Lessons Learned from Failed Pediatric Trials:

Failed Trials and Design Considerations in Pediatric Oncology

March 12, 2016

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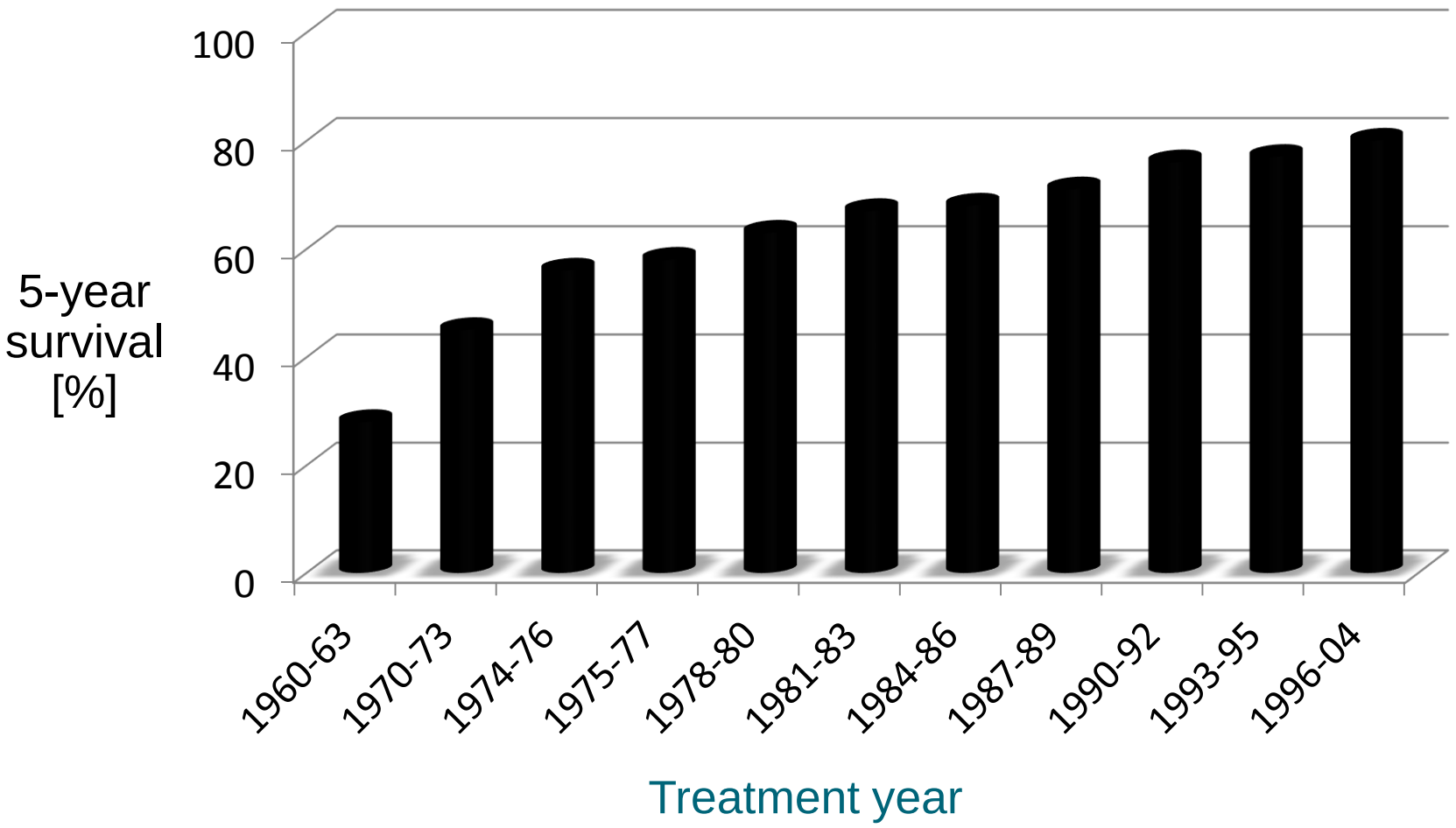
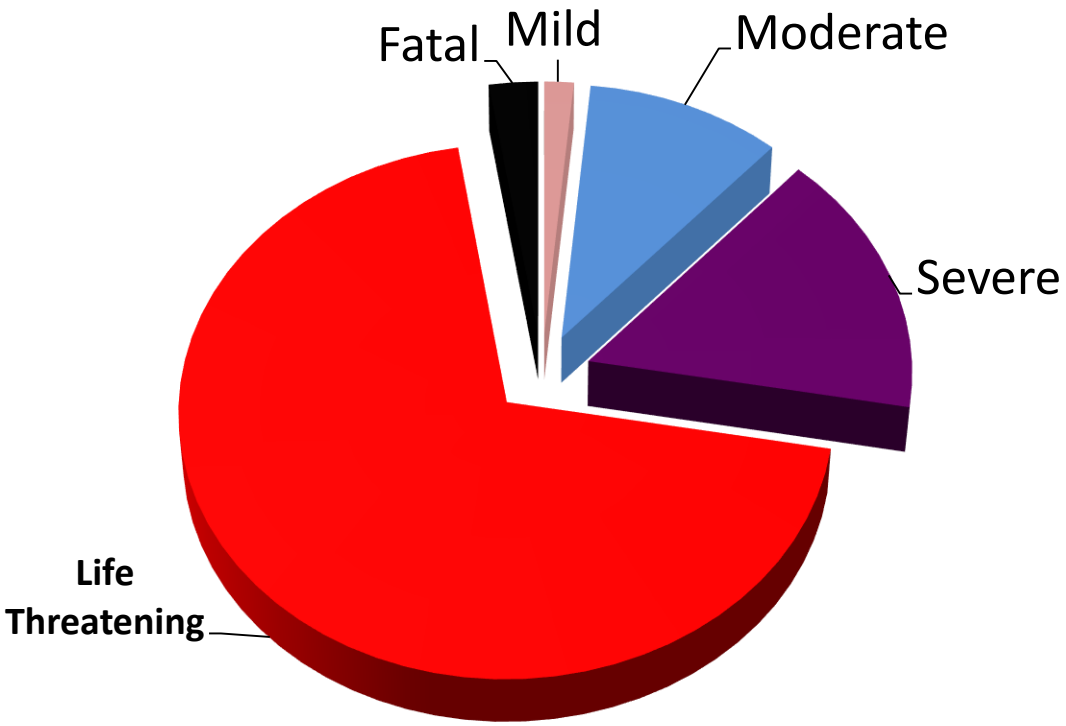
Cure Rates



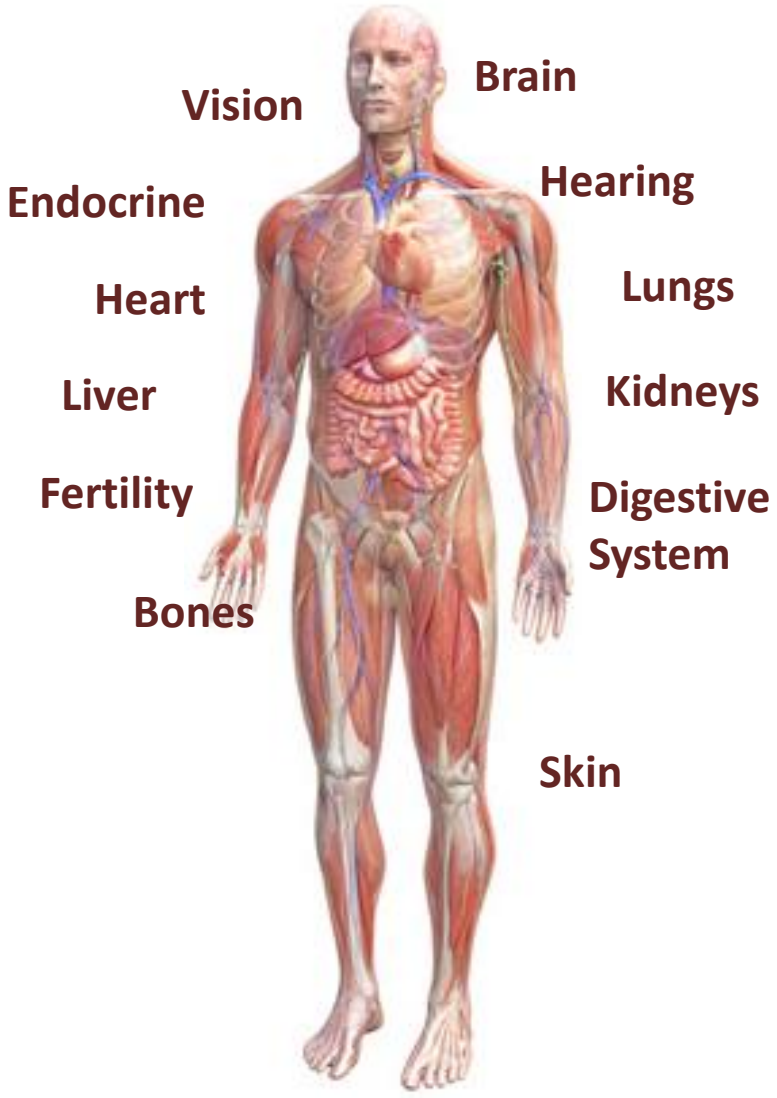
SEER: Adamson

Curing Cancer

Side Effects



Late Effects



Ultimate Challenges in Pediatric Oncology

- Improve cure rates
- Decrease acute toxicity
- Minimize risks for late effects

Strategies to Prioritize Drugs For Pediatric Development

- Biology: Molecular target identification, drug mechanism of action, micro-environment vs tumor effects
- Drug availability and formulation
- Pre-clinical data: Cell lines, validated in vivo models
- Clinical data: Relevant adult trials

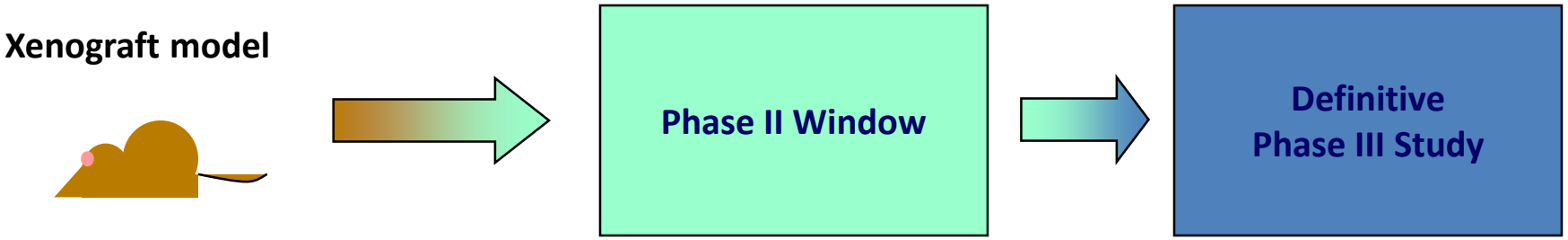
Pre-clinical Data

- Cell lines
  - Readily available for most pediatric cancers
  - Can investigate and understand targets, large screens quickly and relatively inexpensive
  - No understanding of host factors, dose exposure considerations may not reflect in vivo, genetic drift

- Animal Models
  - Issues of immunodeficient mice if using xenografts/PDX
  - Orthotopic vs alternative site: microenvironment issues
  - Dose/schedule/toxicity: labor and resource intense
  - Genetically engineered models may not truly reflect genetic complexity of childhood cancer

New Drug Development in RMS

Xenograft to Phase III Clinical Trials

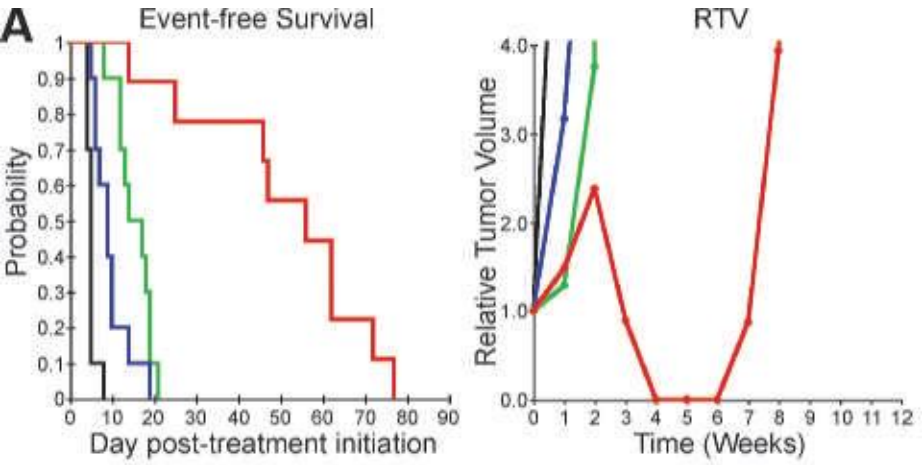


Melphalan	**+ vincristine**	**Active**	**Too toxic**
Ifosfamide	**+ etoposide**	**Active**	***IRS IV***
	+ doxorubicin	**Active**	

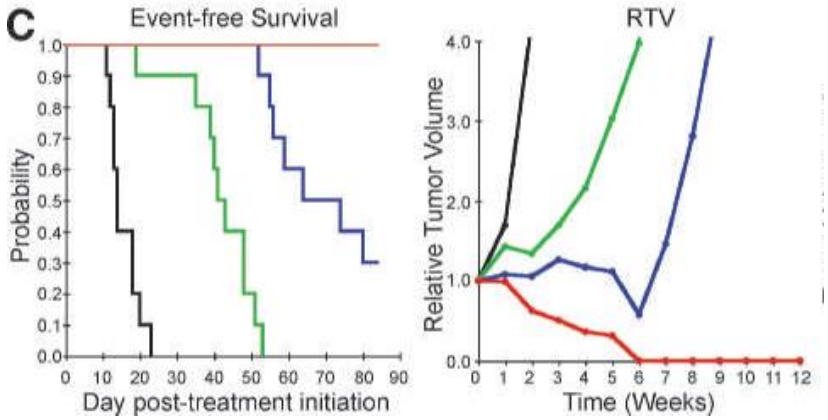
Topotecan	**Single agent (IRS V)**	**Active**	**No activity in relapse**
Cancer Chemother Pharmacol. 1995;36(5):393-403	**+ cyclophos (D9501)**	**Active**	***Intermediate-Risk (D9803) No improvement in FFS***

J Clin Oncol 2001;19:213- *J Clin Oncol 2004;22:1398-403* *J Clin Oncol 2006;24:3415-22* *J Clin Oncol 2009;27:5182-8*

mTOR Inhibitor, VEGFR Inhibition and Chemotherapy in Rhabdomyosarcoma



RAPAMYCIN + VINCRISTINE



RAPAMYCIN + CYCLOPHOSPHAMIDE

Mol Cancer Ther 2011
Pediatric Preclinical Testing Program

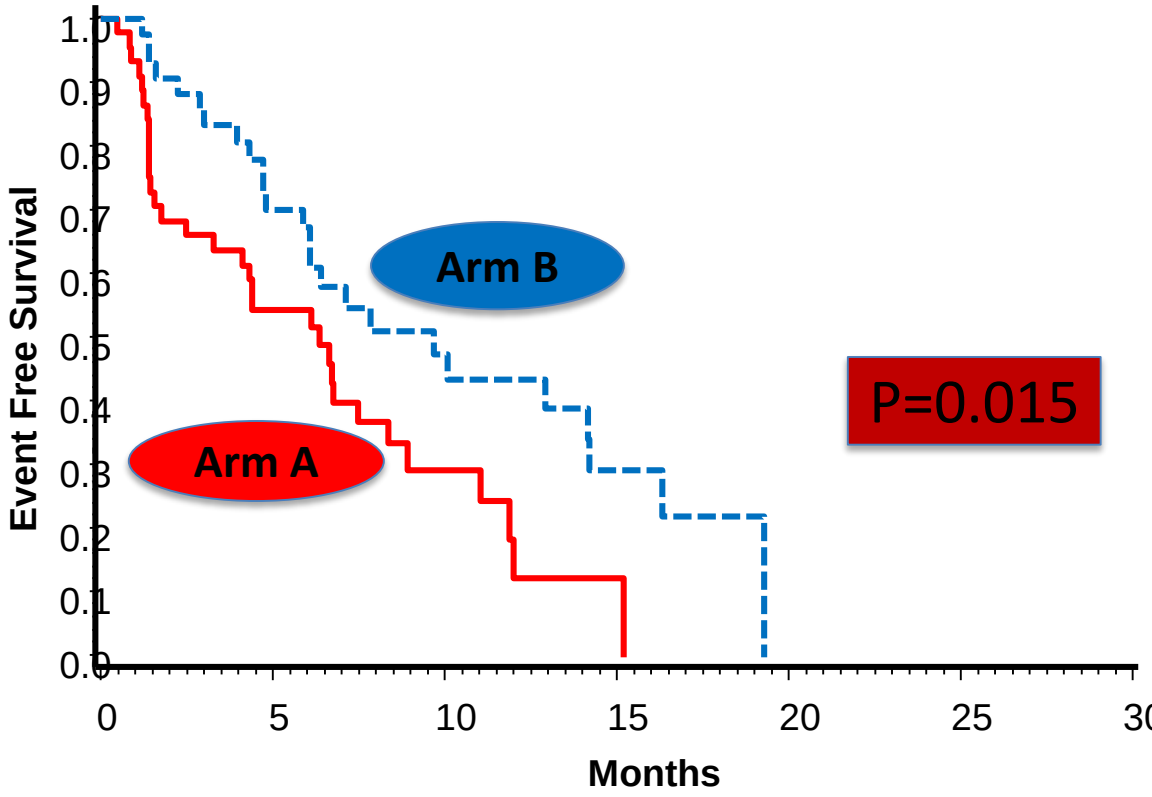
- Vinorelbine and cyclophosphamide are active in relaspsed Rhabdomyosarcoma
  Casanova M, Cancer 2002: Kuttesch JF, PBC 2009: Casanova M, Cancer 2004
- Complete inhibition of RMS xenograft growth and neovascularization with VEGF blockade
- Pediatric Phase 1 trial of bevacizumab completed with no DLT
- Increased mTOR pathway activation in RMS associated with decreased survival PPTP demonstrated activity of Rapamycin in RMS
- Temsirolimus tested in Pediatric Phase 1 trial

Gerber HP, Can Res, 2000; Glade Bender JL, JCO 2008; Petricoin EF, Can Res 2007; Houghton PJ PBC 2008; Spunt SL JCO 2011;

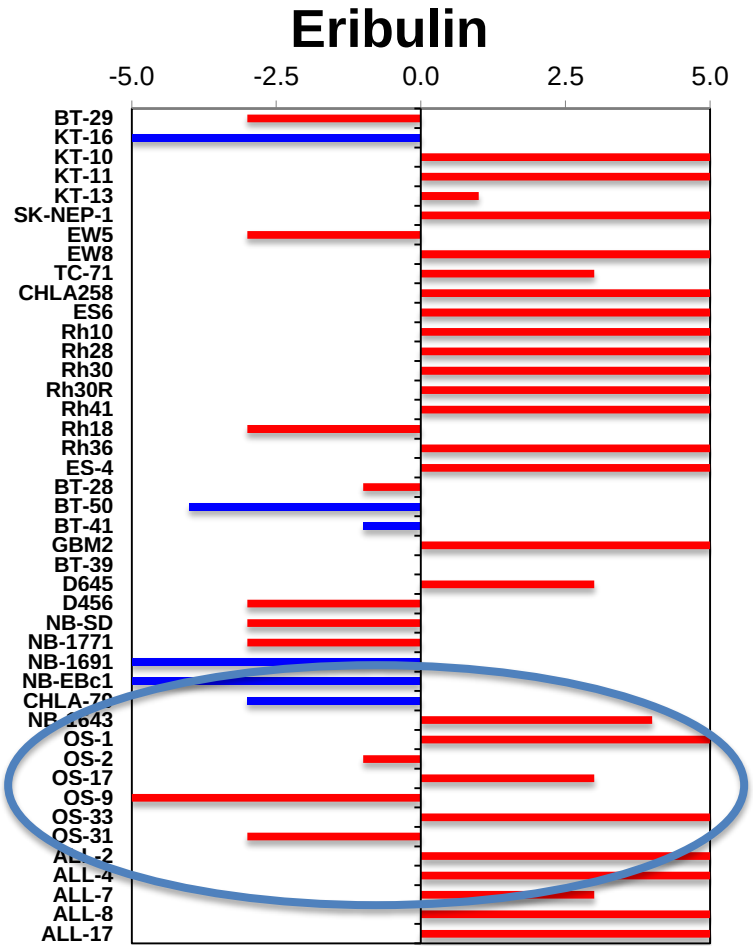
Randomized Phase 2 Trial: Bevacizumab and Temsirolimus in combination with Vinorelbine (V) and Cyclophosphamide (C) for First Relapse/Disease Progression of Rhabdomyosarcoma (RMS)

COG: Mascarenhas

- Randomized selection design: early end point of 6 month EFS
- 6 month EFS: Regimen **A 54%** (95% CI 38%, 65%), Regimen **B 67%** (95% CI 50%, 79%)
- 1 year EFS: Regimen **A 12%** (95% CI 3%, 30%), Regimen **B 43%** (95% CI 26%, 59%)
- Temsirolimus has been selected by COG for further investigation in newly diagnosed intermediate RMS patients randomized with VAC/VI backbone



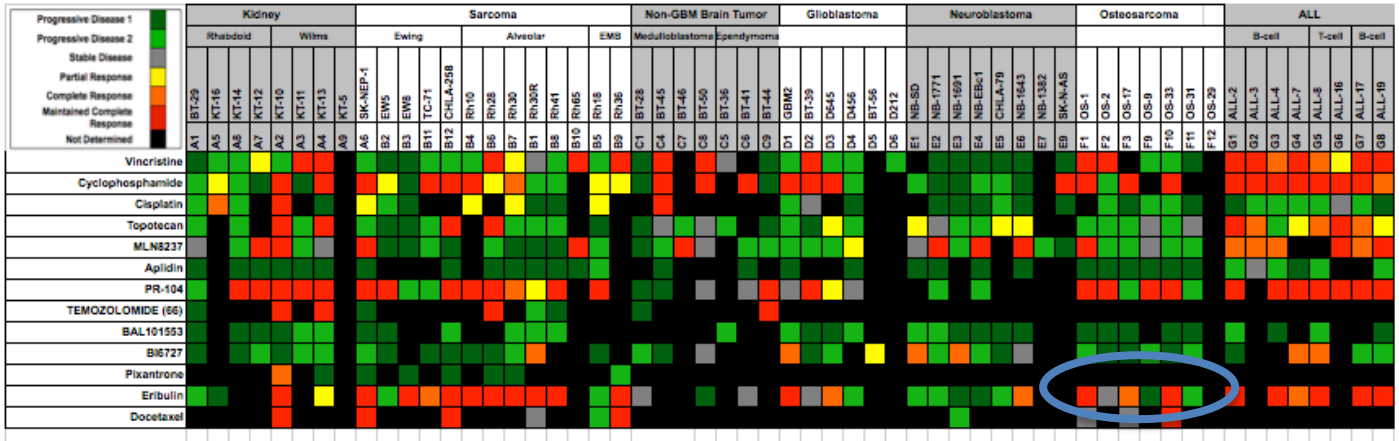
- **Still to come biological correlates of response**



Eribulin and Osteosarcoma

- FDA approved as a single agent for metastatic breast cancer
- Phase 2 activity in adults with soft tissue sarcomas
  Lancet Oncol. 2011 Oct;12(11):1045-52
- Moved to a phase 2 study in osteosarcoma at RP2D based on preclinical data
- 0/19 patients had response
- ?? What predicated response in preclinical model
- ?? How strong a pre-clinical signal do you need
- ?? What about combination strategies

Pediatr Blood Cancer. 2013 Aug;60(8):1325-32.



Parp Inhibition and Ewing Sarcoma

- Drug screen demonstrated highly significant association between *EWS-FLI1* rearrangement and sensitivity to the PARP1 inhibitor olaparib

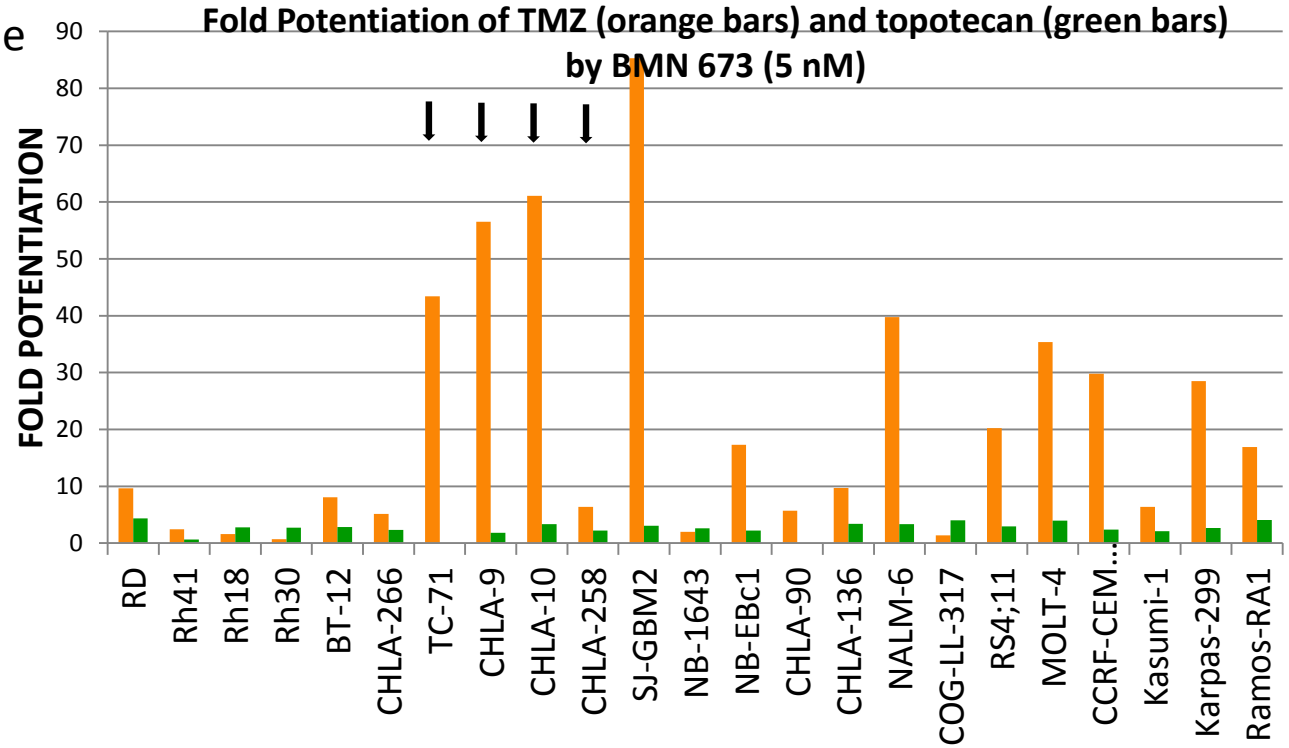
- Ewing sarcoma cell line assays confirmed sensitivity discovered in drug screen
  Cancer Res 2012:72:1608-1613, Nature 2012:483(7391):570-575

- Phase 2 study single agent failed in adults with Ewing

BMC Cancer. 2014 Nov 5;14:813

- Parp inhibition sensitizes to DNA damage prevents repair

Pediatr Blood Cancer 2014;61:145-50
Cell Rep 2014;9(3):829-41
Pediatr Blood Cancer 2015;62:91-8
Mol Cancer Ther 2015;14:2818-30



Clin Cancer Res 2015;21:819-32

Novel Phase 1/2 Study
ADVL1411: Talazoparib with Temozolomide

Part A: dose finding with required PK
Of both Talazoparib and Temozolomide

Part B: Ewing Sarcoma phase 2
Simon 2 stage design
Tissue and biomarker evaluation
(PARP-1 and DNA repair markers)

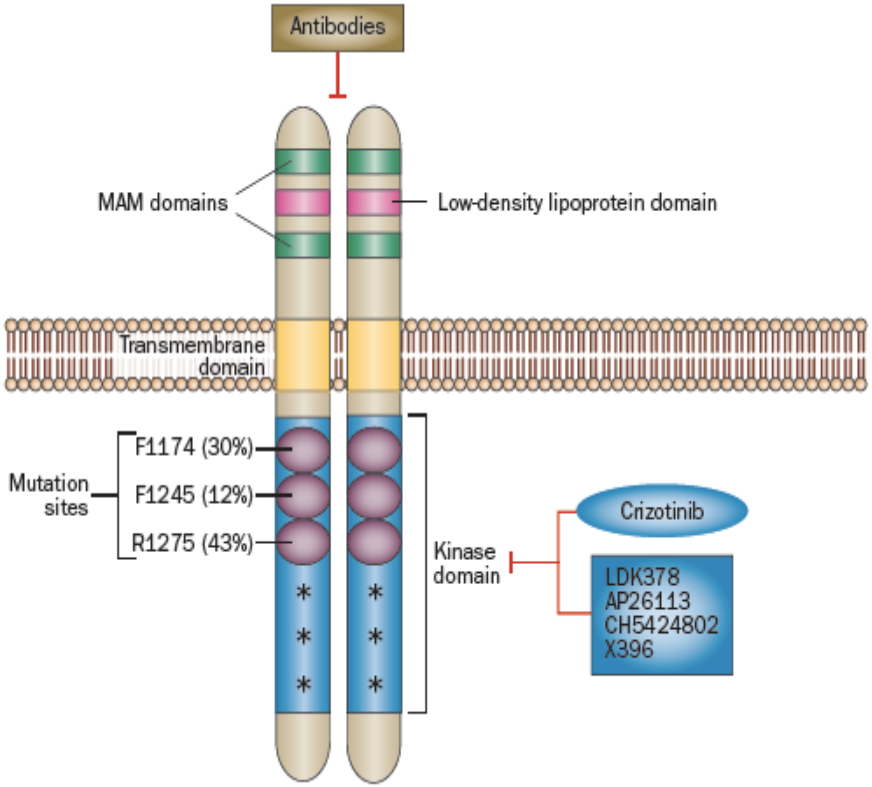
Unique elements:

- No single agent data for parp inhibitor in children needed as agent will be synergistic
- First study to have this design in children

Dose Level	BMN 673		Temozolomide (mg/m^2/dose)
	(mcg/m^2/dose)	Max. Daily Dose (mcg/Day)	
-1	400#	800	15
1*	**400#**	**800**	**20**
2	400&	800	20
3	600&	1000	20
4	600&	1000	30
5	600&	1000	40
6	600&	1000	55

Anaplastic Lymphoma Kinase Gene

- Originally identified in **ALCL** as a fusion transcript t(2;5) (*Morris S et al., Science*, 1994)
- Inflammatory Myofibroblastic Tumors (**IMT**)- 30-50%
- Non-small cell lung cancer (**NSCLC**)- 3-5%
- **Neuroblastoma-** mutations/amplification in 14% of HR group
- Others
  - Renal Cell Ca
  - Anaplastic Thyroid Ca
  - Rhabdomyosarcoma
  - Resistance mechanism to ALKi Rx



ALK-1 Genetic Alterations in Cancer

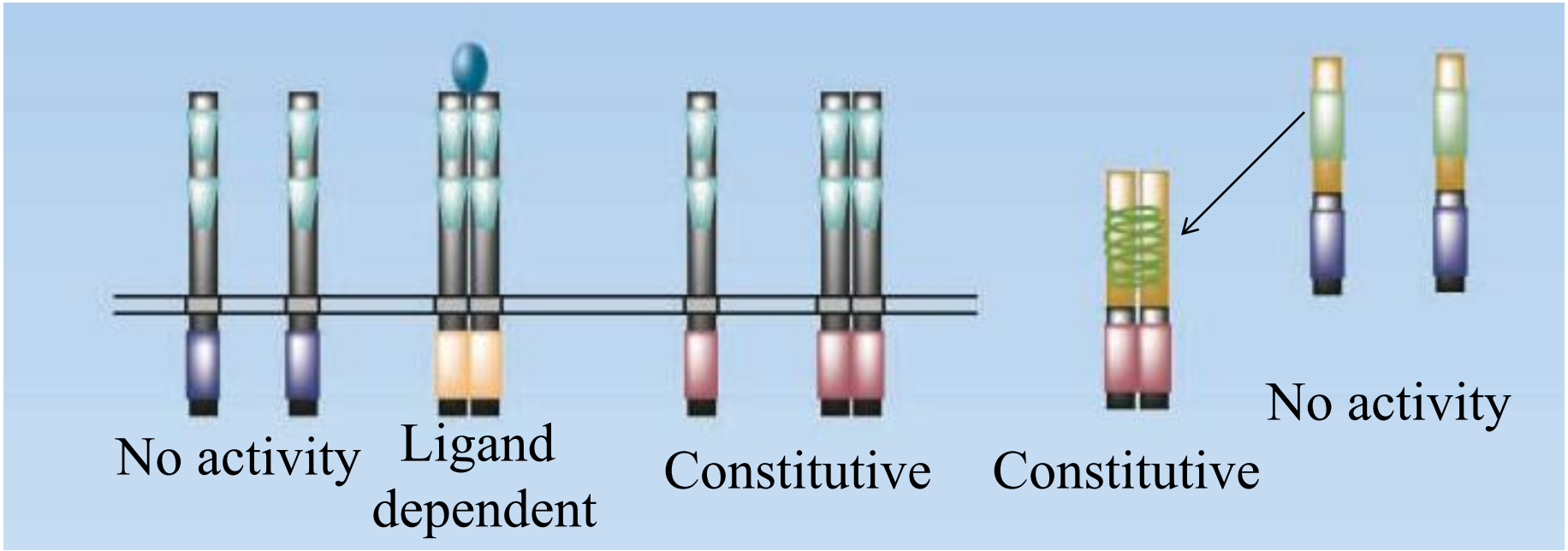
ALK aberrations

Mutations Amplification — Translocations

Neuroblastoma: Somatic, Germline — Somatic

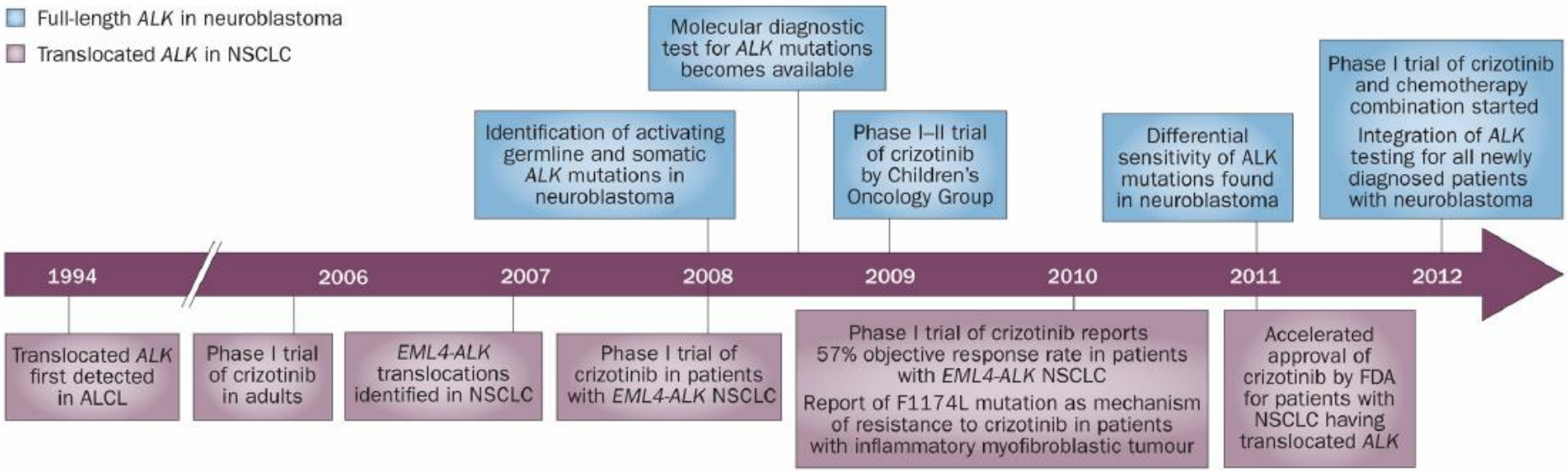
ALCL: unique — shared — IMT: unique

NSCLC: unique



Clin Cancer Res 2009;15:5609-14

Crizotinib Development Timeline

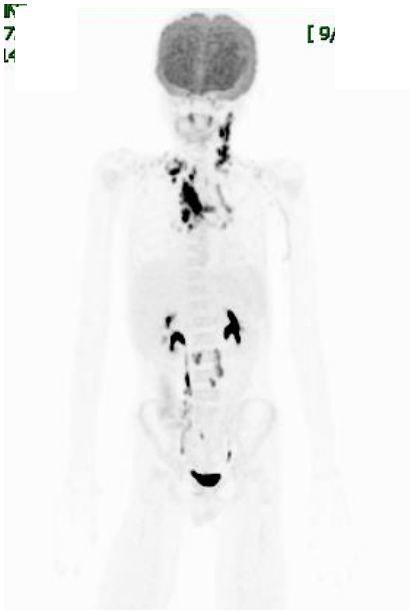


Nat Rev Clin Oncol:9(7):391-399,2102

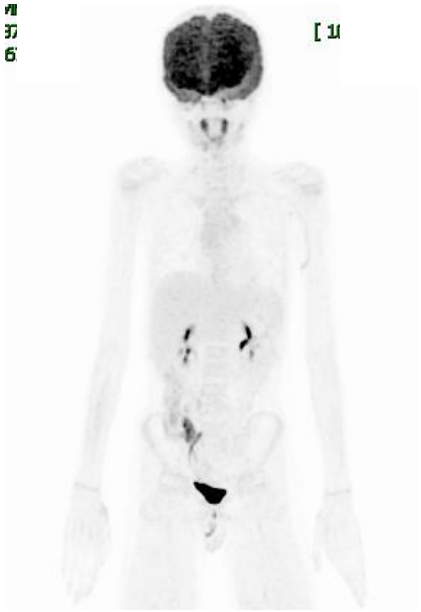
Targeted Responses to Crizotinib

Patient with ALCL- CR by FDG-PET

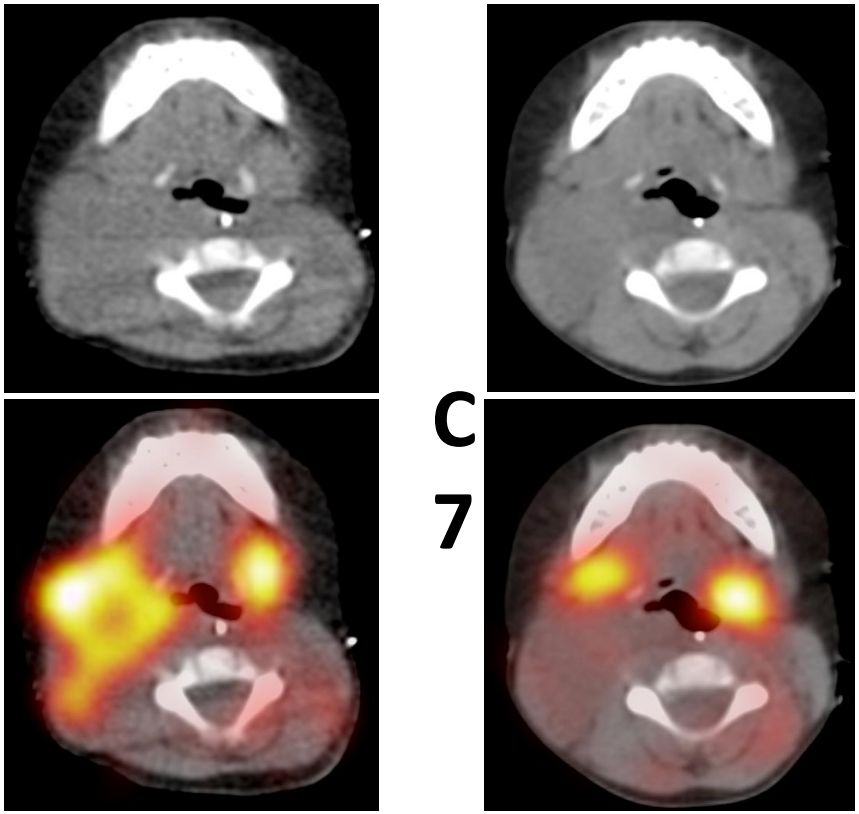
Pre-Cycle 1



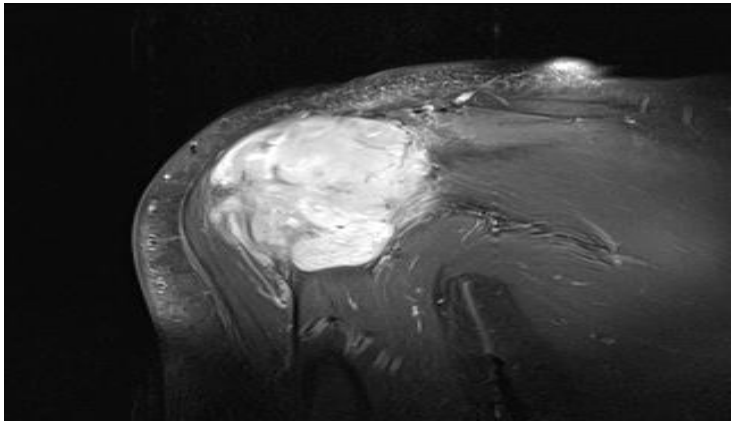
Post-Cycle 1 (28 days)



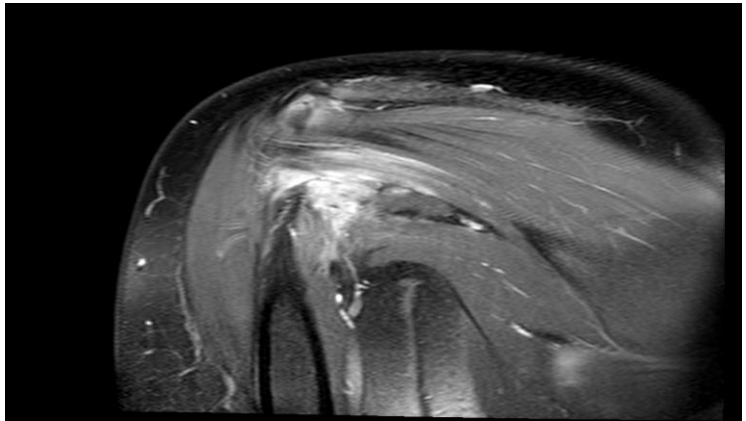
Patient with NB-germline mutation



Pre-Cycle 1



Post-Cycle 24



On-going Learning from ALK

- Mild side effects, long term administration tolerable; single agent MTD at 280 mg/m^2 (almost twice the adult dose) *The Lancet Oncology, 2013May;14(6):472-80*
- Response in ALCL met phase 2 endpoint for efficacy
  - Frontline trial incorporating crizotinib has opened (ANHL12P1, ClinicalTrials.gov Identifier: NCT01979536)
- Crizotinib may have a role in treatment of ALK+ IMT
- Phase 2 in patients with ALK+ NB continues
- Differential sensitivity to crizotinib dependent on variant ALK mutation: in vitro *Cancer Cell. 2014 Nov 10;26(5):682-94*.

Pediatric-MATCH Study

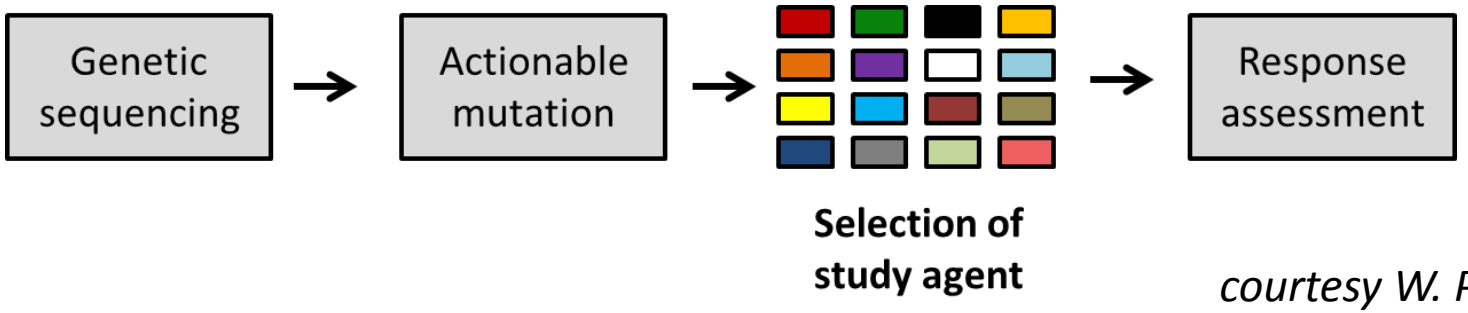
PROJECT:EVERYCHILD

CHILDREN'S ONCOLOGY GROUP

Precision oncology trial

NATIONAL CANCER INSTITUTE

Objective: to open a COG-wide single stage phase II trial of genomically-directed therapies for children with refractory solid tumors and lymphomas



courtesy W. Parsons

Antibodies: IMC-A12

Table 4. Pharmacokinetic Parameters (mean ± standard deviation) After First Infusion

Dose Level (mg/kg)	C_{min} (μg/mL)*	C_{max} (μg/mL)	Clearance (mL/h/kg)	$AUC_{0-\infty}$ (hr × mg/mL)	Half-Life (days)
6	59 ± 31	252 ± 95	0.25 ± 0.12	32.6 ± 21.1	4.2 ± 1.3
No. of patients	17	7	7	7	7
9	106 ± 57	400 ± 141	0.22 ± 0.08	46.3 ± 20.8	4.4 ± 1.1
No. of patients	17	14	9	9	9

Abbreviations: $AUC_{0-\infty}$, area under concentration versus time curve extrapolated to infinity; C_{max}, peak concentration; C_{min}, trough concentration.
*Trough concentration 7 days after initial infusion.

Adult target Cmin: 60 ug/ml at 6 mg/kg

Cixutumumab: recommended phase 2 dose higher then adults

- Greater variability in clearance
- Higher dose to hit desired adult target concentrations

J Clin Oncol 30:256-262., 2011

Lessons Learned and Opportunities for the Future in Pediatric Cancer Trials

- Beware of pre-clinical: models, exposure comparisons, surrogate markers of response
- Some agents may need very little dose finding in pediatrics e.g antibodies, agents with minimal toxicity
- Need early decision point to move a drug into up front therapy: randomized phase 2 studies
- Combinations
  - How to evaluate for up front therapy? What data is needed?
- Molecularly guided therapy: only 10-20% of patients at best

Conclusions

- To develop new agents to enhance the care of children and adolescents with cancer:
  - Requires coordination of pre-clinical, clinical and biologic resources
    - Needs understanding of the tumor/host/drug factors
    - Requires access to agents of interest with appropriate formulations for children
  - Requires collaboration
    - NCI/Academia/Industry
    - International

Acknowledgements

- COG: Peter Adamson
- Study Chairs:
  - Eric Shafer
  - Leo Mascarenhas
  - Suman Mulampati
  - Michael Isakoff
  - Carola Arndt
  - Yael Mosse
- PEC-MATCH: Will Parsons
- CTEP: Malcolm Smith
- PPTP: Malcolm Smith, Peter Houghton

Patients, Families, Dedicated Pediatric Oncology Community

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FOUNDATION FOR CHILDHOOD CANCER™

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