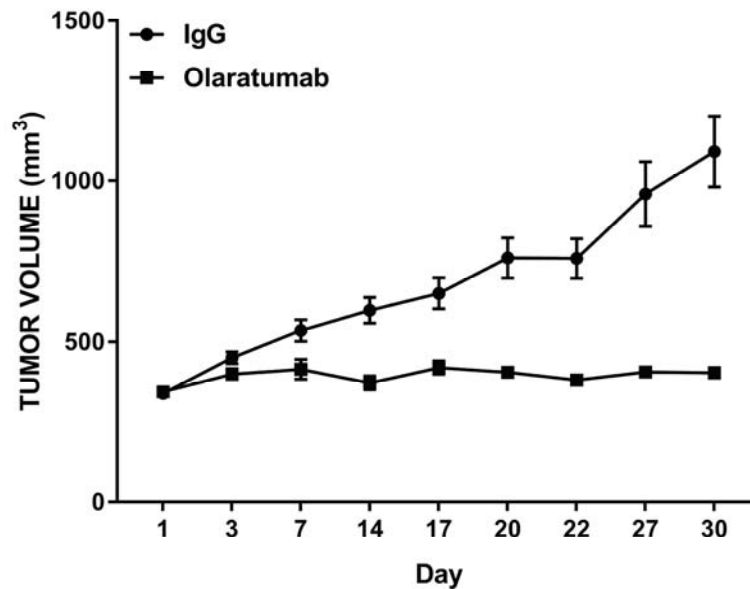
Waterfall Plot from the HUO9 Osteosarcoma Xenograft Model Showed Improved Response with Olaratumab Plus Cisplatin or Doxorubicin



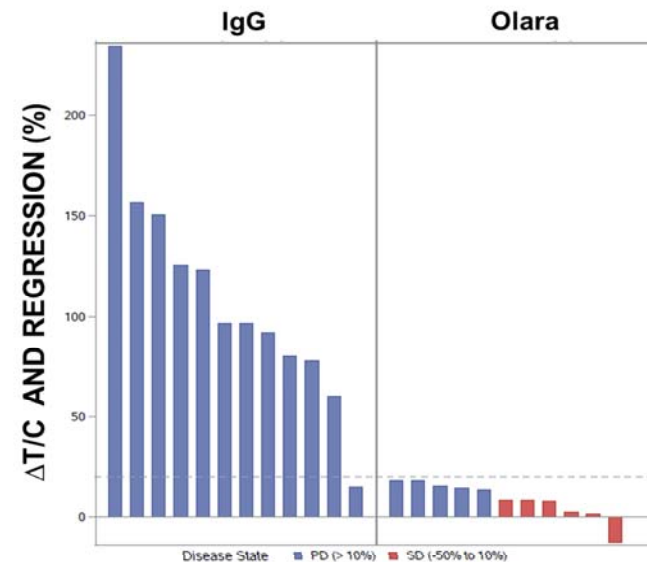
Rhabdomyosarcoma (RMS) and Rhabdoid Tumor

- ◆ Olaratumab was inactive in two xenograft models of RMS, one of which significantly expressed both the PDGFR α and ligand (data not shown)
- ◆ Olaratumab was efficacious in an in vivo xenograft model of rhabdoid tumor (A204 below) that expresses PDGFR α and ligand

A



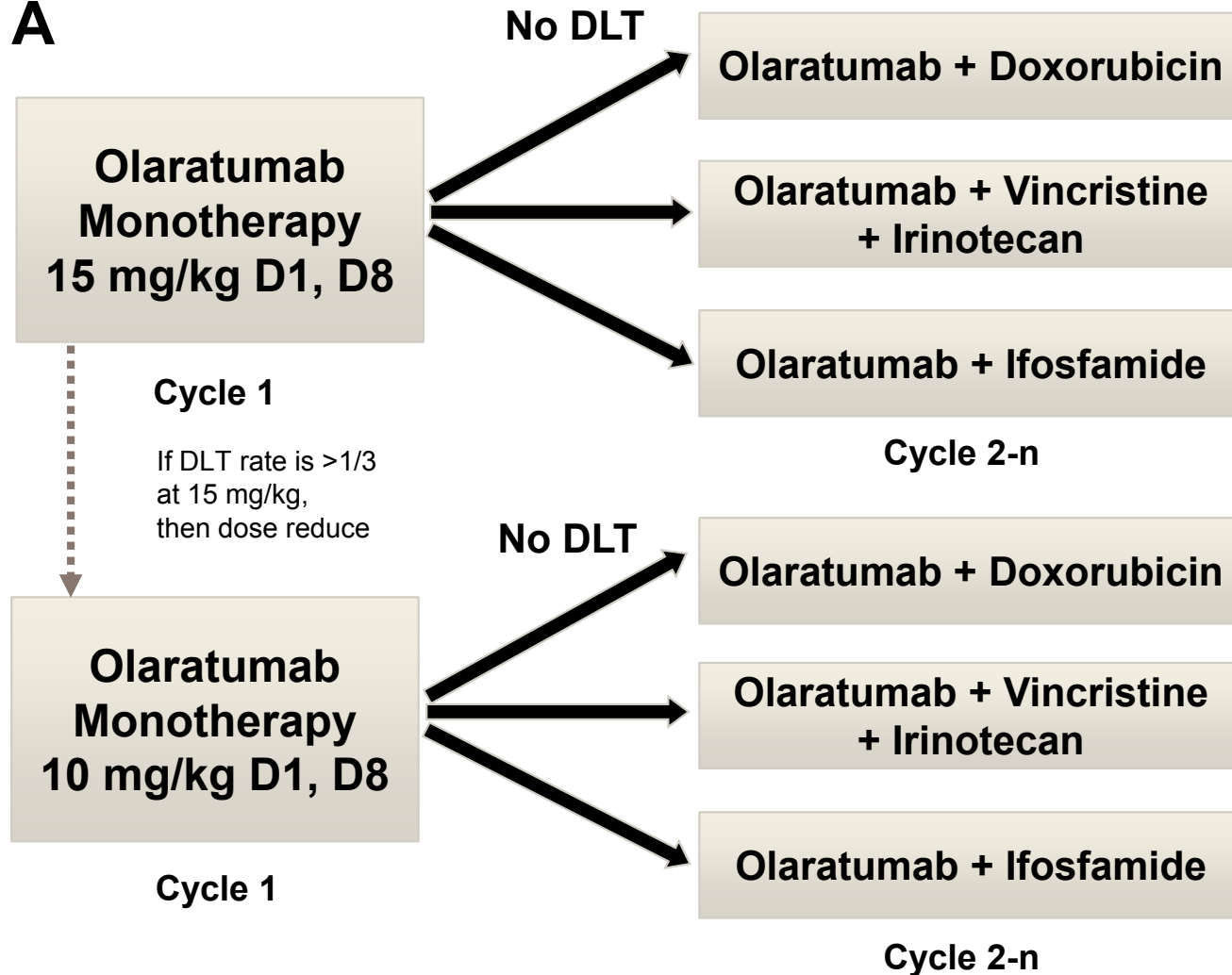
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Pediatric Development Clinical Studies

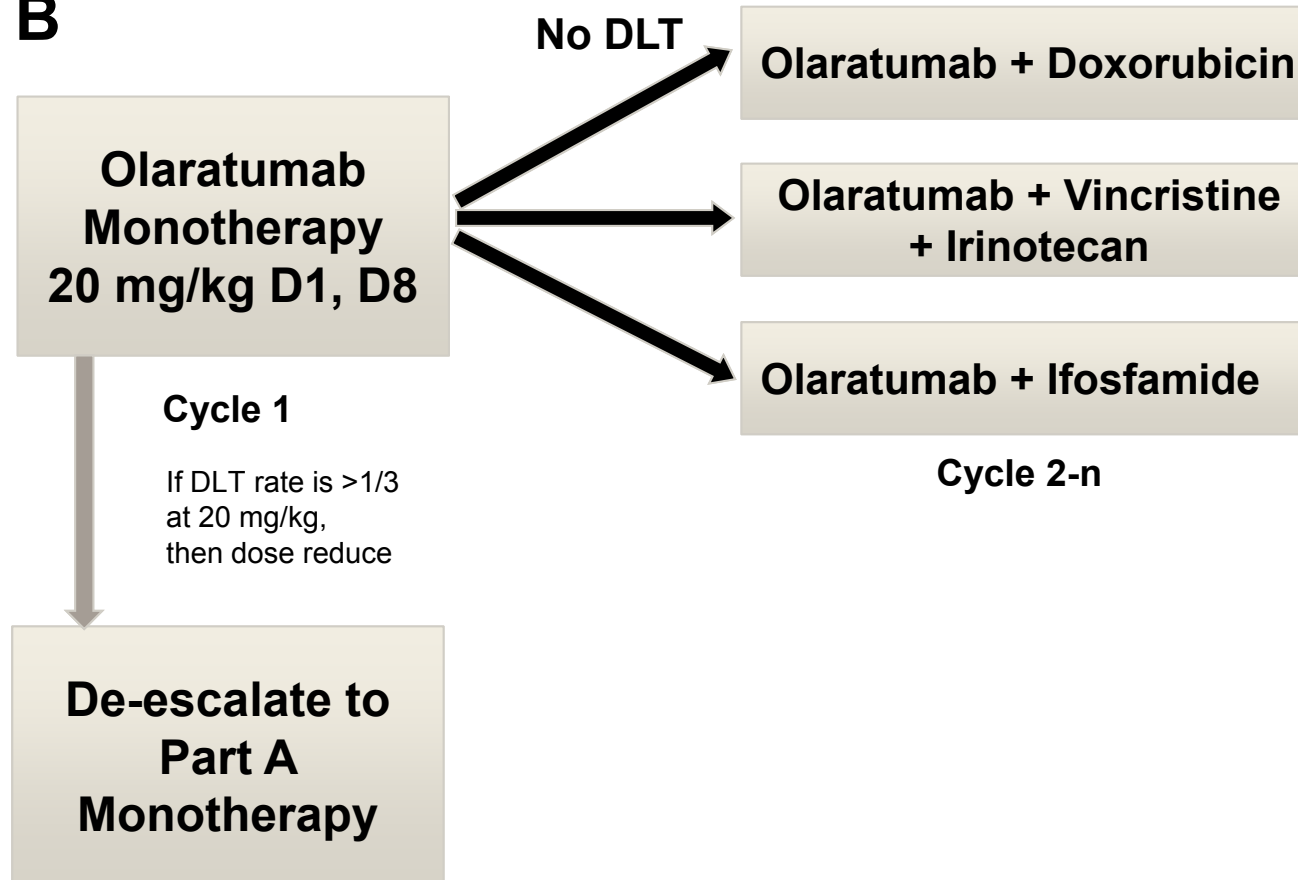
Phase 1 Dose-escalation Study Design for JGDN (Part A)

Part A



Phase 1 Dose-escalation Study Design for JGDN (Part B)

Part B



Pediatric Dosing Strategy

- ◆ Objective: achieve olaratumab serum levels similar to those observed in study JGDG
- ◆ Methods: olaratumab serum levels in pediatric patients simulated using 2 assumptions for the relationship between CL, V and body weight (BW)
 - The relationship characterized in the adult PopPK model is preserved in the pediatric population
 - CL, V and BW follow traditional allometry when examined over a broad range of BW values
- ◆ Results: simulations indicate that a dose of 20 mg/kg may be necessary in patients with low BW (<40 kg) to achieve serum levels similar to those in study JGDG
- ◆ Doses selected for study JGDN are 15 and 20 mg/kg
 - Start at 15 mg/kg to ensure safety and escalate to 20 mg/kg to accommodate possible under-prediction of olaratumab CL in patients with low BW
 - Based on observed PK and safety from study JGDN, other doses may be considered

Conclusions and Next Steps for Pediatric Development

- ◆ Nonclinical data support osteosarcoma as one of the pediatric tumor types for clinical evaluation
- ◆ The JGDN study is designed to rapidly characterize monotherapy PK and safety in children, followed by safety in combination therapies commonly used in pediatric cancer
- ◆ Estimated study JGDN enrollment and timelines are as follows:
 - Enroll approximately 70 patients
 - First Patient Visit: August 2016
 - Estimated Study Completion Date: June 2019
- ◆ The ultimate decision of which path to take will be determined by ongoing nonclinical data, data from the JGDN study and discussion with cooperative groups, thought leaders and regulatory agencies

Conclusions

- ◆ The PDGFR pathway has been implicated in several pediatric tumors including rhabdomyosarcoma, osteosarcoma and rhabdoid tumors
- ◆ The clinical benefit of olaratumab plus doxorubicin in adults with STS has the potential to influence the outcomes of pediatric patients
- ◆ A Phase 1 study in pediatric cancers (JGDN) is ongoing to determine a safe dose when combined with chemotherapy, which may guide further studies
- ◆ Upon the availability of the results of study JGDN and nonclinical data, a further pediatric efficacy study in either osteosarcoma or rhabdomyosarcoma or other tumor type is planned

Questions and Discussion