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# Pediatric Phase I / Pilot Consortium

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November 2011

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# Pediatric Phase I / Pilot Consortium – Children Are Different

- Multi-institutional studies required:
  - Substantial infrastructure required for site training, for study monitoring, and for implementing PK/PD/Imaging studies
- Ethical issues limit risks to children participating in correlative research studies
  - Direct impact on type of PD studies that can be performed
- Pharmaceutical interest is limited →
  - Limited non-NIH funding stream for pediatric drug development
  - NCI plays unique role in supporting teams of experienced investigators to safely & efficiently conduct multi-institutional "first-in children" studies

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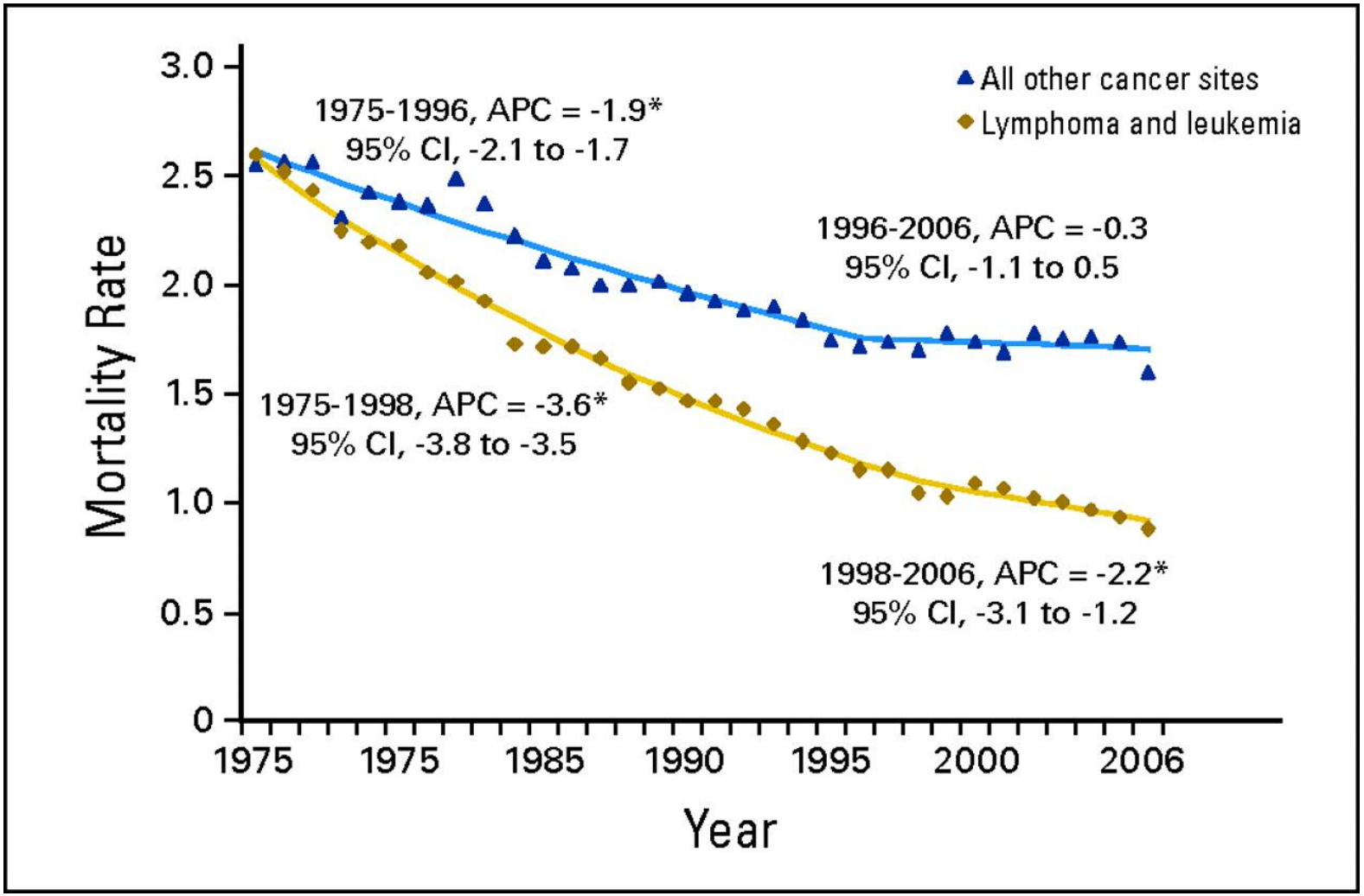
# US childhood mortality trends for lymphoma and leukemia, and all other cancer sites combined




Smith M A et al. JCO **2010;28:2625-2634**

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# Strategy for Discovering Effective New Treatments for Children with Cancer

**TARGET Discovery Programs**

**PPTP Preclinical Evaluation**

TARGET

St. Jude Children's Research Hospital
Pediatric Cancer Genome Project
Washington University

**COG Phase 1 Clinical Trial**

**COG Definitive Clinical Trial**

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# COG Phase 1/Pilot Consortium

- History of NCI support:
  - Pediatric phase 1 clinical trials resource supported by NCI since 1992
  - COG Phase 1 Consortium supported since 2002
  - NCI continues providing primary support for pediatric phase 1 trials in children with cancer in North America
- Ongoing need:
  - Approximately 20% of children for whom current treatments not sufficiently effective. Continued need for NCI support of an experienced team of investigators to conduct first-in-children studies for new anticancer agents with novel mechanisms of action and molecular targets

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# Consortium Contributions

- Phase 1 evaluations of targeted agents building on genomic and preclinical discoveries:
  - ALK inhibitor crizotinib phase 1 study focusing on patients with neuroblastoma and ALCL and other tumors with ALK mutations.
  - JAK inhibitor ruxolitinib (INCB018424) phase 1 study following up on discovery of JAK mutations in high-risk B-precursor ALL.
  - Aurora A kinase inhibitor MLN8237 phase 1 study following up on PPTP findings of high activity for MLN8237 against ALL and neuroblastoma preclinical models.
  - NTX-010 (Seneca Valley Virus, SVV-001) oncolytic virus phase 1 study focusing on patients with neuroendocrine tumors
- COG Phase 1 Consortium conducts phase 1 studies with intensive monitoring and PK / PD evaluations
- COG builds on Consortium phase 1 studies by developing phase 2 and subsequently phase 3 clinical trials using dose/schedule/PK data generated by the Consortium.

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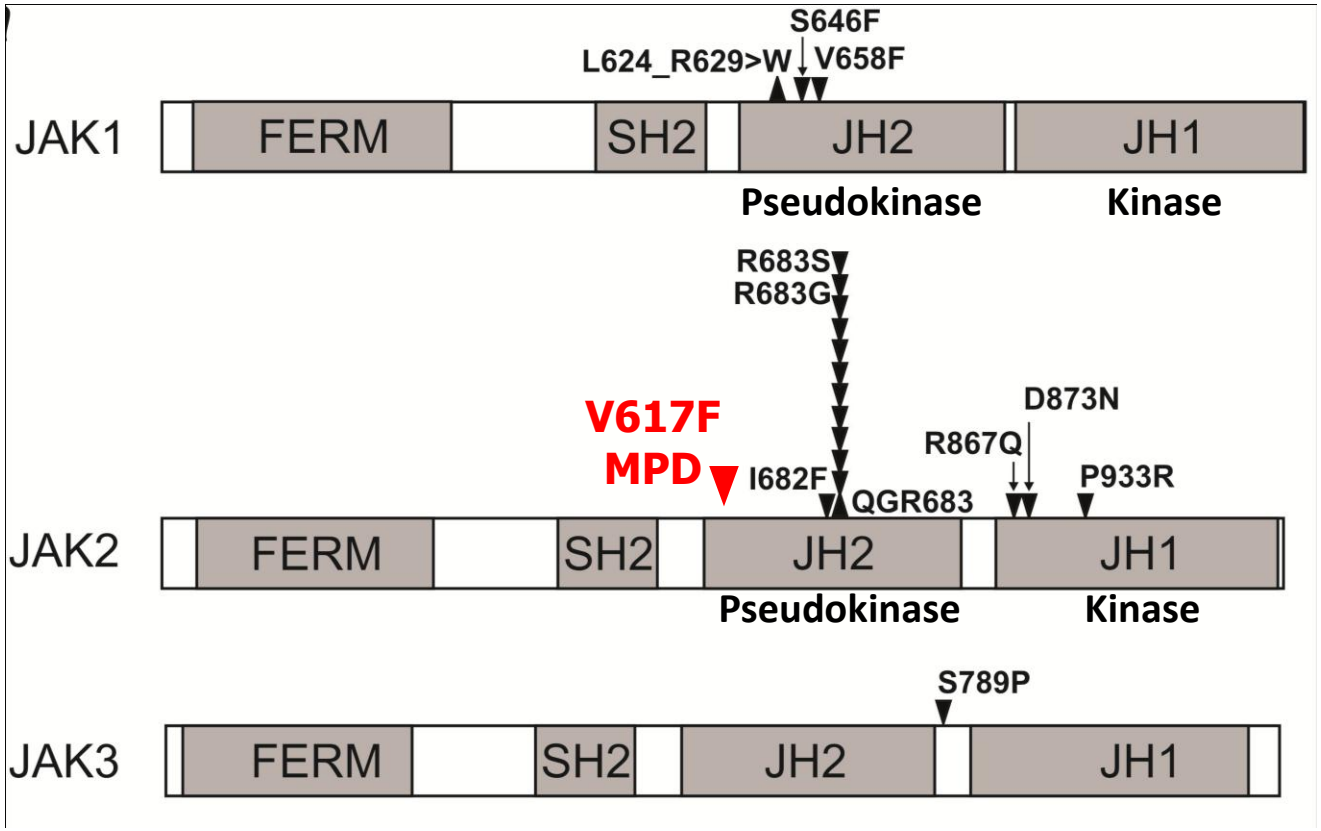
# JAK mutations in "BCR-ABL1-like" ALL

- JAK2 (n=16): 10 R683G;  3 non-R683G pseudokinase domain; 3 kinase domain
- JAK1 (n=3): 3 pseudokinase domain
- JAK3 (n=1):  uncertain functional consequences




*Mullighan CG, et al. PNAS 2009:106(23):9414-9418*

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# Clinical Translation by COG Phase 1 Consortium

- Phase 1 trial of JAK inhibitor ruxolitinib (INCB18424) in Sept 2010 in collaboration with Incyte.
- Ruxolitinib in development for adults with myelofibrosis (MF):
  - JAK2 mutations common for this condition
  - NDA filed in June 2011
- Eventual COG plan for combining JAK inhibitor for JAK-mutant ALL in same way that imatinib has been added to standard chemotherapy for BCR-ABL ALL.

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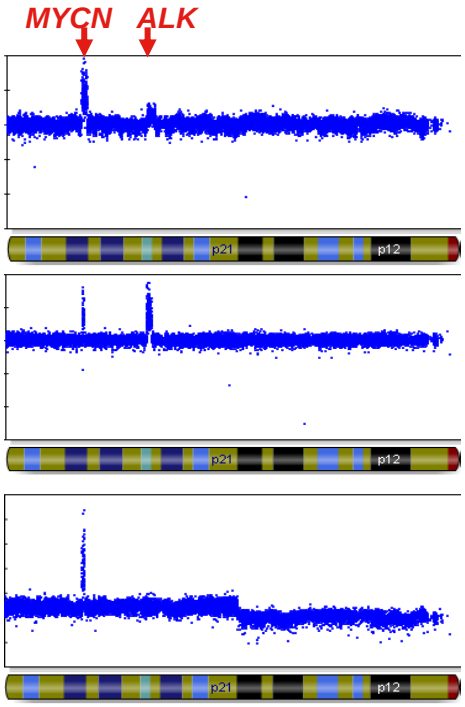
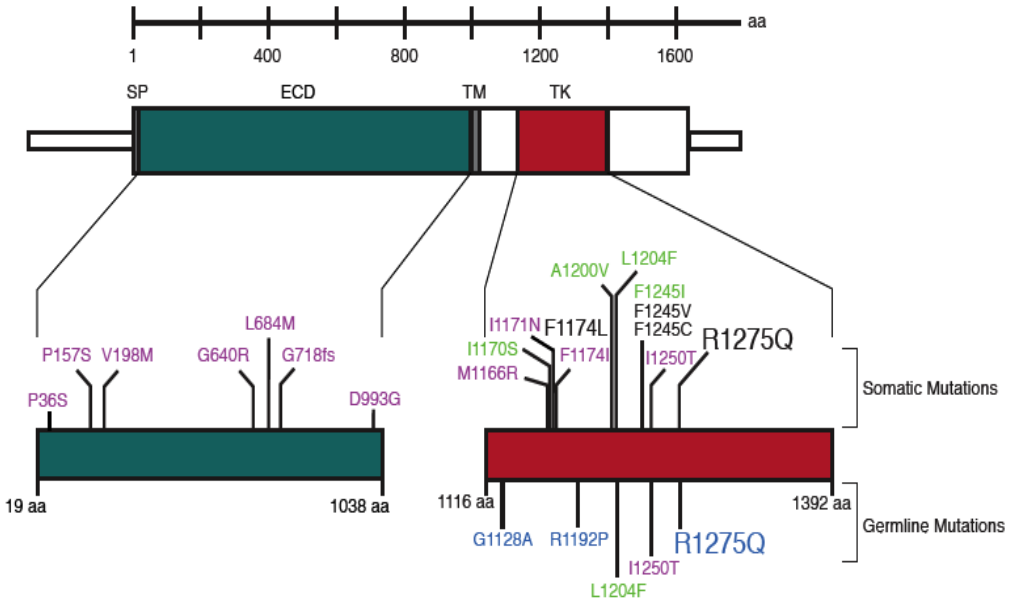
# ALK is an Oncogenic Kinase in Neuroblastoma

- Co-discovery of ALK as the familial neuroblastoma gene (Mosse, Nature 2008) and frequent somatic amplification and mutation (TARGET)
  - Amplification: 31/599 (5.2%)
  - Focal gain: 102/599 (17.0%)
  - Mutations in kinase domain: 43/552 (7.2%)
  - Mutations in extracellular domain: Present, frequency still be defined



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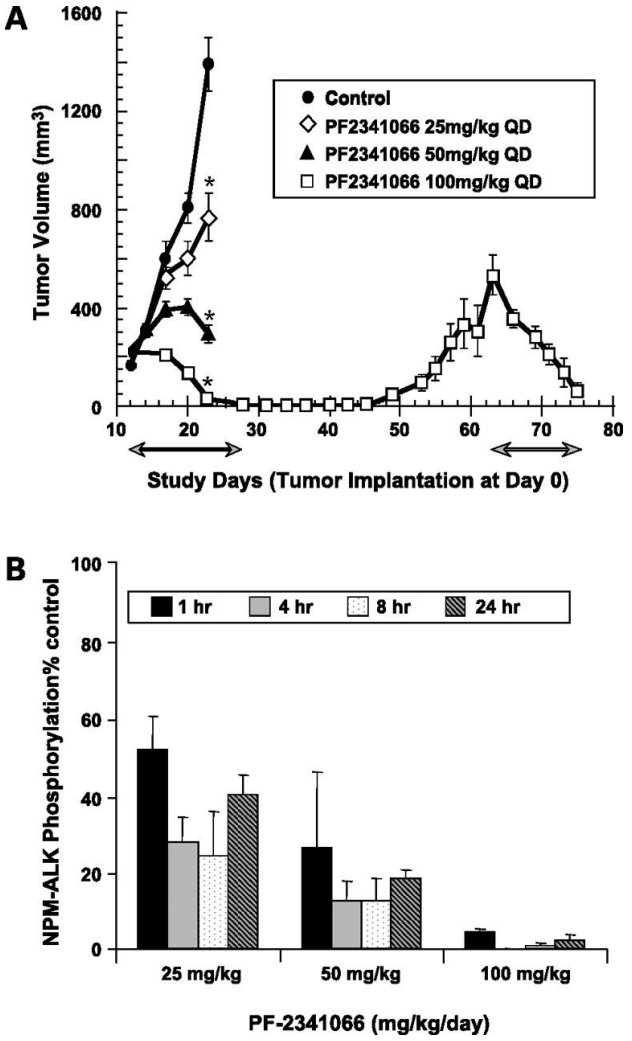
# ALK-mutated (translocated) tumors are highly sensitive to ALK inhibitors

- PF-02341066 in the Karpas299 xenograft model (NPM-ALK ALCL).
- 1st cycle of treatment initiated on day 11 through day 23 (except the 100 mg/kg group, which was treated through day 28).
- A 2nd cycle of treatment initiated on day 62 - 76 for the 100 mg/kg/d group after tumor regrowth.
- COG Phase 1 Consortium initiated phase 1 trial of ALK inhibitor crizotinib (PF-02341066) Sept 2009.




Christensen J G et al. Mol Cancer Ther 2007;6:3314-3322

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# Further Clinical Evaluations of Agents Recently Studied by COG Phase 1 Consortium

| Trial | Agent(s) | Current status |
|---|---|---|
| ADVL0319 | Lenalidomide | Phase 2 CNS trial in children with recurrent low-grade gliomas |
| ADVL0413 | Sorafenib | Frontline for FLT3 positive AML |
| ADVL0414 | VOIT | Frontline COG pilot study for high risk rhadomyosarcoma |
| ADVL0416 | SAHA + Cis RA | Frontline PBTC trial for infants with CNS embryonal tumors |
| ADVL0419 | Valproic acid | Frontline Texas-Oklahoma Pediatric Neuro-Oncology trial in BSG and unresectable HGG |
| ADVL0515 | CBDCA + VBL | Under consideration by CNS tumor committee |
| ADVL0516 | Dasatinib | Frontline COG trial for children/young adults with Philadelphia chromosome positive ALL |
| ADVL0517 | Ispinesib | No further development; CTEP withdrew IND |
| ADVL0612 | Sunitinib | Phase 2 COG trial for children with recurrent CNS tumors |
| ADVL0712 | IMC-A12 | Phase 2 COG trial for children with sarcomas and other solid tumors and frontline study for metastatic rhabdomyosarcoma |
| ADVL0714 | VEGF Trap | No further pediatric development due to toxicity and PK profile |
| ADVL0812 | MLN8237 | Phase 2 COG trial in refractory/recurrent solid tumors including neuroblastoma and ALL |

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# Would making the Phase 1 Consortium part of COG be a more efficient use of resources?

- The Consortium is integrated with COG in appropriate ways:
  - Clinical data management system
  - Protocol development resources
  - Shared meetings
  - Thus, no duplicative infrastructure
- Scope of clinical trials for the Consortium is very different from those of COG:
  - Intensity of monitoring and data reporting
  - Numbers of patients per trial and numbers of participating institutions
  - Emphasis on PK, PD, and imaging endpoints
  - If COG were to take responsibility for phase 1 trials, it would need to replicate the Consortium's capabilities in these areas
- There would be little or no budgetary savings from incorporating the Consortium into COG assuming that the same scope of work was maintained

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# What is gained by having the Phase 1 Consortium distinct from COG?

- Focused NCI and peer review to ensure that the Consortium has the following:
  - Strong scientific leadership,
  - Data collection and management procedures that meet the high standards for granularity, accuracy, and timeliness required for phase 1 trials,
  - Appropriate integration of PK and PD
  - High productivity in developing and completing clinical trials
- Phase 1 studies would represent a small percentage of COG accrual if Consortium were merged into COG:
  - Risk that phase 1 trials would be de-emphasized because of the higher priority for COG of larger phase 2 and 3 trials

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# Budget Considerations

- Flat Budget relative to FY10:
  - Direct cost in Year 1 of $3 million
  - Total cost in Year 1 of $3.47 million

- Apportioning of funds:
  - Scientific Leadership (~10%)
  - Protocol Development & Regulatory (15%-20%)
  - Statistics and Data Management (~10%)
  - Imaging (15%-20%)
  - Pharmacokinetic/Biology Support (~5%)
  - Travel (4%)
  - Basic Member Institution Site Support (~40%)

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# Conclusions

- COG Phase 1 / Pilot Consortium is premier organization for conduct of “first in children” clinical trials for anticancer agents
- Record of accomplishment:
  - Protocols activated and completed
  - Patients enrolled
  - Publications and presentations
  - Contributions to COG PK studies
  - Mentoring junior faculty
  - Integrating new imaging methods into pediatric phase 1 trials
- Consortium is needed so that children can benefit from advances in cancer biology and drug development in coming years.