Pediatric Preclinical Testing Program Lessons Learned

Peter J. Houghton, PhD

Raushan T. Kurmasheva, PhD

Greehey Children's Cancer Research Institute

NCI Pediatric Preclinical Testing Consortium

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UT Health San Antonio

Greehey Children's Cancer Research Institute

Disclosure Information

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Peter J. Houghton/Raushan Kurmasheva

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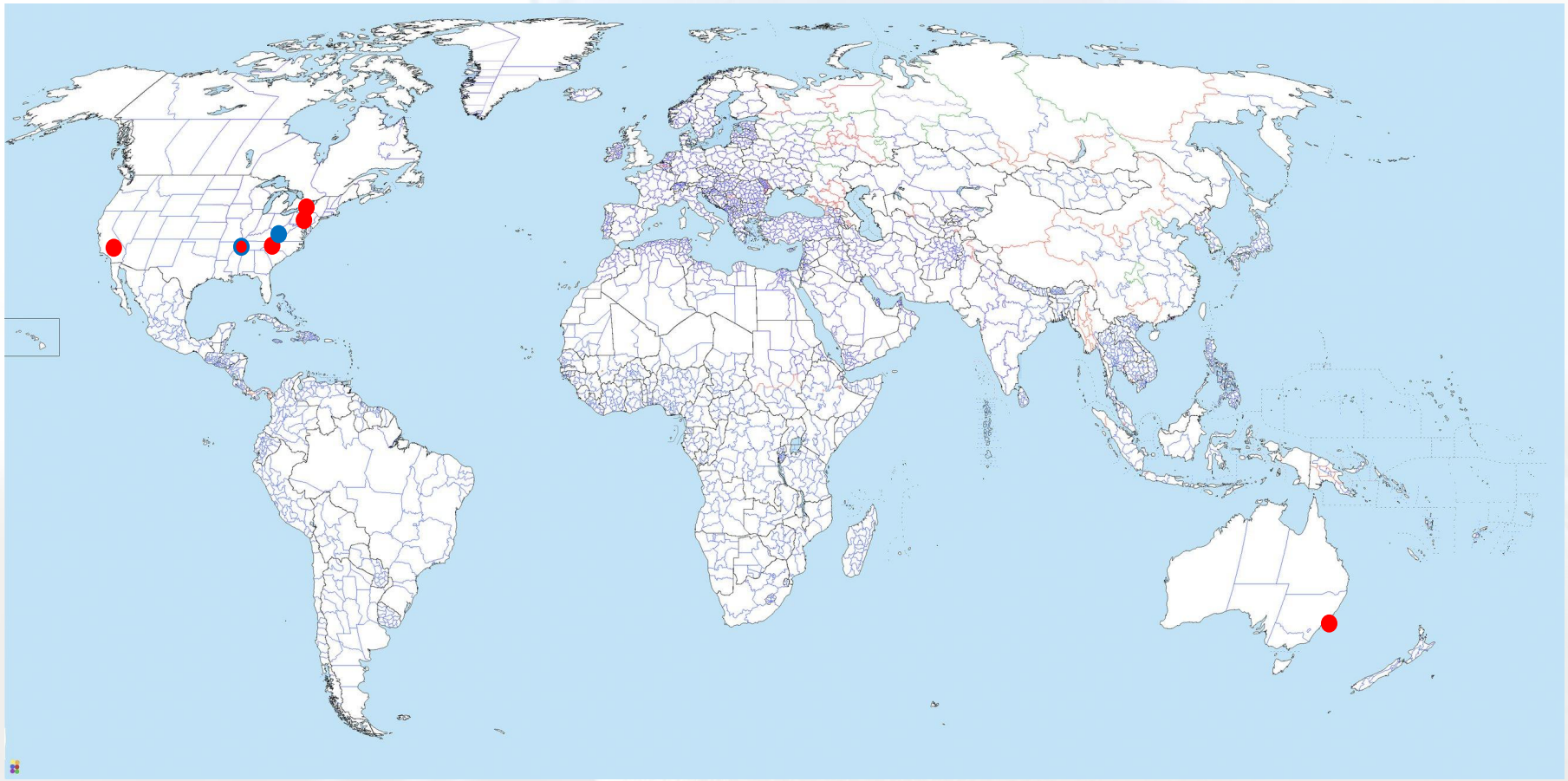
- and -

I will not discuss off label use and/or investigational use in my presentation.

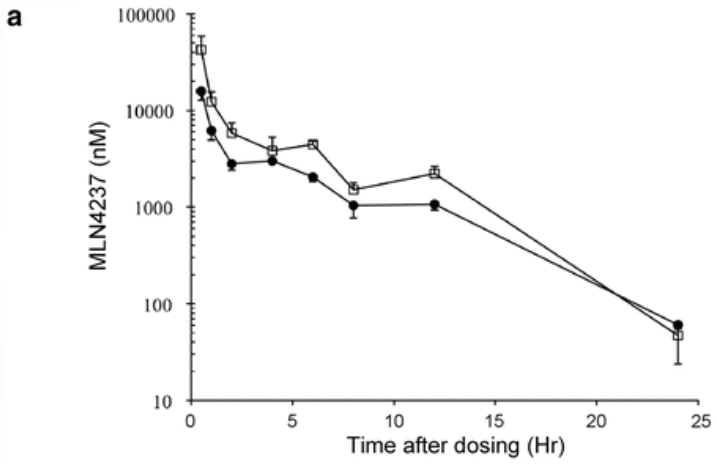
PPTP: Lesson 1 – you can run a successful long-range testing program



Lessons Learned

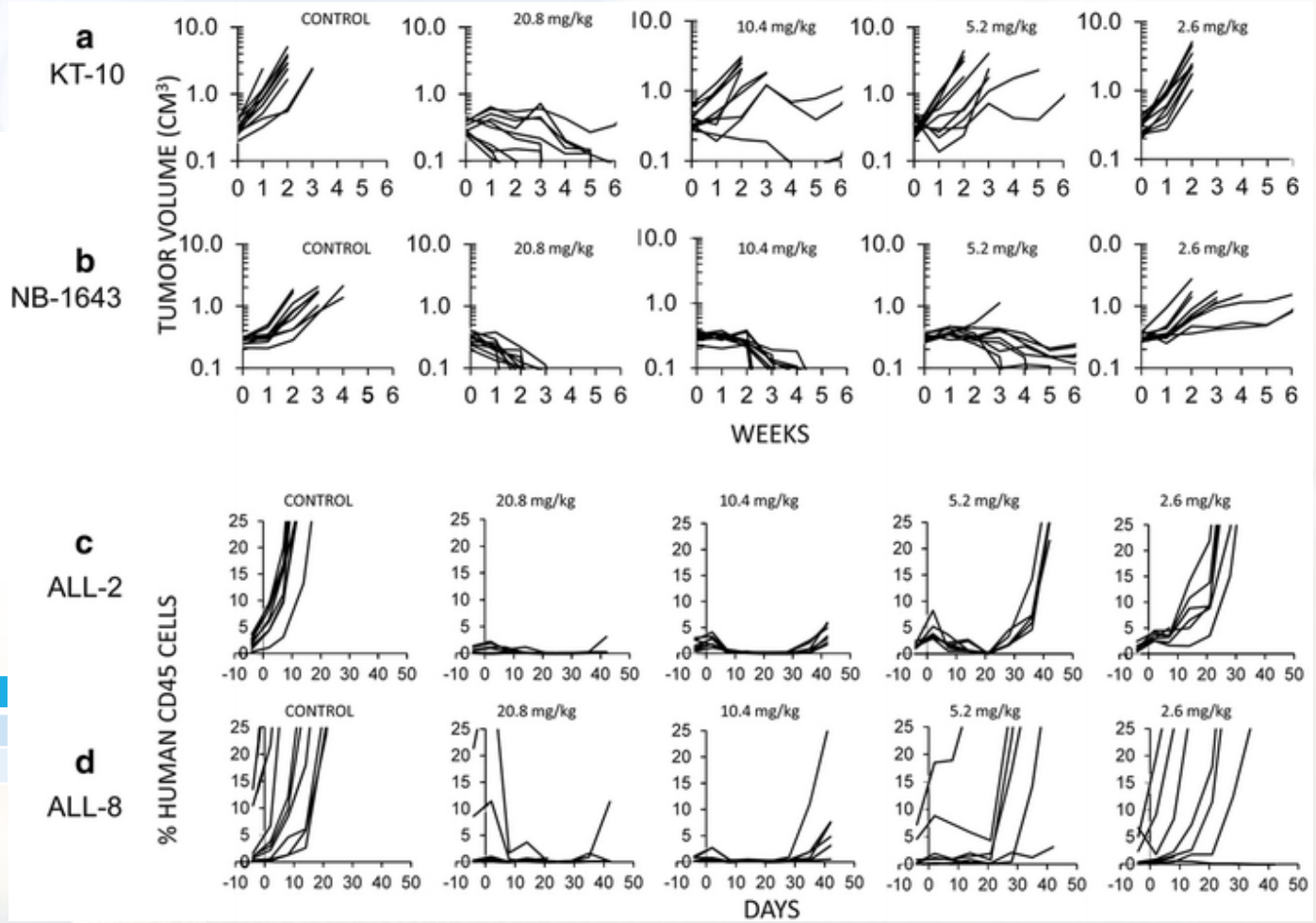
- Understanding interspecies drug exposure is critical for accurate translation to clinical trials.
- Kinase/signaling inhibitors cannot be developed the way we developed cytotoxic agents.
- Screening can identify active novel agents
- Lack of in vitro synergy does not predict lack of in vivo synergy.
- Big effects need fewer mice: value of single mouse analysis.
- For screening and orthotopic models ‘blinded’ experimental design is essential.
- The co-ordinating center should be staffed by vested scientists and not run through a contract research organization (CRO).
- For efficiency a drug pipeline should be established at least 1 year in advance.

1. Relevant Drug Exposure is Essential: MLN8237 (Alisertib)



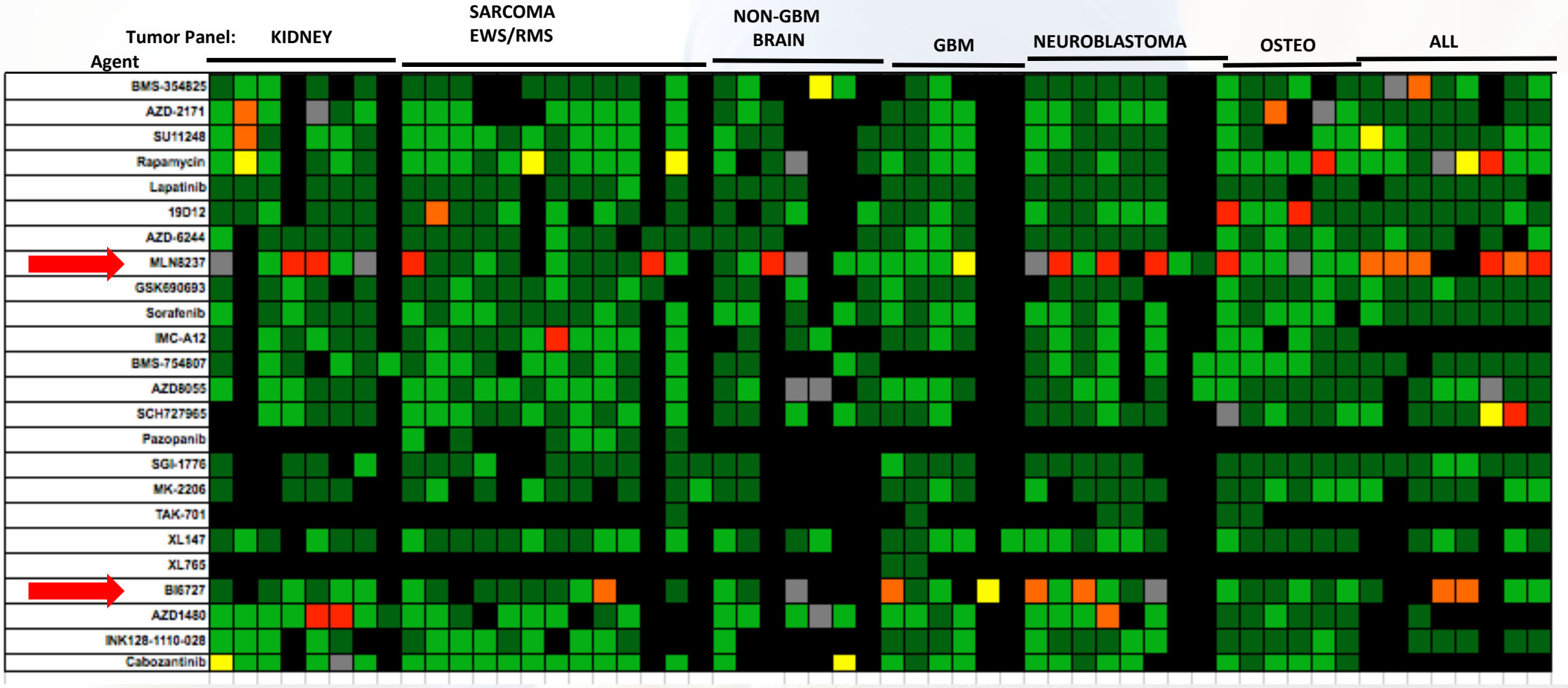
Species	Dose	C_{max}	AUC (μM*h)
Mouse	10 mg/kg	16	39
Human	50 mg BID	1.3	40

Cumulative exposure (3 weeks)
Mouse: 1200 μM*h
Human: 400 μM*h



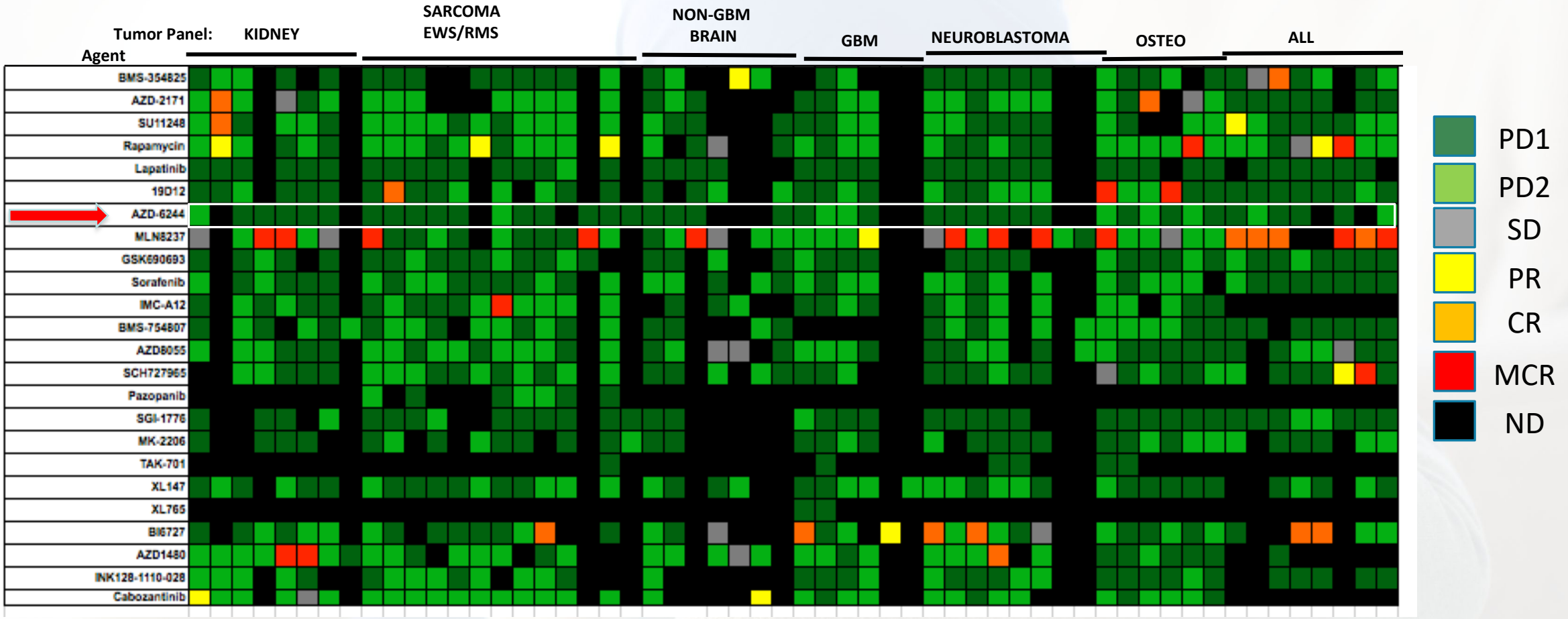
Carol H et al. Cancer Chemother Pharmacol 2011

2. Kinase/Signaling Inhibitors Have Modest Single-Agent Activity



3. Kinase/signaling inhibitors cannot be developed the way we developed cytotoxic agents.

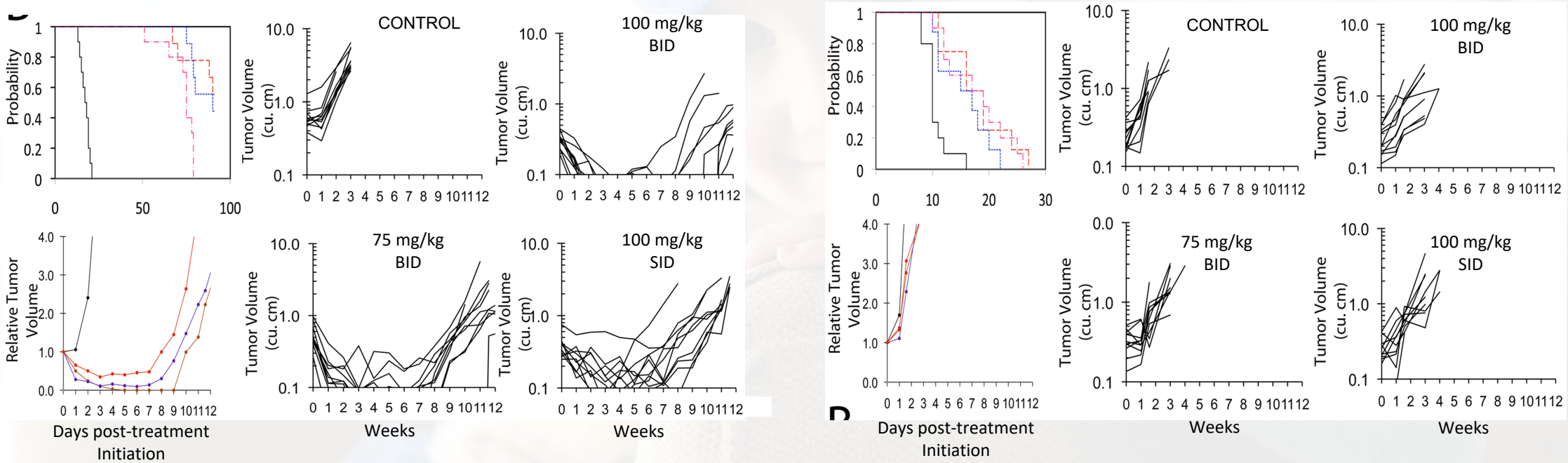
The MEK Inhibitor Selumetinib (AZD-6244) has Modest Single-Agent Activity



Selumetinib (MEK inhibitor) is Selectively Active in a BRAF(V600E) Anaplastic Astrocytoma

BT-40
V600E

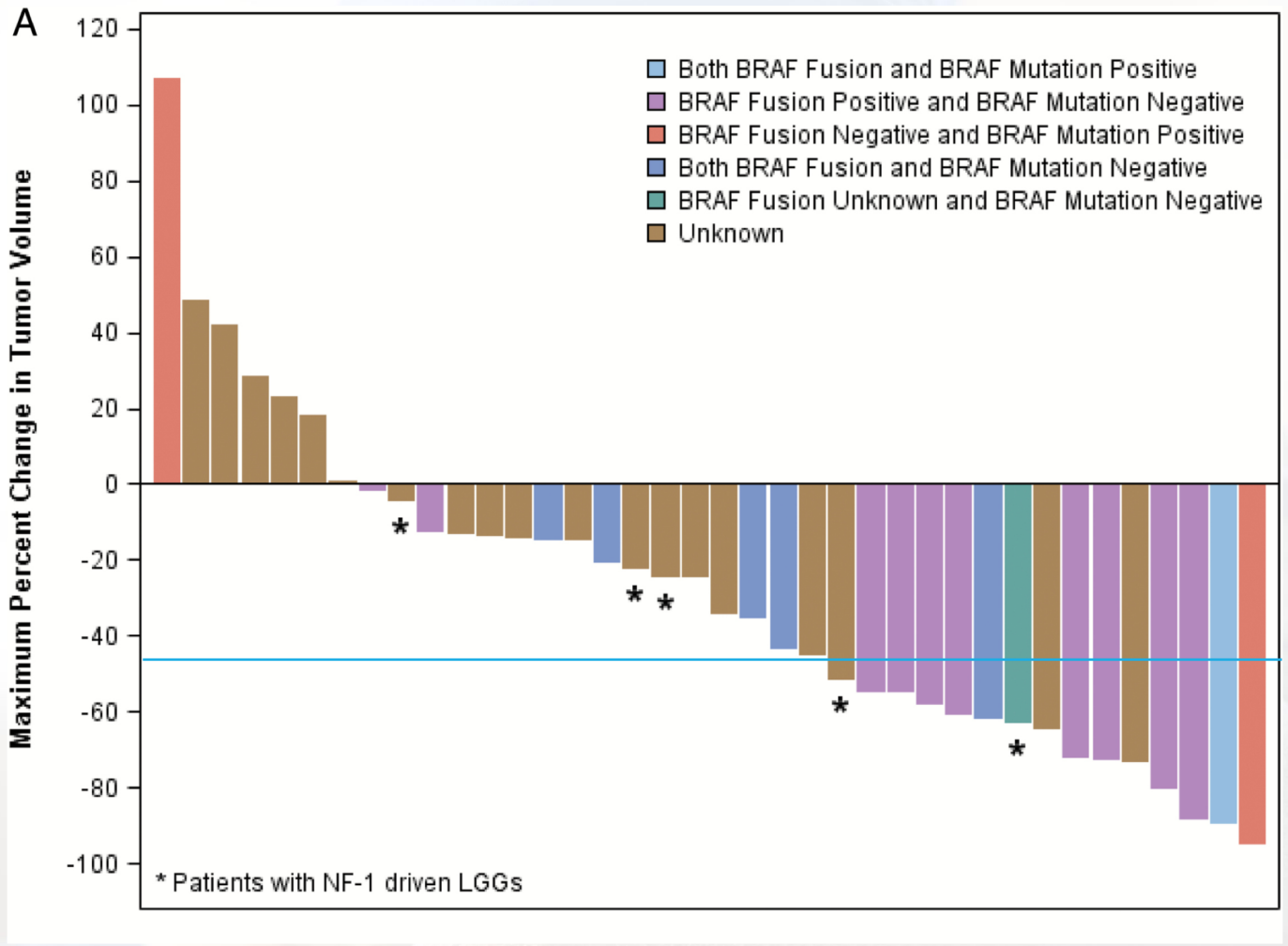
BT-35
WT BRAF



Kolb et al., PB&C 2010

PBTC 029 Trial of Selumetinib (AZD6244) Percent Volume Change Using FLAIR

T2/fluid attenuated inversion recovery (FLAIR)



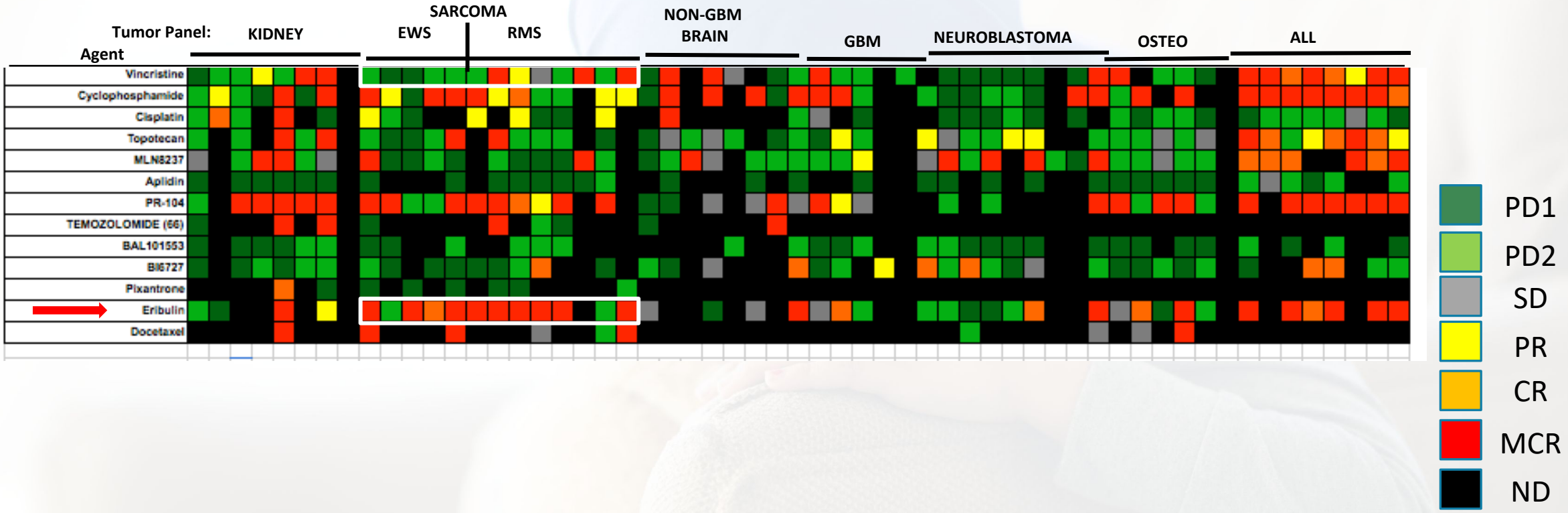
PD 6 (16%)
SD 18 (47%)
PR 14 (37%)

Banerjee A et al., Neuro-Oncology, 2017

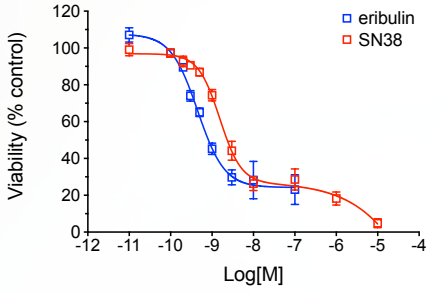
4. Screening can Identify Active Drugs

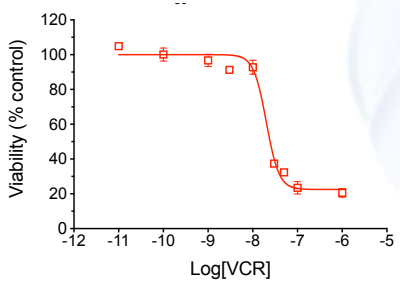
Eribulin vs Vincristine Against Ewing Sarcoma Xenografts

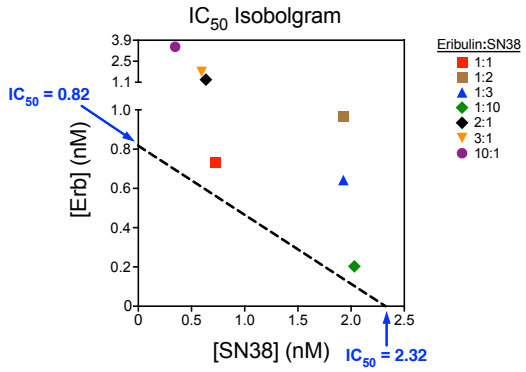
(Sublession: Don’t make assumptios)

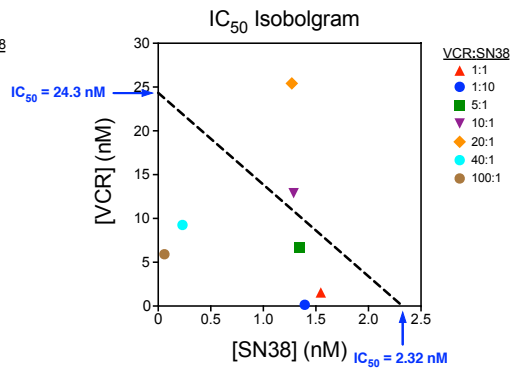


5. Lack of in vitro synergy does not predict lack of in vivo synergy.

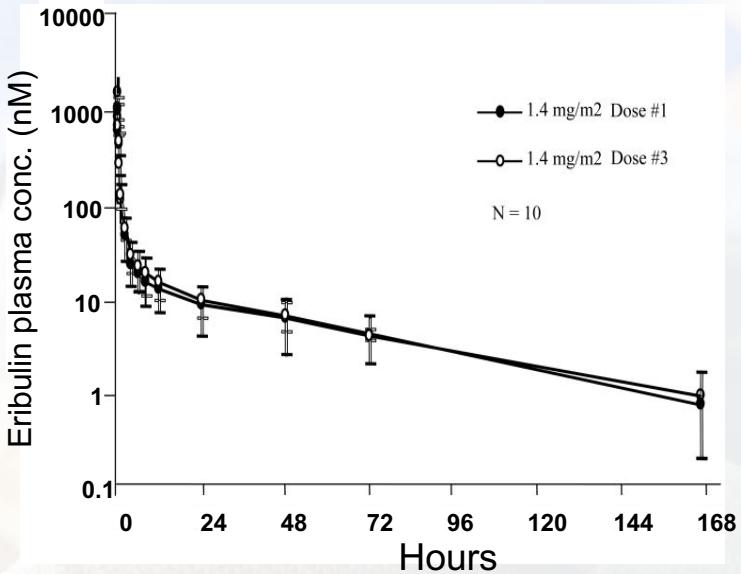






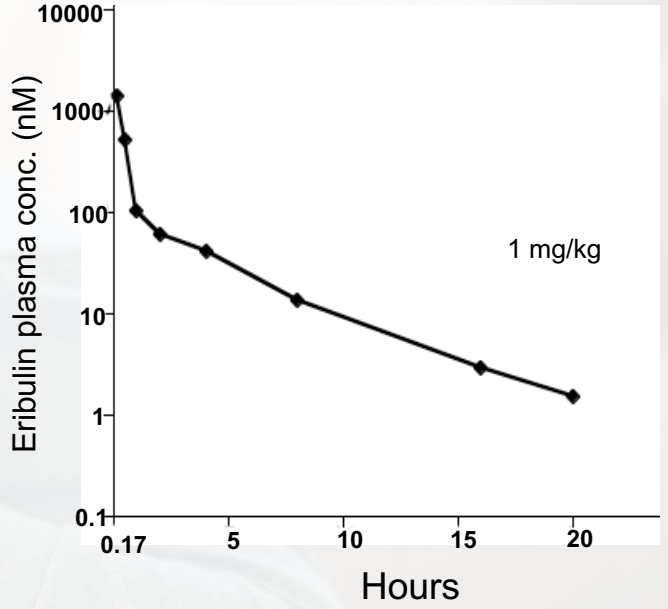


Human



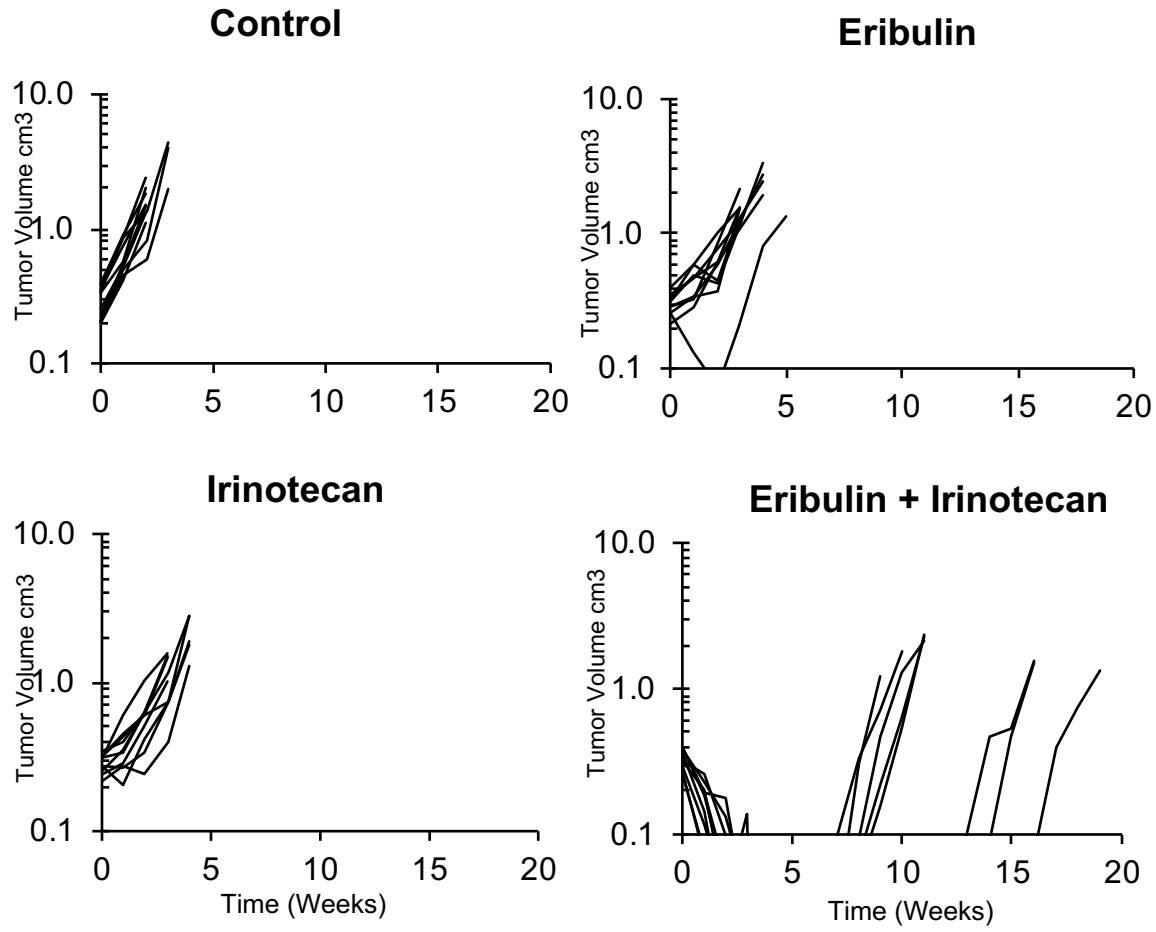
Morgan RJ et al. Cancer Chemother Pharmacol 2015

Mouse



Kolb EA et al Ped Blood Cancer 2013

Eribulin Combined with Irinotecan is Synergistic ES-4 Ewing Sarcoma Xenografts



The Combination of Eribulin + Irinotecan is Superior to Vincristine + Irinotecan in 6 of 11 Xenograft Models.

Xenograft Model	Tumor Type	Eribulin + Irinotecan	Vincristine + Irinotecan	P
		EFS (days)		
Rh10	Alveolar rhabdomyosarcoma	>91	59.3	<0.001
Rh30	Alveolar rhabdomyosarcoma	90.8	>160	<0.001
Rh41	Alveolar rhabdomyosarcoma	80.2	79.2	0.735
Rh65	Alveolar rhabdomyosarcoma	>133	121.1	0.011
ES-4	Ewing sarcoma	62.9	35.7	<0.001
CHLA258	Ewing sarcoma	81.6	35.7	<0.001
SKNEP1	Ewing sarcoma	>133	>133	1.000
KT-11	Wilms	>77	29.7	<0.001
KT-13	Wilms	74.7	77.9	0.312
RBD1	Rhabdoid	>96.1	>96.1	1.000
KT-14	Rhabdoid	96.4	56.3	0.004

6. Alternative Experimental Designs that Enable Greater Inclusion of Molecular Heterogeneity

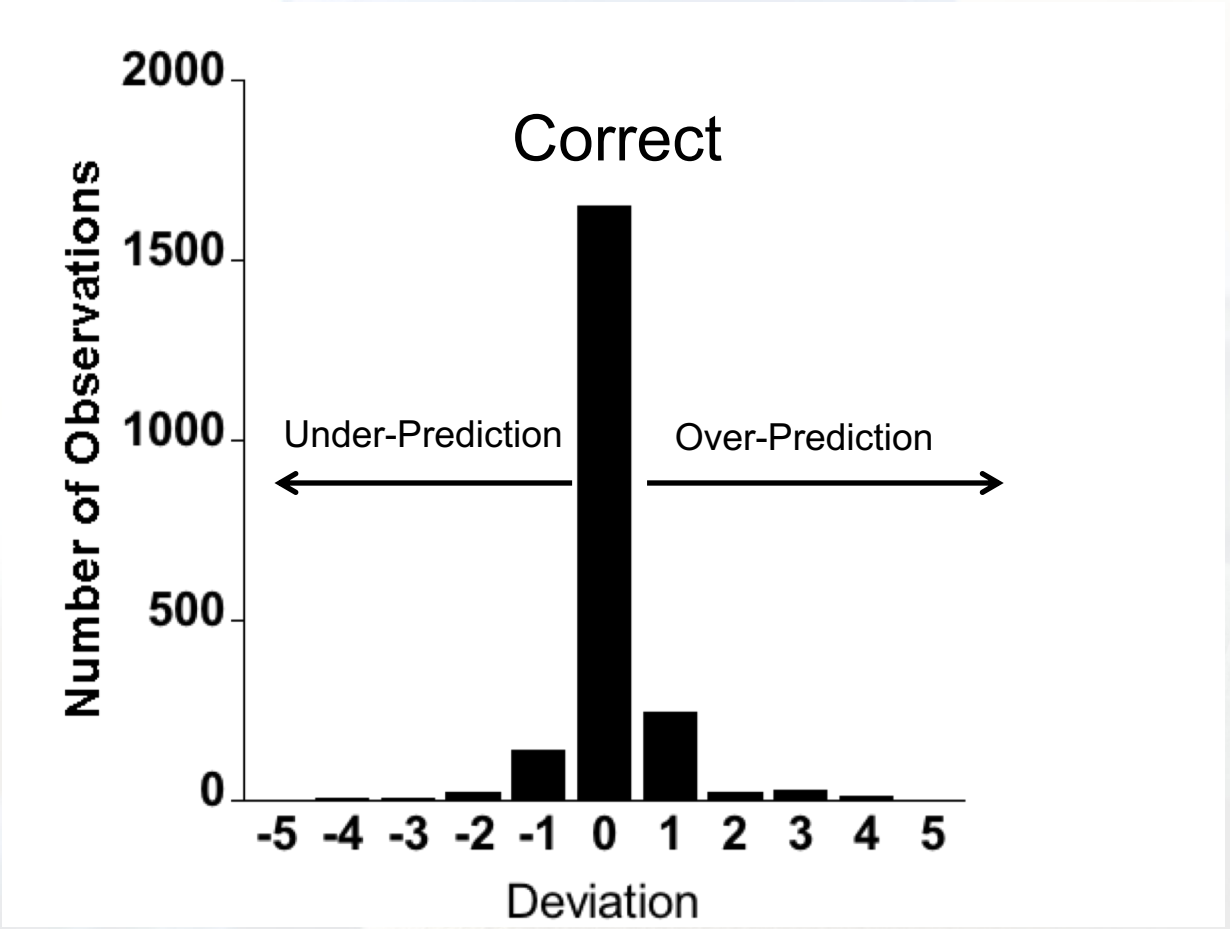
Retrospective analysis of 2106 tumor drug experiments in PPTP using 8-10 mice/treatment group.

Question:

Would we obtain the same result if we used a single mouse rather than 8-10 mice per treatment group?

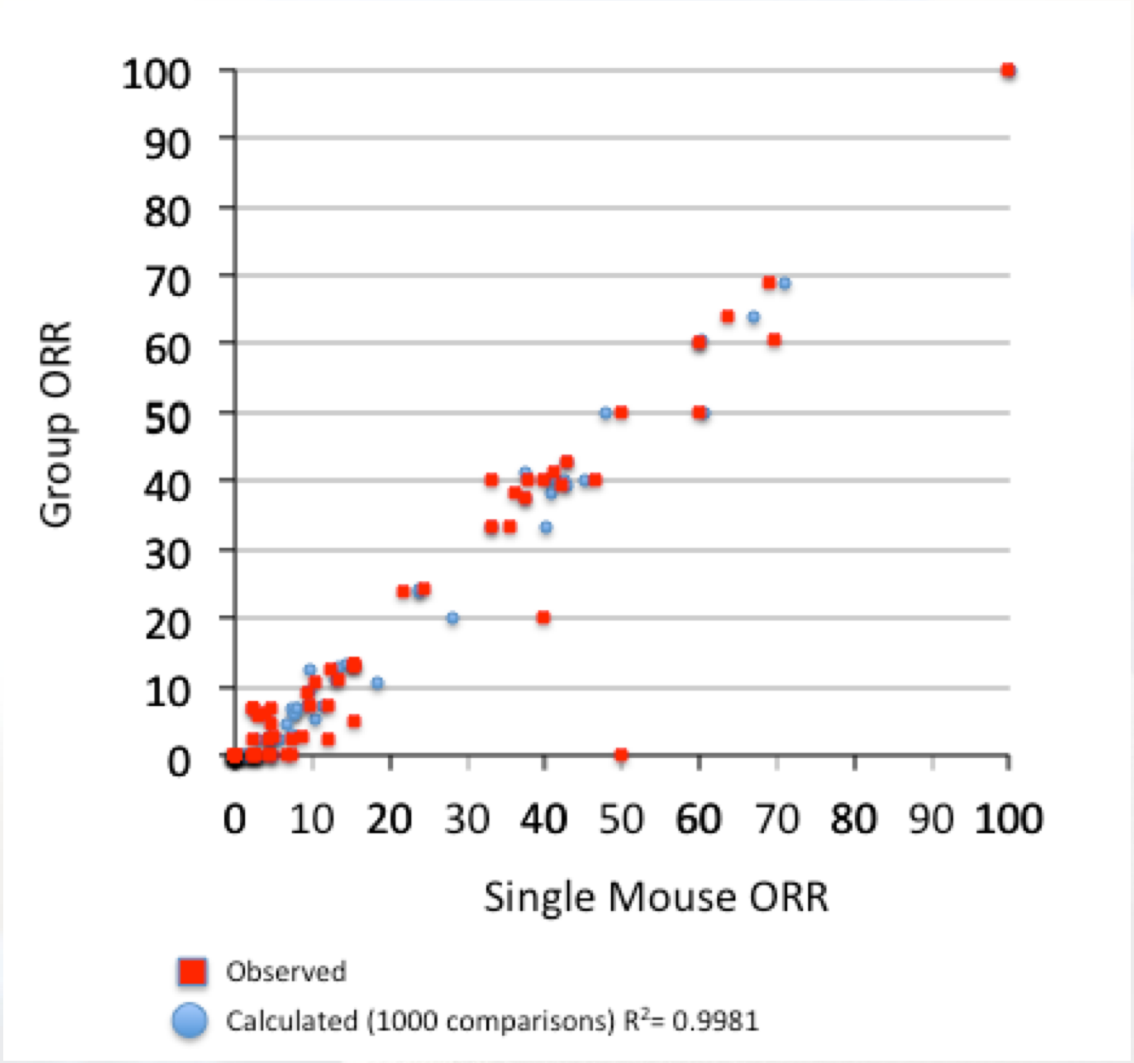
Murphy B et al., Cancer Res. 2016

Single Mouse per Group Accurately Predicts Group Response in 78% of Experiments



Murphy B et al., Cancer Res. 2016

Single Mouse Data Accurately Predicts Objective Response Rates (ORR)



Murphy B et al., Cancer Res. 2016

7. ‘Blinded’ experimental design is essential.

- Coding of agents reduces investigator/selection/reporting bias[1].
- ‘Blinding’ to experimental treatment is essential when determining endpoints for ‘non-measured’ tumors (e.g. brain tumors where EFS is the endpoint)
- Coding allows an agent to be evaluated on several occasions, consequently the reproducibility of a model can be assessed without investigator bias.
- Statistical analysis should be ‘blinded’ to experimental treatments
- All data should be analyzed, not selected data.
- All data should be analyzed prior to revealing the identity of the drug or combination to the investigators.
- All data should be made publicly available.

[1] Van der Worp et al. PLoS Medicine, 2010.

Lessons from PPTP and PPTC

- **The co-ordinating center should be staffed by vested scientists and not run through a contract research organization (CRO).**

  PPTP: 20 papers published in initial 3 years of starting

  PPTC: 0 papers submitted

- **For efficiency a drug pipeline should be established at least 1 year in advance.**

  for ‘general’ screens or combinations

  for ‘omically’ focused screens or combinations.

Summary

- Essential to address drug scheduling and systemic exposure for accurate clinical translation.
- Genomic information can be useful for predicting drug sensitivity (BRAF, PALB2 etc).
- Models can identify novel efficacious agents (selumetinib, eribulin), and combinations (eribulin/irinotecan, temsirolimus/cyclophosphamide-*Vinca* etc).
- PDX models can be developed that adequately represent the genomic heterogeneity of pediatric cancers.
- Single mouse designs will allow more rapid/efficient screening of single agents and combinations.

Thanks

CHILDHOOD CANCER

RESEARCH CHALLENGES AND THE FUTURE OF THERAPY

SYMPOSIUM HOSTED BY

UT Health San Antonio

Greehey Children's Cancer Research Institute

MARCH 3-6, 2019

SAN ANTONIO - TEXAS

GRAND HYATT RIVERWALK
SAN ANTONIO - TEXAS

On March 3-6, 2019, the Greehey Children's Cancer Research Institute (GCCRI) will host the symposium "Childhood Cancer: Research Challenges and the Future of Therapy" at the Grand Hyatt on the world-renowned San Antonio Riverwalk. It will bring together some of the most respected childhood cancer researchers in academia and industry, along with science advocates, to discuss current advances in basic and translational sciences and their impact on therapy and diagnosis.

Session topics will include:

- Genomics
- Epigenetics & Pathways in Pediatric Cancer
- Immunotherapy

EVENT ORGANIZERS

Peter J. Houghton
Luiz O. F. Penalva
Gregory J. Aune
Raushan Kurmasheva

Greehey Children's Cancer Research Institute, *UT Health San Antonio*

REGISTRATION AND MORE INFORMATION

gccrisymposium.org

SPEAKERS

KEYNOTE:

Brigitte C. Widemann
NCI

Genomics

David Malkin
Sick Kids
Charles G. Mullighan
St. Jude Children's Research Hospital
Marc Remke
University of Duesseldorf
Paul S. Meltzer
NIH

Epigenetics & Pathways in Pediatric Cancer

Charles W.M. Roberts
St. Jude Children's Research Hospital
Eleanor Y. Chen
University of Washington - Seattle
Kimberly Stegmaier
Harvard Medical School
Stephen L. Lessnick
Nationwide Children's Hospital

Immunotherapy

Paul Sondel
University of Wisconsin - Madison
Terry J. Fry
University of Colorado - Denver
Crystal Mackall
Stanford University
Michael C V Jensen
Seattle Children's Research Institute

Advocacy & Outcomes

Gregory J. Aune
UT Health San Antonio
Susan L. Weiner
Children's Cause for Cancer Advocacy
Kevin C. Oeffinger
Duke Cancer Institute
Saro H. Armenian
City of Hope

Therapy & Drug Discovery

Louis F. Stancato
Eli Lily
Craig M. Crews
Yale Cancer Center
Cigal Kadoch
Dana-Farber Cancer Institute