

**A Phase I Study of AC220, a FLT3  
Inhibitor, in Combination with Cytarabine  
and Etoposide in Relapsed/Refractory  
Childhood ALL and AML  
A Therapeutic Advances in Childhood  
Leukemia & Lymphoma (TACL) Study**

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**JOHNS HOPKINS**  
MEDICINE

**TACL**

Therapeutic Advances in  
Childhood Leukemia &  
Lymphoma

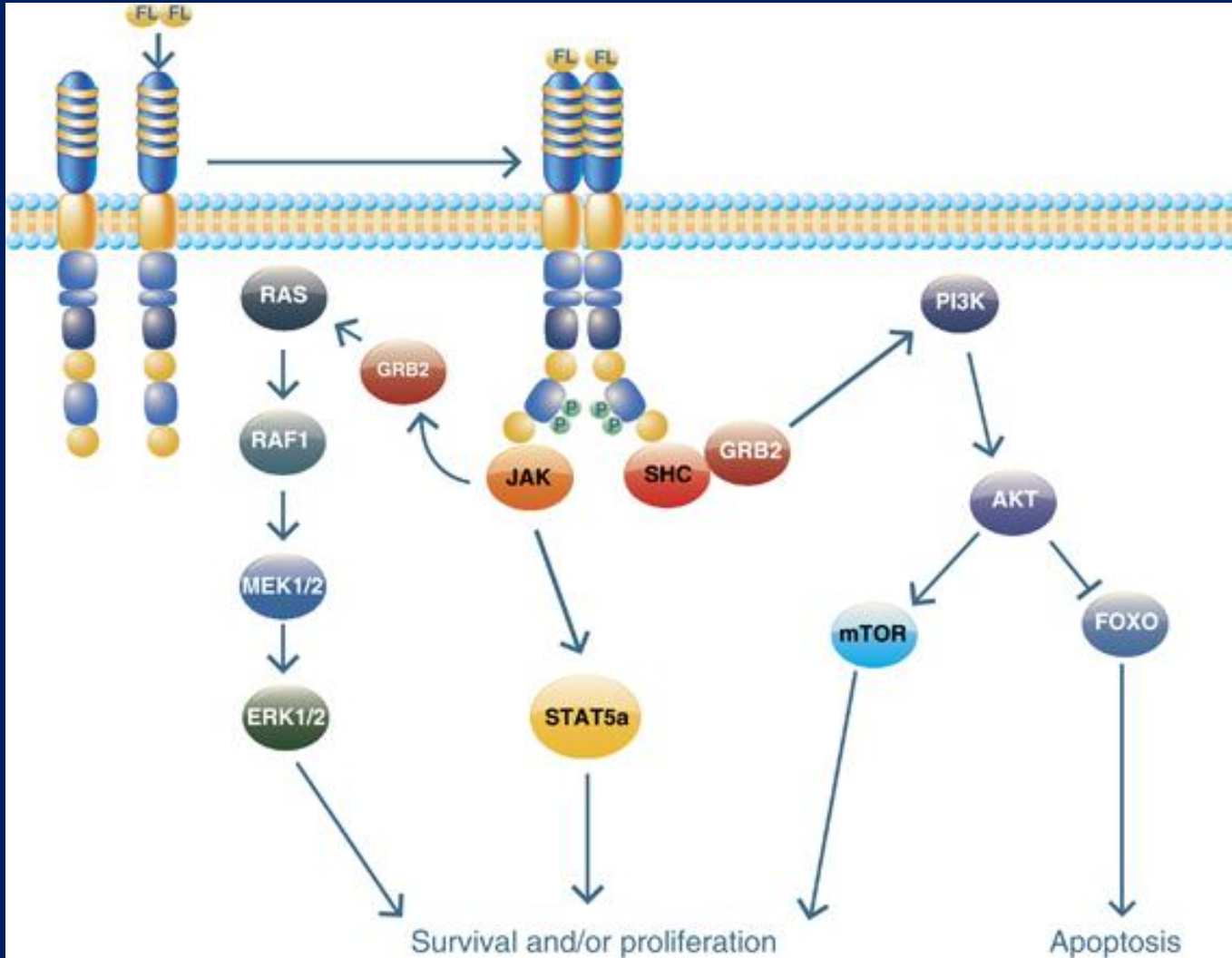


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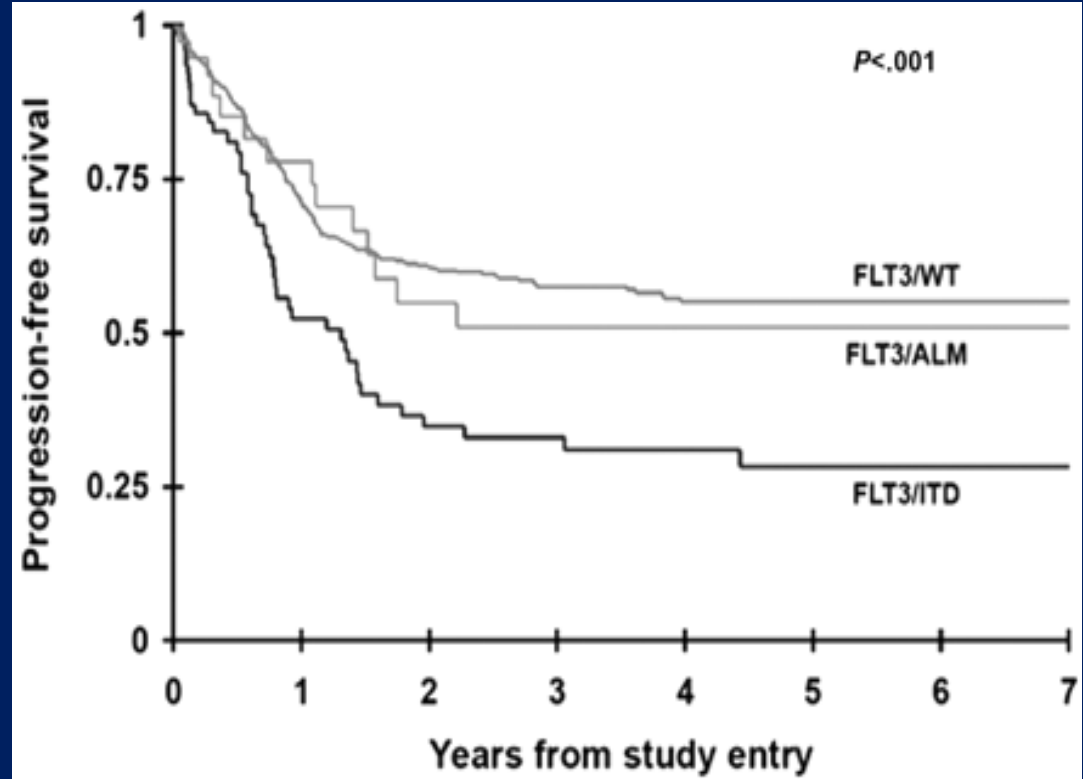
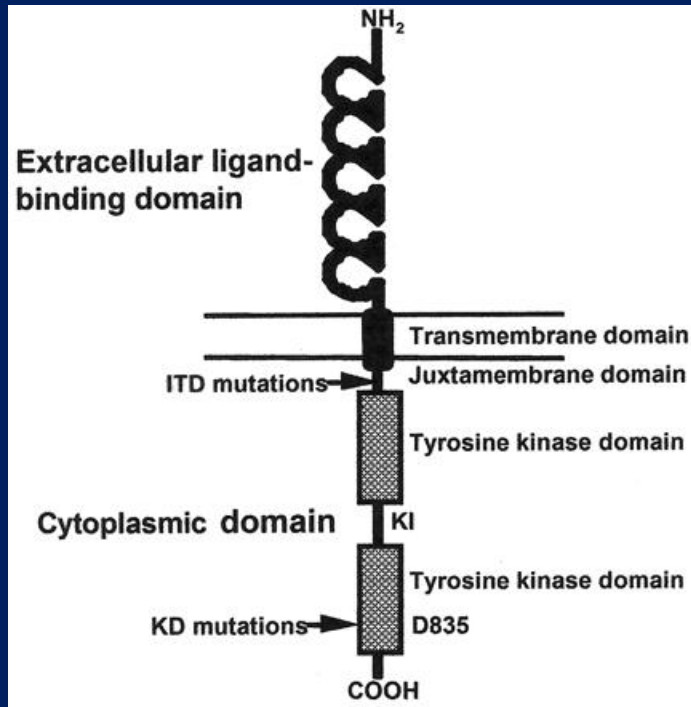
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# FLT3 SIGNALING



# FLT3 MUTATIONS



# FLT3: An Attractive Target in Childhood Leukemia

- **AML**
  - ITD mutations (15%)
  - Subset of KD mutations (5%)
  - High FLT3-WT expression (10%)
- **ALL**
  - MLL-r (5% kids, 80% infants)
  - Hyperdiploid (30% kids)
- **SUMMARY**
  - ≈ One-third of pediatric acute leukemia is FLT3 driven

# TACL 2009-004:

## OBJECTIVES AND ELIGIBILITY

- Primary Objective
  - To determine a safe and biologically active dose of AC220 given in sequential combination with ara-C/etoposide
- Secondary Objectives
  - To relate clinical responses with the ability to achieve adequate FLT3 plasma inhibitory activity levels (PIA)
- Eligibility:
  - $\leq 21$  yoa
  - Relapsed/refractory AML
  - ALL that has hyperdiploidy or MLL rearrangement



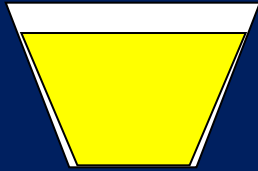
# DOSE ESCALATION SCHEMA

Dose Level	AC220 Dose
0	15 mg/m <sup>2</sup> /day
1	25 mg/m <sup>2</sup> /day
2	40mg/m <sup>2</sup> /day
<b>3</b>	<b>60 mg/m<sup>2</sup>/day</b>
4	90 mg/m <sup>2</sup> /day
5	130 mg/m <sup>2</sup> /day

- Complete responses seen in adult Phase I as low as 40 mg dosing
- PIA assay demonstrates p-FLT3 inhibition as low as 12 mg dosing
- Prolongation of QTcF at higher doses (90mg and 135 mg)
- Adult Phase IIb study evaluated both 30mg/day and 60 mg/day

# Plasma Inhibitory Activity (PIA) Assay

Patient takes AC220



Plasma



FLT3/ITD  
AML  
cell line



Western blot for P-FLT3

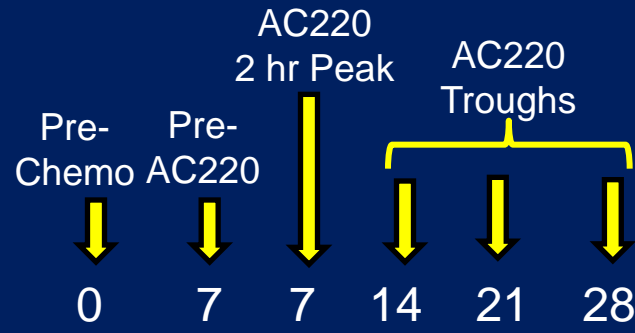
Does plasma have  
inhibitory activity  
against FLT3?

Whole blood





# Plasma Inhibitory Assay



**DOSE  
LEVEL 1  
25 mg/m<sup>2</sup>**

p-FLT3



FLT3

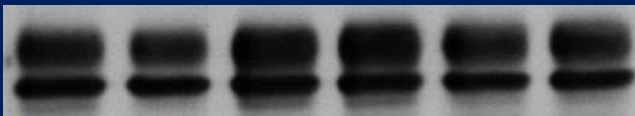


**DOSE  
LEVEL 2  
40 mg/m<sup>2</sup>**

p-FLT3



FLT3



**DOSE  
LEVEL 3  
60 mg/m<sup>2</sup>**

p-FLT3



FLT3



•Near  
complete  
inhibition of  
p-FLT3 in all  
patients at all  
dose levels

- DL1 – 3 pts
- DL2 – 6 pts
- DL3 – 9pts

# PATIENT CHARACTERISTICS

Total Evaluable pts	ALL (N=4)	AML (N=18)
<b>Age (years)</b>		
<b>Median</b>	<b>2.79 yr</b>	<b>13.13 yr</b>
<b>Range</b>	<b>11mo-19 yr</b>	<b>1.8-21 yr</b>
<b>Gender</b>		
<b>Male</b>	<b>1</b>	<b>7</b>
<b>Female</b>	<b>3</b>	<b>11</b>
<b>#Prior Therapies</b>		
<b>Median</b>	<b>2</b>	<b>3</b>
<b>Range</b>	<b>1-10</b>	<b>1-5</b>
<b>Prior HSCT</b>		
<b>No</b>	<b>4</b>	<b>8</b>
<b>Yes</b>	<b>0</b>	<b>10</b>
<b>FLT3/ITD+</b>		
<b>No</b>	<b>-</b>	<b>9</b>
<b>Yes</b>	<b>-</b>	<b>8</b>

# TOXICITIES

## Dose Limiting Toxicities

Dose Level	Name of Toxicity	Toxicity Grade	Attribution to AC220
2 (40 mg/m <sup>2</sup> )	Lipase increased	3	Related
3 (60 mg/m <sup>2</sup> )	Blood bilirubin increased	4	Related

# RESPONSE

Response	Overall	ALL	AML FLT3-WT	AML FLT3-ITD	AML Unknown FLT3 Status
Evaluable for response	18	3	8	6	1
Overall Response					
CR	3	-	1	2	
CRi	1	-	-	1	
SD	9	1	4	3	1
PD	5	2	3	-	
In-evaluable	4				

ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia

FLT3-ITD= internal tandem duplication; FLT3-WT= wild type

CR=Complete Response; CRi=Complete Response with incomplete platelet recovery;

SD=Stable Disease; PD=Progressive Disease

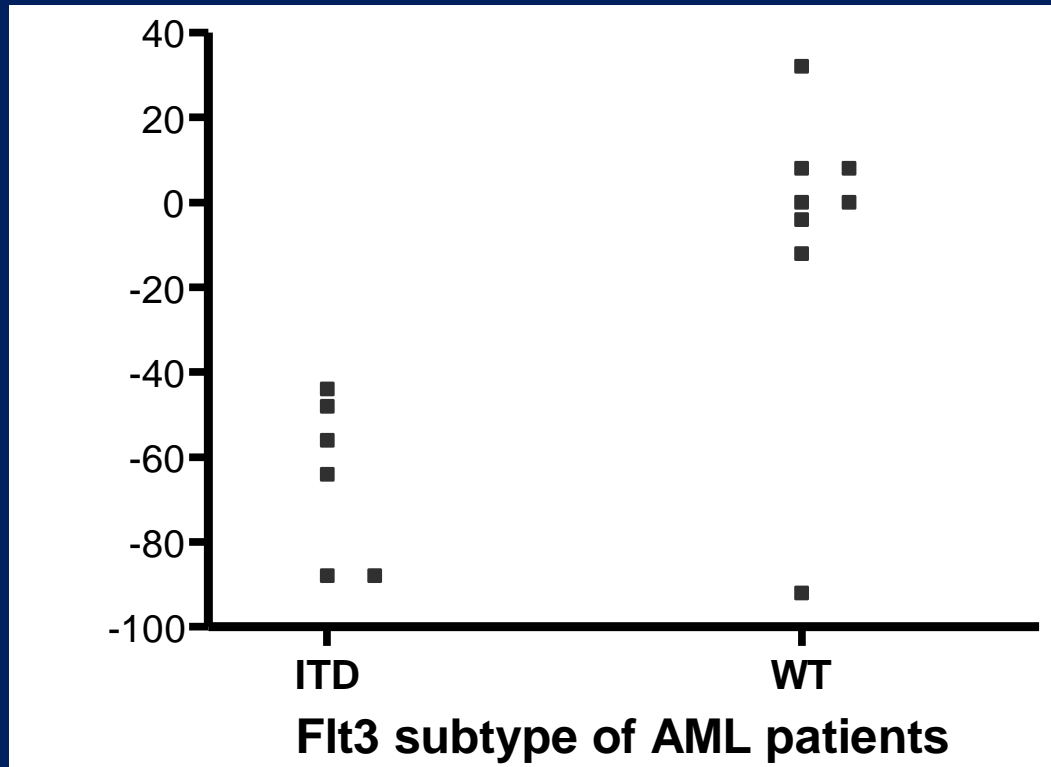
# CHARACTERISTICS OF RESPONDERS

Dose Level	Age	Diagnosis	FLT3 Status	Prior Regimens	Prior HSCT	Best Response	Post Study HSCT	Status
1	10	AML	ITD	2	Yes	CR	Yes	A/R
2	3	AML	WT	1	No	CR	Yes	A/R
2	21	AML	ITD	5	Yes	CRi	No	DOD

**A/R = Alive and In Remission**

**DOD = Died of Disease**

# FLT3-ITD Patients Have Greater Improvement in Blast Count Percentage



Flt3 subtype	Mean difference <sup>1</sup> (SE)	95% CI	p-value
WT (n = 8)	-7.88 (12.95)	(-38.50, 22.75)	<b>0.004</b>
ITD (n = 6)	-65.67 (7.74)	(-85.55, -45.78)	

<sup>1</sup> Difference in blast count = Bone Marrow blast count post-treatment minus bone marrow blast count pre-treatment.

# FLT3-ITD Patients Trend Toward Improved Survival

Survival Probabilities Patient subset	6-month survival (95% CI)	1-year survival (95% CI)
<b>Evaluable AML patients only (n = 14)</b>		
<b>WT (n = 8)</b>	<b>62.50%</b> <b>(22.93, 86.07)</b>	<b>15.63%</b> <b>(14.19, 49.09)</b>
<b>ITD (n = 6)</b>	<b>83.33%</b> <b>(27.31, 97.47)</b>	<b>66.67%</b> <b>(19.46, 90.44)</b>

<sup>1</sup> One AML patient had unknown Flt3 status, and is excluded for these estimates

<sup>2</sup> Standard error is high (or wide CI) due to the very small sample size

# TACL 2009-004: Conclusions

- AC220 plus AE is well tolerated at 60 mg/m<sup>2</sup>/day
- Toxicities were consistent with intensive AML chemotherapy regimens
- Plasma inhibitory assay revealed near complete inhibition of FLT3 phosphorylation in all patients at all dose levels
- Responses are encouraging in FLT3-ITD patients (50% CR or Cri), and seems to provide bridge to HSCT
- Further testing in children with FLT3-ITD is warranted



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