

Gilteritinib

Mark Levis MD PhD

Director, adult leukemia program

Sidney Kimmel Comprehensive Cancer Center

Johns Hopkin University



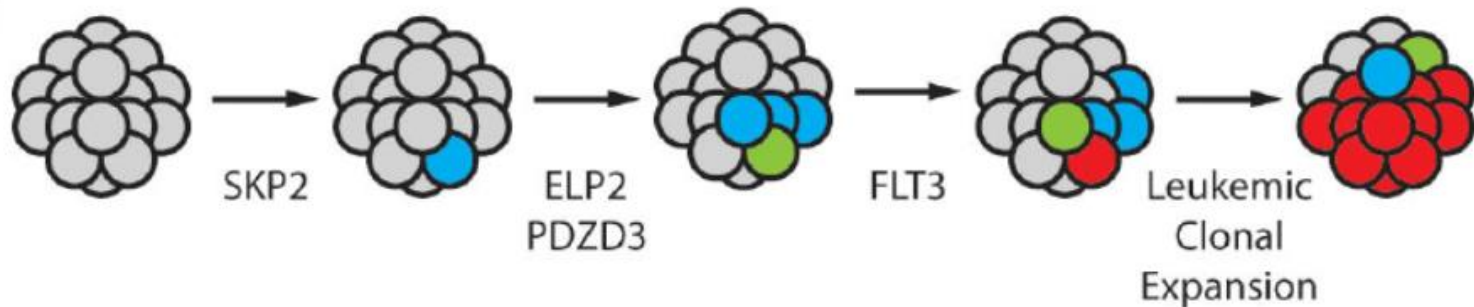
JOHNS HOPKINS
M E D I C I N E

**THE SIDNEY KIMMEL
COMPREHENSIVE CANCER
CENTER**

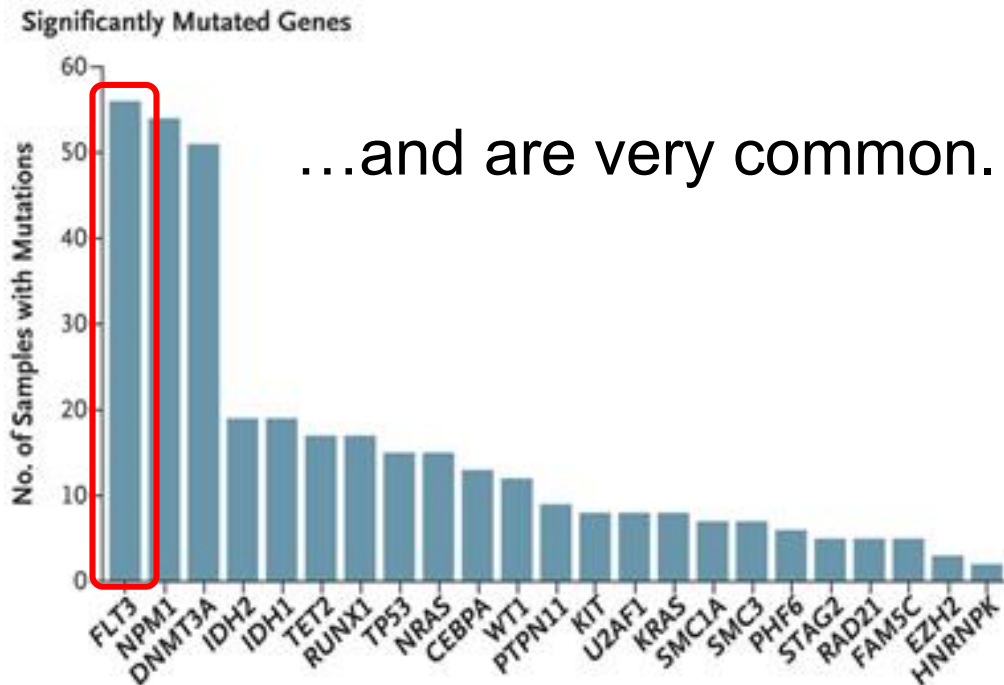
Disclosures

- Astellas Global Pharma
 - Research funding
- Daiichi-Sankyo
 - Consulting/honoraria
- FujiFilm
 - Research funding
- Novartis
 - Research funding
 - Consulting/honoraria

FLT3 mutations occur relatively late in the pathogenesis of AML....



Sci Transl Med. 2012 4:149ra118

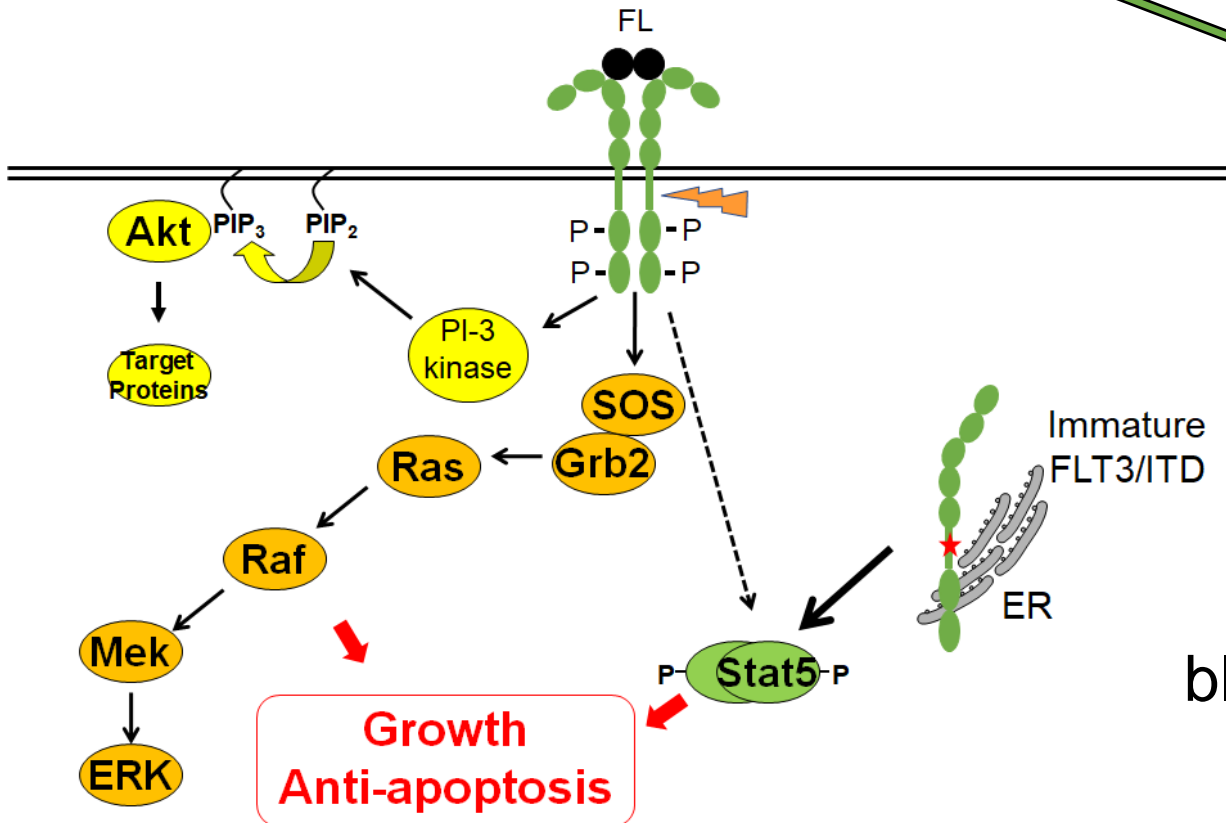
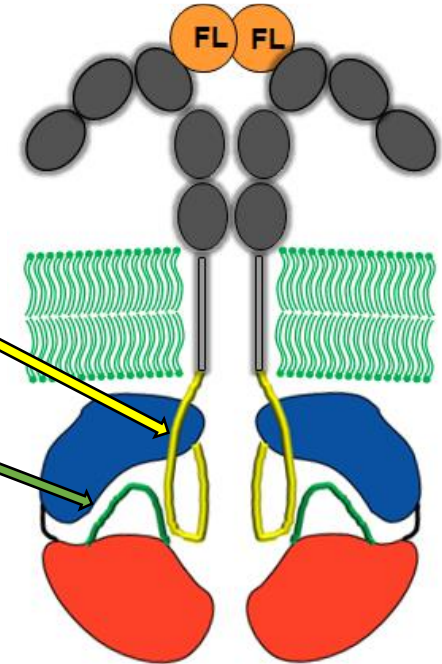


Two types of FLT3 activating mutations

~23% of AML **FLT3-ITD mutation**

~7% of AML **FLT3-TKD mutation**

The receptor tyrosine kinase
FLT3



FLT3 signaling promotes growth, blocks differentiation and apoptosis

FLT3 mutations make everything worse!

- In general:
 - Clinical: high white count, aggressive disease
 - High relapse rate, poorer overall survival
 - Best treated with allogeneic transplant
 - *Hematology Am Soc Hematol Educ Program.2013;2013:220-6*
- Acute promyelocytic leukemia
 - FLT3 mutated in ~30%
 - Higher relapse rate, worse survival
 - *Ann hematol 2014;93:2001-10*
- NPM1
 - FLT3-mutated in ~30%
 - FLT3-ITD confers higher relapse rate, worse survival
 - *Blood. 2008;111:2776-2784*
- Core-binding factor AML
 - FLT3 mutated in ~20%
 - Higher relapse rate
 - *Blood. 2016;127:2451-2459*
- Bcl-2 inhibitors (venetoclax)
 - FLT3-ITD mutations confer resistance
 - ASH 2017 abstract #1348



Newly-diagnosed
FLT3-mutated
AML patient

Induction



Consolidation



Maintenance



When during AML therapy should we use a FLT3 inhibitor?

Relapsed/refractory
FLT3-mutated AML
patient



Salvage

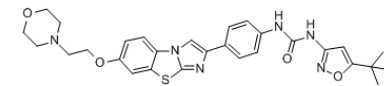
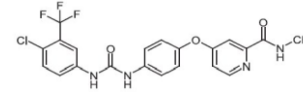
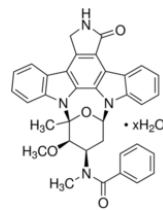
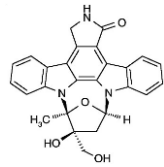
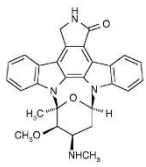


Maintenance





A brief history of FLT3 inhibitors



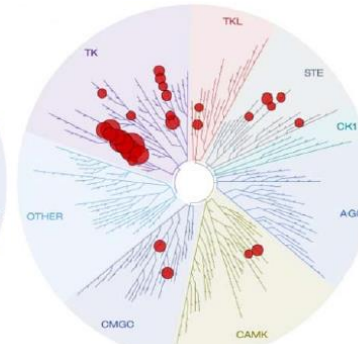
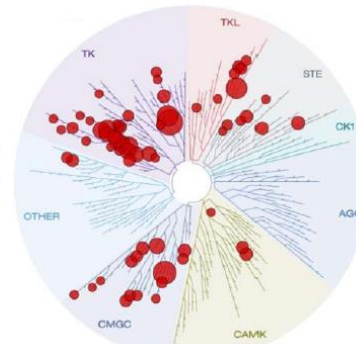
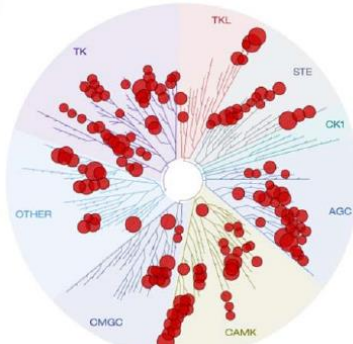
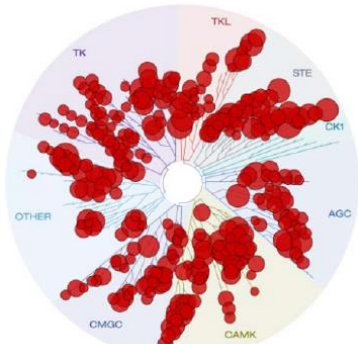
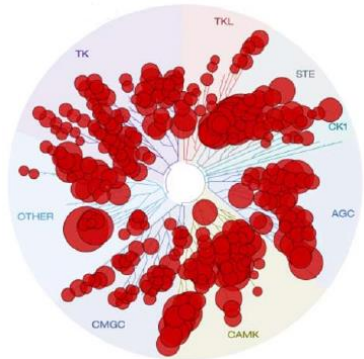
Staurosporine

Lestaurtinib

Midostaurin

Sorafenib

Quizartinib

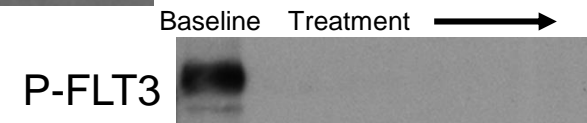
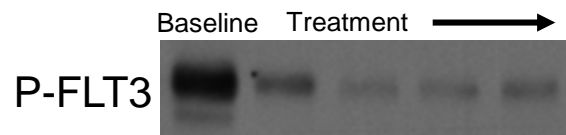
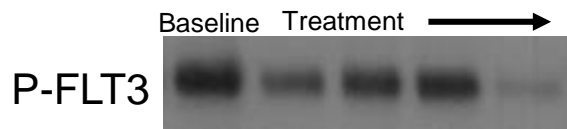
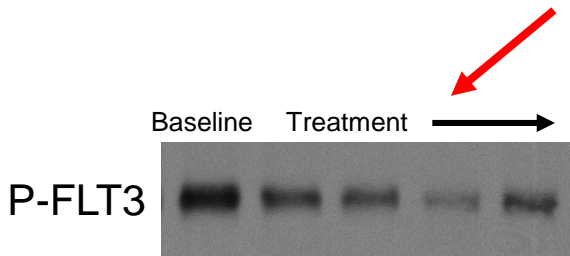


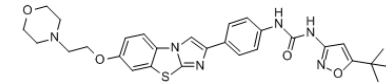
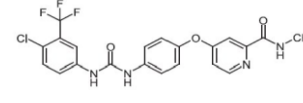
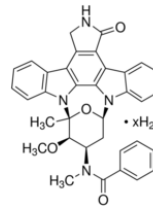
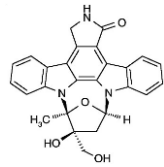
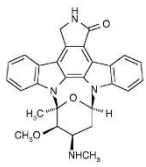
Levis et al. *Blood*.
2002; 99:3885

Weisberg et al. *Cancer Cell*.
2002; 1:433

Auclair et al. *Leukemia*.
2007; 21:439

Zarrinkar et al. *Blood*.
2009; 114:2984





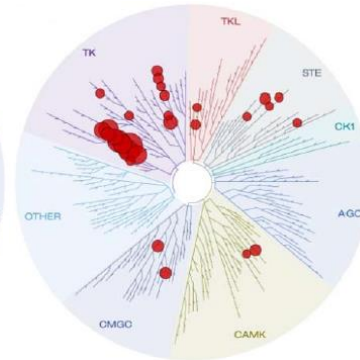
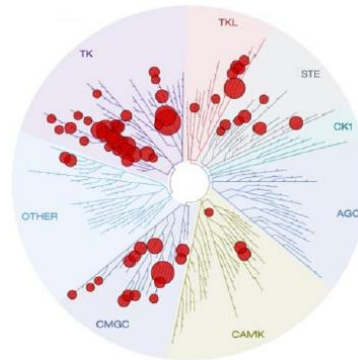
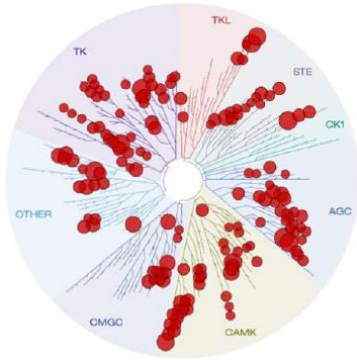
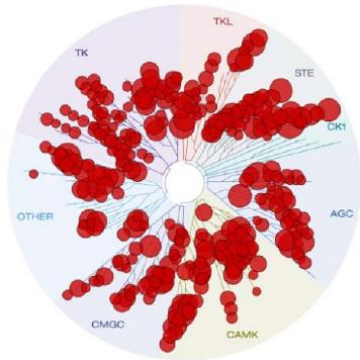
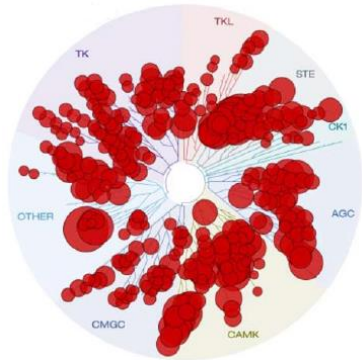
Staurosporine

Lestaurtinib

Midostaurin

Sorafenib

Quizartinib



Levis et al. *Blood*.
2002; 99:3885

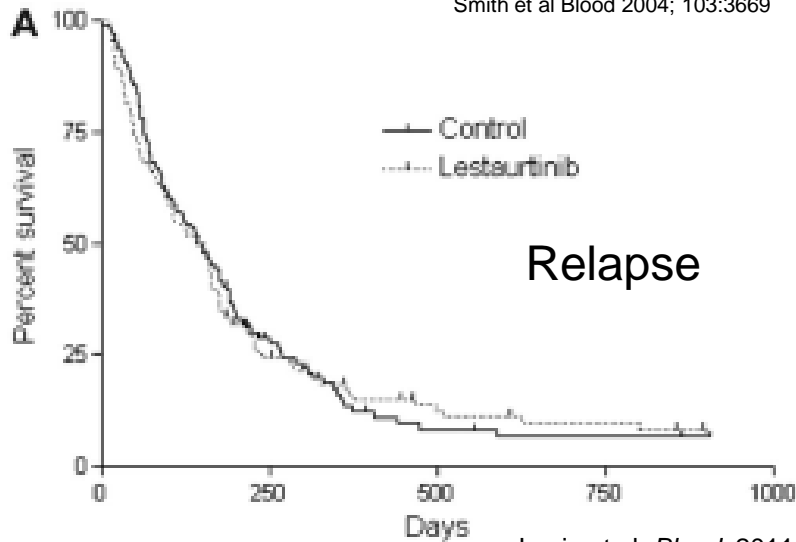
Weisberg et al. *Cancer Cell*.
2002; 1:433

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2007; 21:439

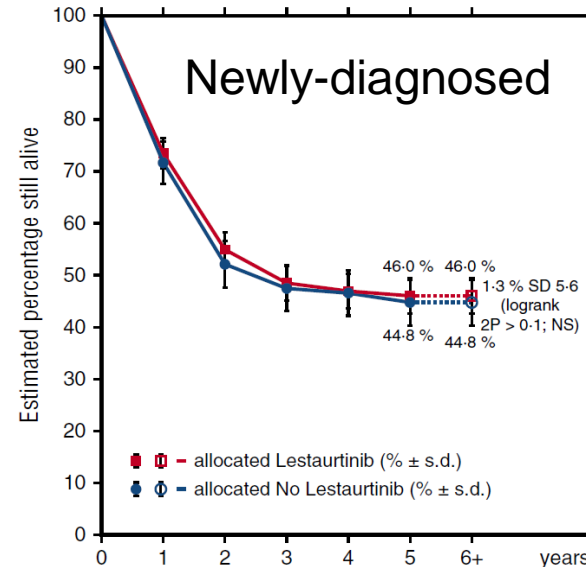
Zarrinkar et al. *Blood*.
2009; 114:2984

Minimal single agent activity

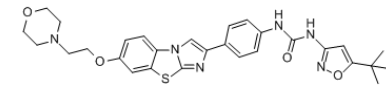
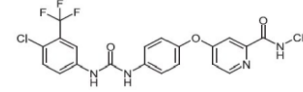
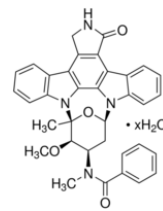
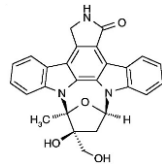
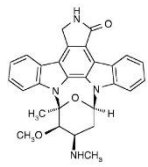
Smith et al *Blood* 2004; 103:3669



Levis et al. *Blood*. 2011; 117:3294



Knapper et al. *Blood*. 2017; 129:1143



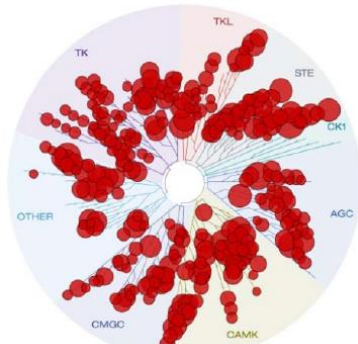
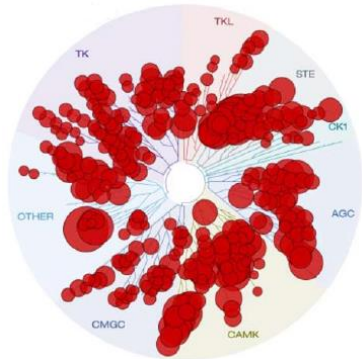
Staurosporine

Lestaurtinib

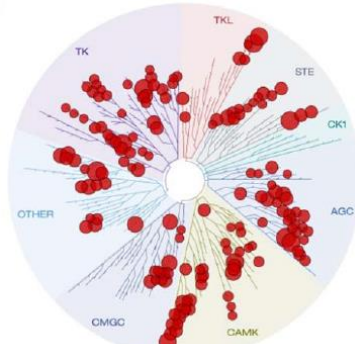
Midostaurin

Sorafenib

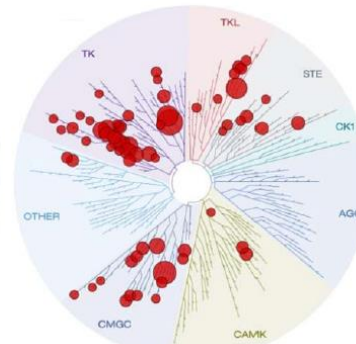
Quizartinib



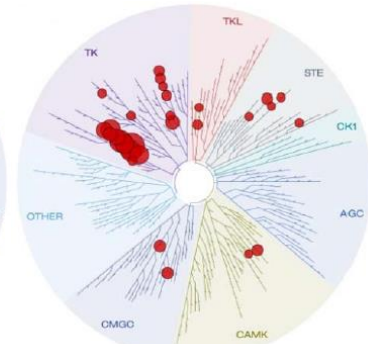
Levis et al. *Blood*. 2002; 99:3885



Weisberg et al. *Cancer Cell*. 2002; 1:433



Auclair et al. *Leukemia*. 2007; 21:439



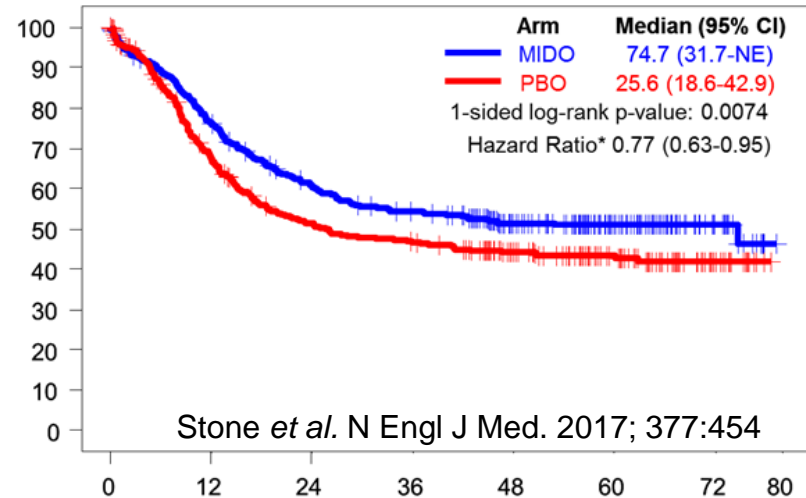
Zarrinkar et al. *Blood*. 2009; 114:2984

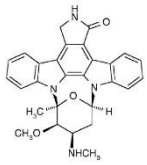


Minimal single agent activity

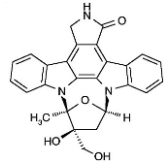
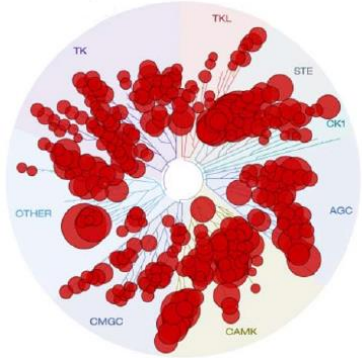
Fischer et al *J Clin Oncol* 2010; 28:4339

- Newly-diagnosed FLT3-mutated AML
- Combination of midostaurin and chemotherapy
- 5 year survival:
 - Chemo + midostaurin 50.9%
 - Chemo + placebo 43.3%

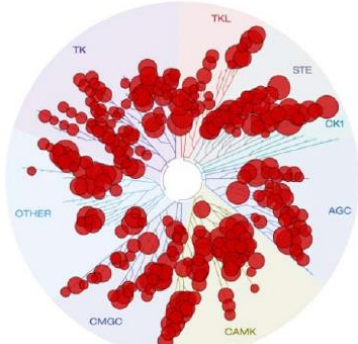




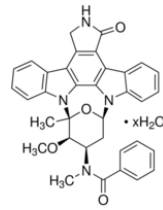
Staurosporine



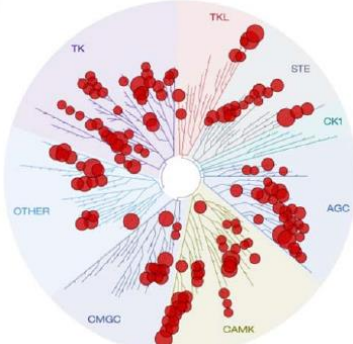
Lestaurtinib



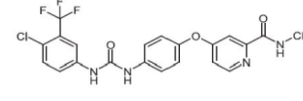
Levis et al. *Blood*.
2002; 99:3885



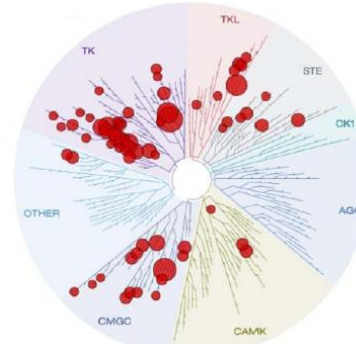
Midostaurin



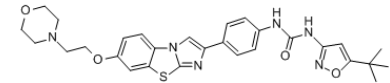
Weisberg et al. *Cancer Cell*.
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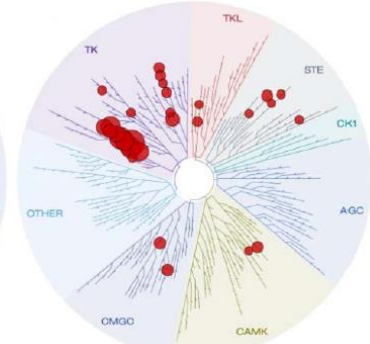
Sorafenib



Auclair et al. *Leukemia*.
2007; 21:439



Quizartinib

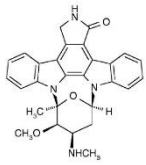


Zarrinkar et al. *Blood*.
2009; 114:2984

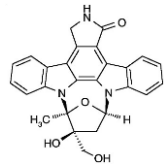
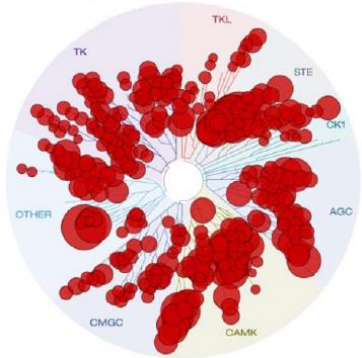
Modest single agent activity

Borthakur et al. *Haematologica* 2011;96:62

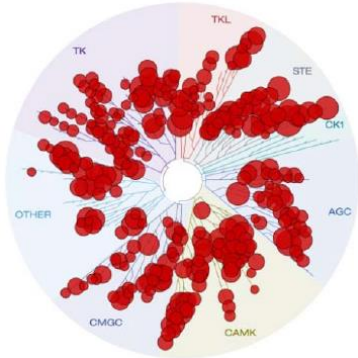
Difficult to tolerate...



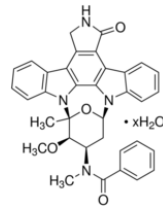
Staurosporine



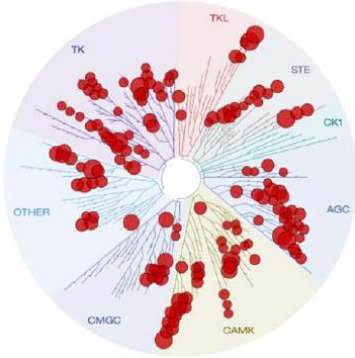
Lestaurtinib



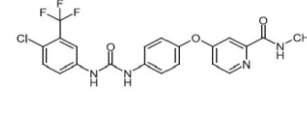
Levis et al. *Blood*.
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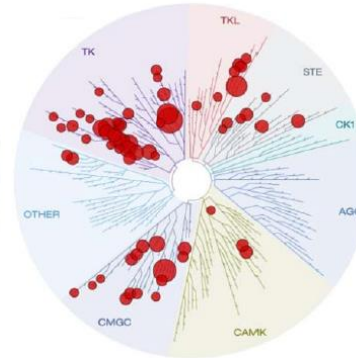
Midostaurin



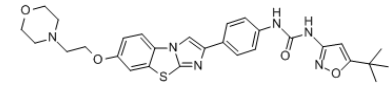
Weisberg et al. *Cancer Cell*.
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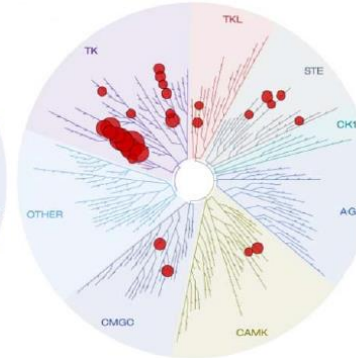
Sorafenib



Auclair et al. *Leukemia*.
2007; 21:439



Quizartinib



Zarrinkar et al. *Blood*.
2009; 114:2984

Encouraging single agent activity!

See next talk...

Quizartinib:

A great drug, but still one with a couple of problems...

Kit inhibition leads to hypopigmentation....



Day 1



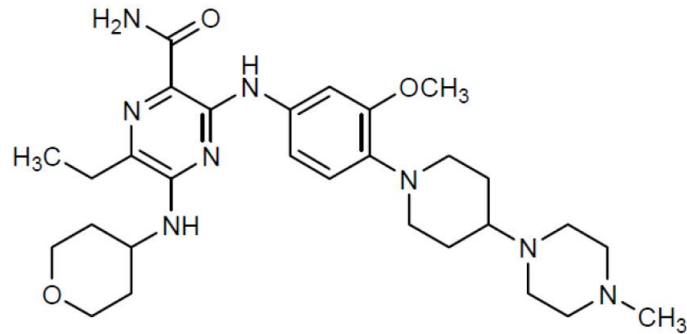
Day 54

Resistance to quizartinib conferred by point mutations in FLT3

<u>Subject number</u>	<u>Age</u>	<u>Gender</u>	<u>New Mutation at Relapse</u>	<u>Weeks on Study</u>
1005-004	60	F	F691L	19
1005-006	43	M	D835Y	6
1005-007	59	F	D835V	23
1005-009	68	M	D835Y	18
1005-010	52	M	F691L	19
1009-003	75	F	D835Y	12
1009-007	64	F	F691L, D835V	10
1011-006	70	M	D835Y	7
1011-007	56	F	D835Y	8

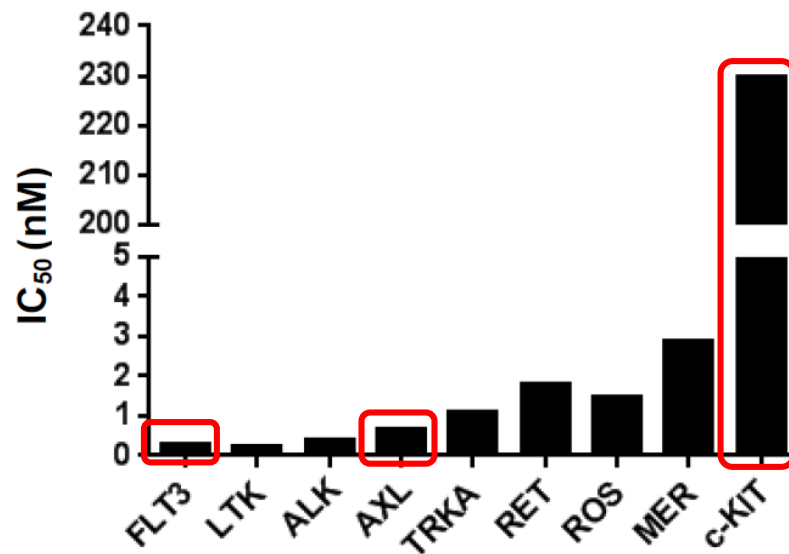
...and myelosuppression.

Gilteritinib



Active against the tyrosine kinase domain mutations that confer resistance to quizartinib and sorafenib:

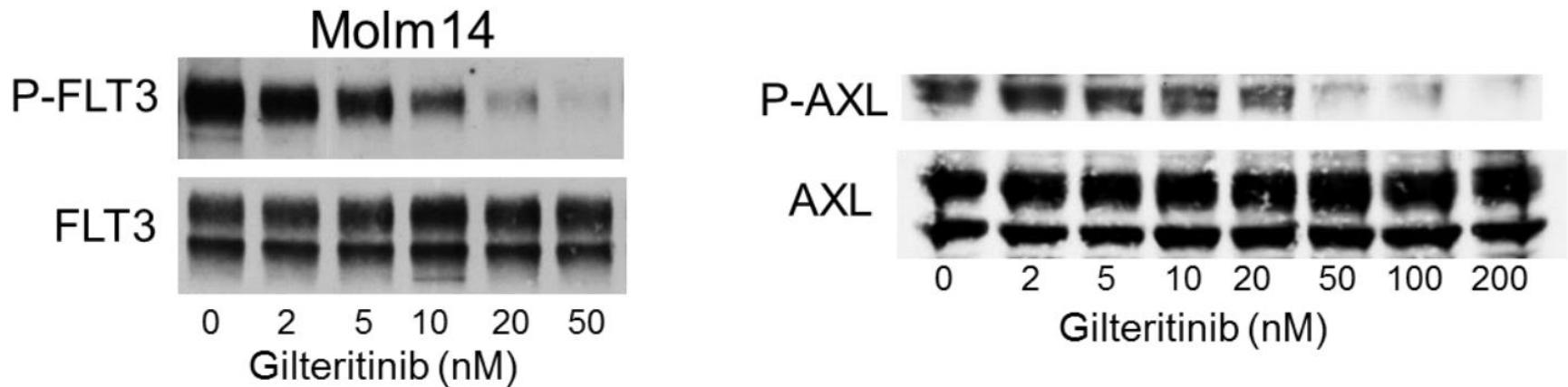
Inhibitory Activity of Gilteritinib Against Select Kinases



FLT3 receptor subtype	Gilteritinib IC ₅₀
Wild type	5 nM
Molm14 (ITD)	1.8 nM
TF/ITD	1.4 nM
Ba/F3 ITD	0.7 nM
Ba/F3 D835Y	0.5 nM
Ba/F3 D835H	1.9 nM
Ba/F3 D835V	0.7 nM
Ba/F3/ITD F691L	17.6 nM

Gilteritinib

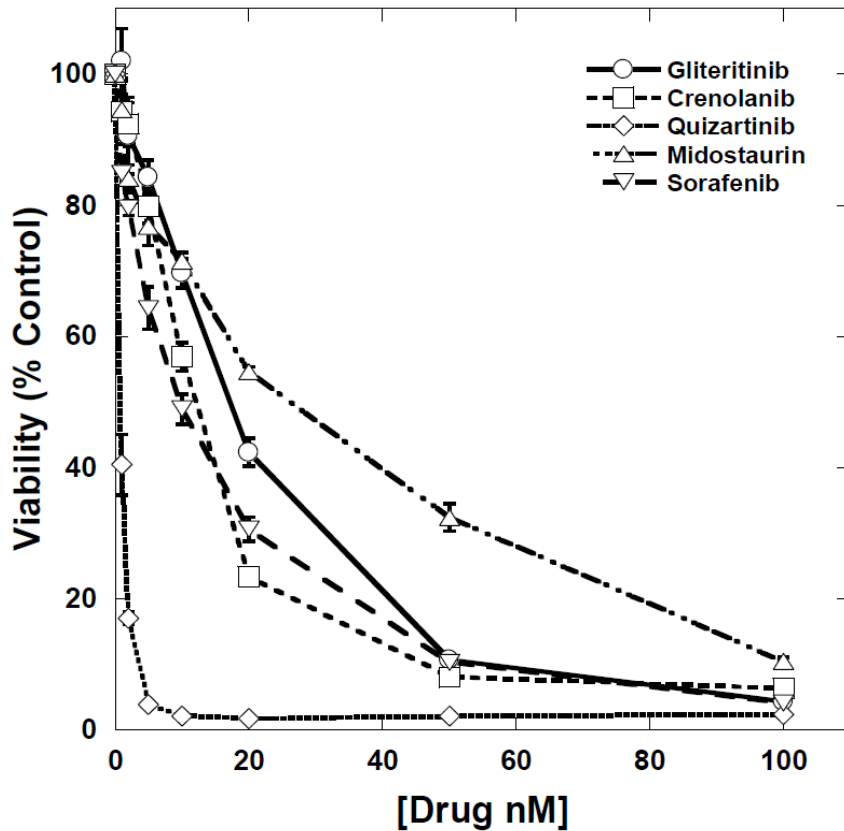
Active against FLT3 and (to a lesser extent) Axl:



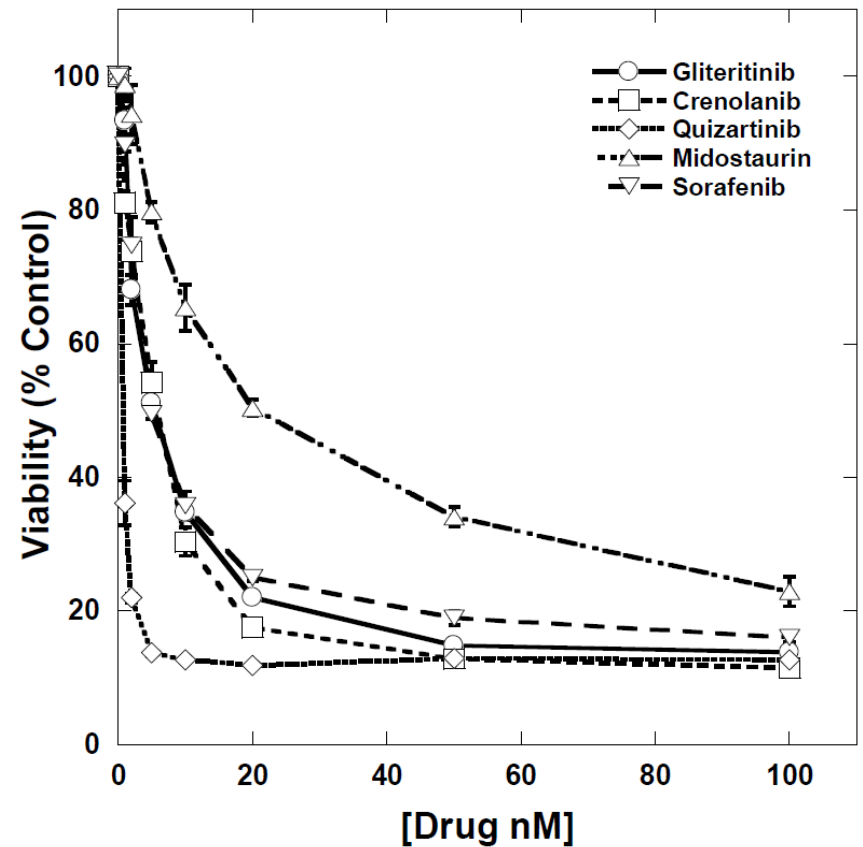
Gilteritinib

Activity against FLT3-ITD cell lines:

Molm14

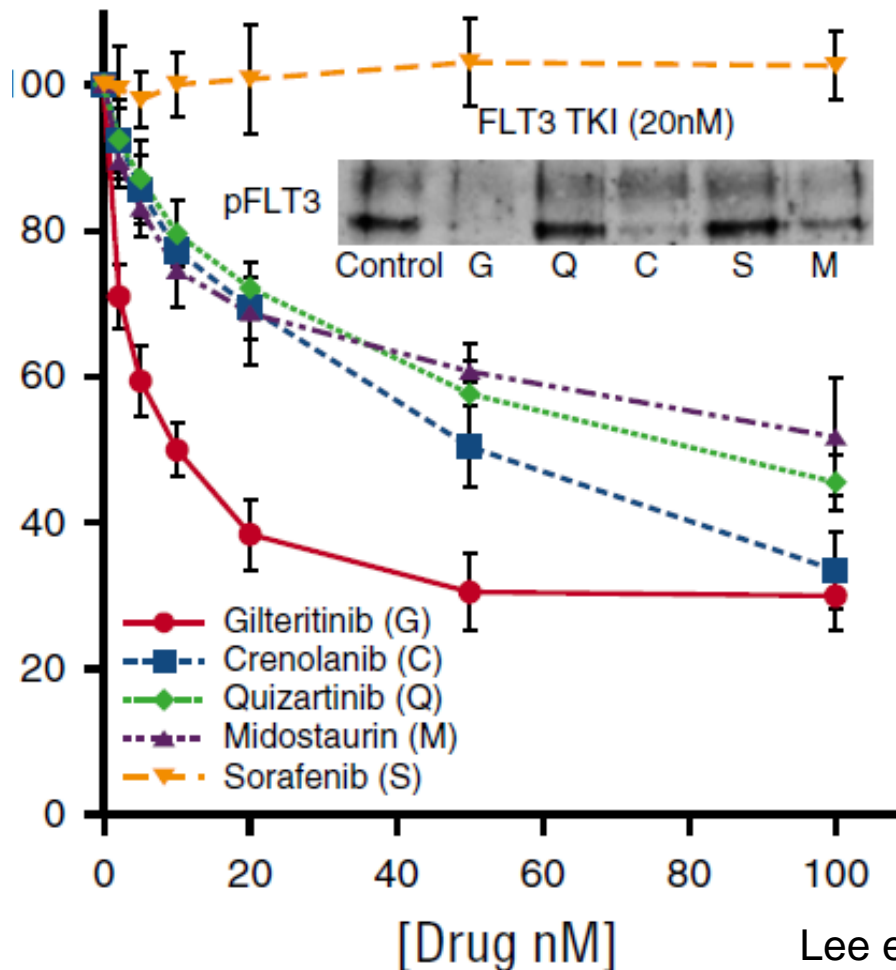


MV4-11



Gilteritinib

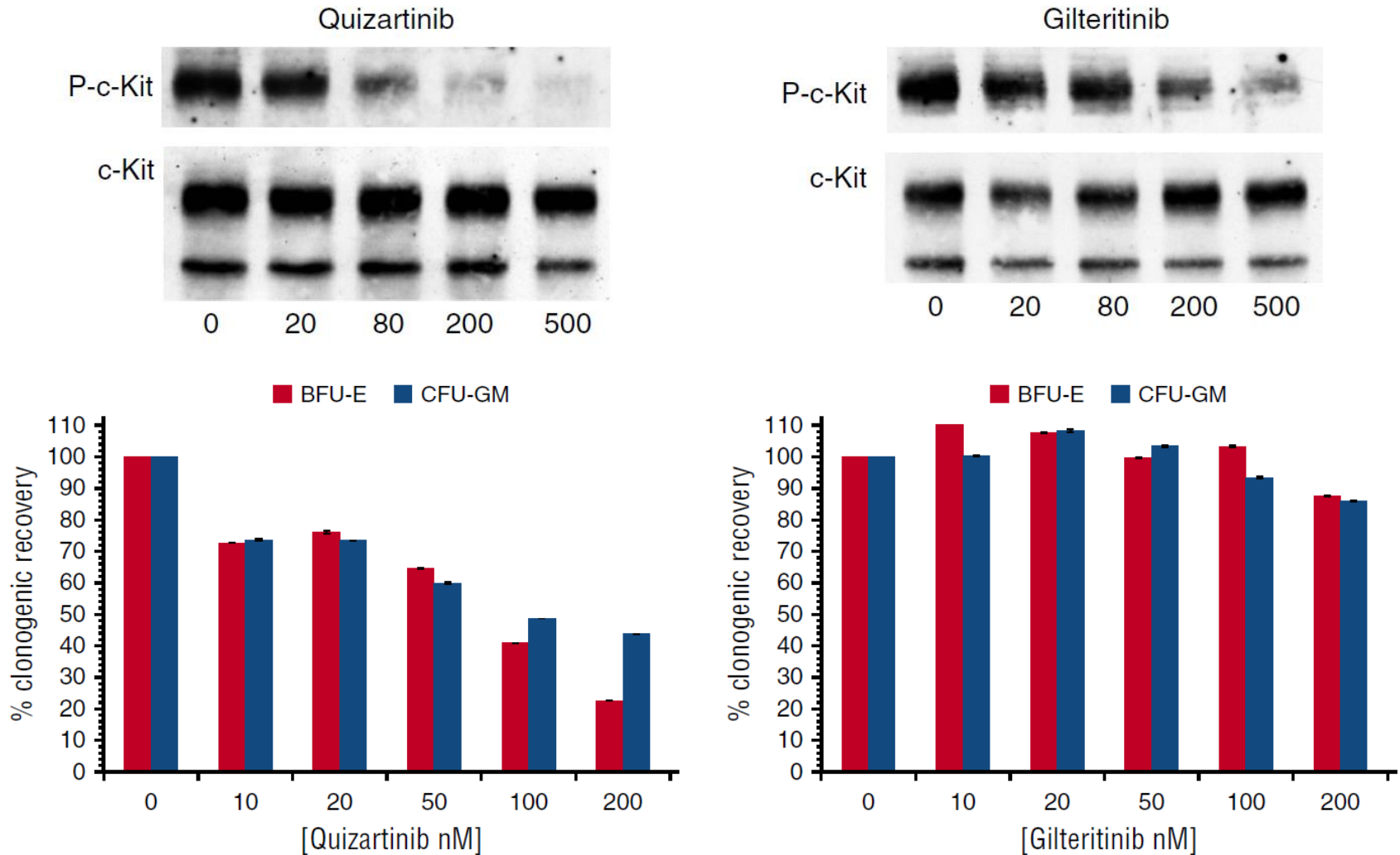
Activity against a primary blast sample with a resistance mutation:



Patient with a FLT3-ITD and FLT3-D835Y mutation

Gilteritinib

Less myelosuppressive than quizartinib:



First-in-human study of gilteritinib

- Phase 1/2
- Gilteritinib monotherapy
- Relapsed/refractory AML
- Expansion cohorts with FLT3-mutated AML

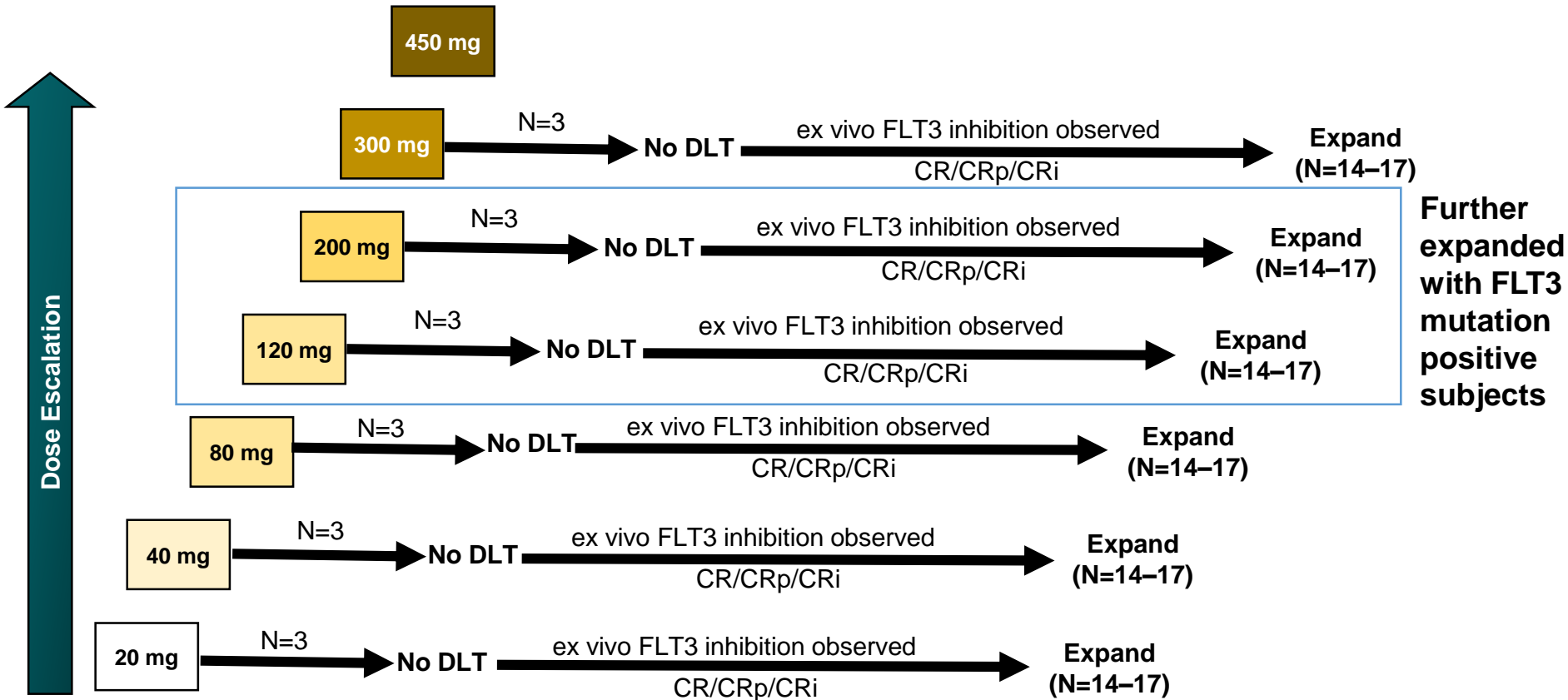
“Chrysalis”

NCT02014558

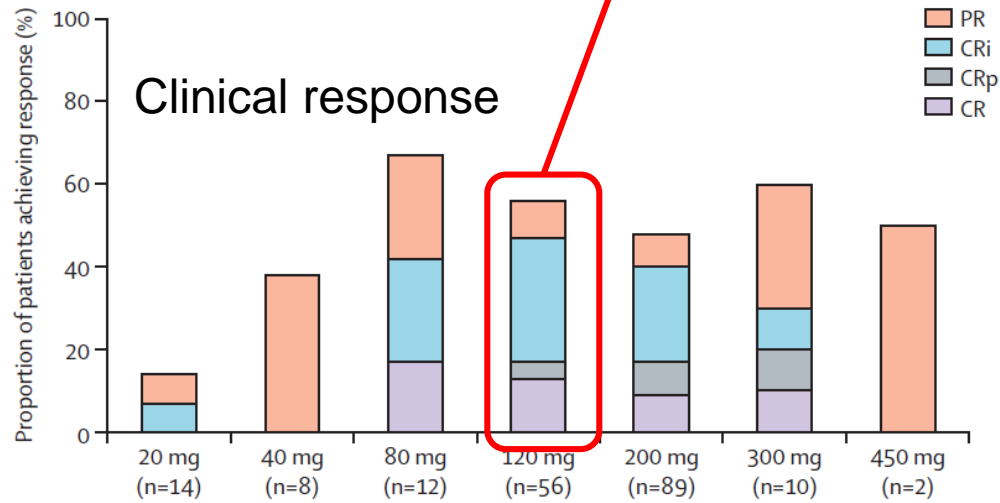
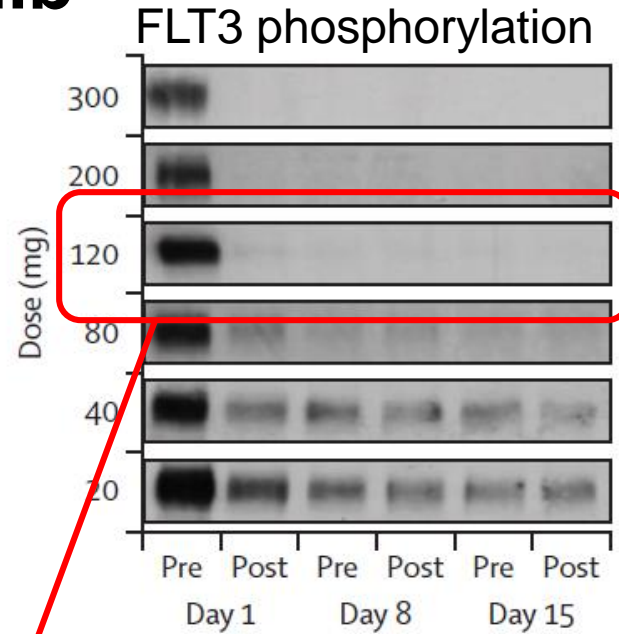
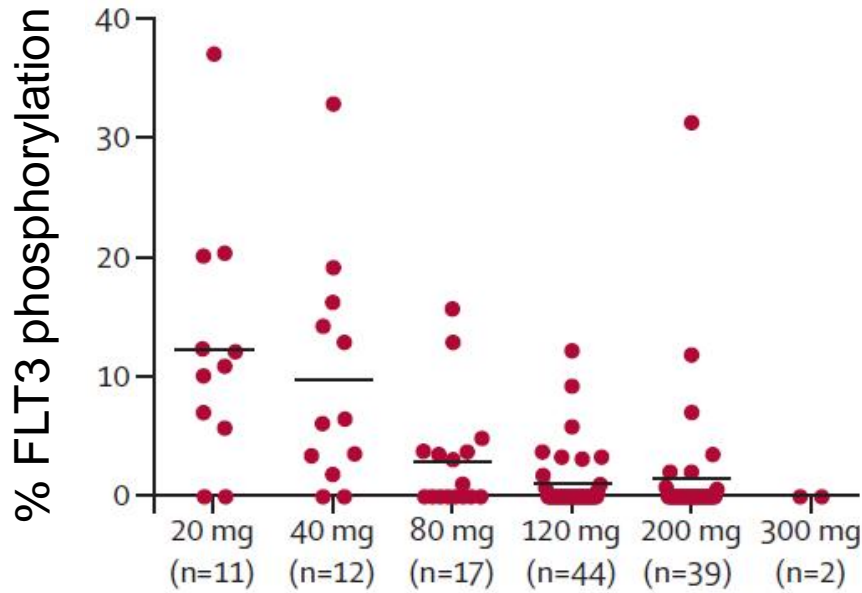


- October 2013-
November
2015
- 258 patients
accrued

CHRYSALIS Study Design



Gilteritinib





Gossamer

Newly-diagnosed:
Maintenance gilteritinib
versus placebo after
chemotherapy
NCT02927262



Morpho

Maintenance with
gilteritinib versus placebo
after allo transplant
NCT02997202

Chrysalis

NCT02014558



Admiral

Relapsed/refractory:
Gilteritinib versus
salvage chemo
NCT02421939



Lacewing

Older, newly-diagnosed:
Azacitidine +/- gilteritinib
NCT02752035

Press Release

Astellas Announces Approval in Japan for XOSPATA[®] 40 mg Tablets for the Treatment of FLT3mut+ Relapsed or Refractory AML

TOKYO, September 21, 2018 -Astellas Pharma Inc. (TSE: 4503, President and CEO: Kenji Yasukawa, Ph.D., “Astellas”) today announced that XOSPATA[®] Tablets 40 mg (generic name: gilteritinib), a FLT3 (FMS-like tyrosine kinase 3) inhibitor received manufacturing and marketing approval for the treatment of FLT3 mutation-positive relapsed or refractory acute myeloid leukemia (AML) in Japan.

This approval is based on the CR/CRh² rate results from the interim analysis of the multinational Phase 3 ADMIRAL study. In October 2015, gilteritinib was designated as one of the first products in Japan to be included in the SAKIGAKE³ designation system. A similar application for approval was filed in the United States in March, 2018 and is currently under review.

Press Release

Astellas Submits New Drug Applications for Approval of Gilteritinib for the Treatment of FLT3mut+ Relapsed or Refractory Acute Myeloid Leukemia

Apr 24, 2018

TOKYO, April 24, 2018 - Astellas Pharma Inc. (TSE: 4503, President and CEO: Kenji Yasukawa, Ph.D., “Astellas”) today announced that it submitted on March 23, 2018, a new drug application (NDA) for marketing approval of gilteritinib (generic name) in Japan for the treatment of adult patients with FLT3 mutation-positive (FLT3mut+) relapsed or refractory acute myeloid leukemia (AML). Astellas also submitted a NDA for approval of gilteritinib in the same patient population to the U.S. Food and Drug Administration (FDA) on March 29, 2018 (U.S. time) following the submission in Japan. The applications for marketing approval for gilteritinib are based on data from the ongoing pivotal Phase 3 ADMIRAL study investigating gilteritinib in adult patients with FLT3mut+ relapsed or refractory AML.

Newly-diagnosed
FLT3-mutated
AML patient

Induction



Consolidation



Maintenance



When during AML therapy should we use a FLT3 inhibitor?

Relapsed/refractory
FLT3-mutated AML
patient



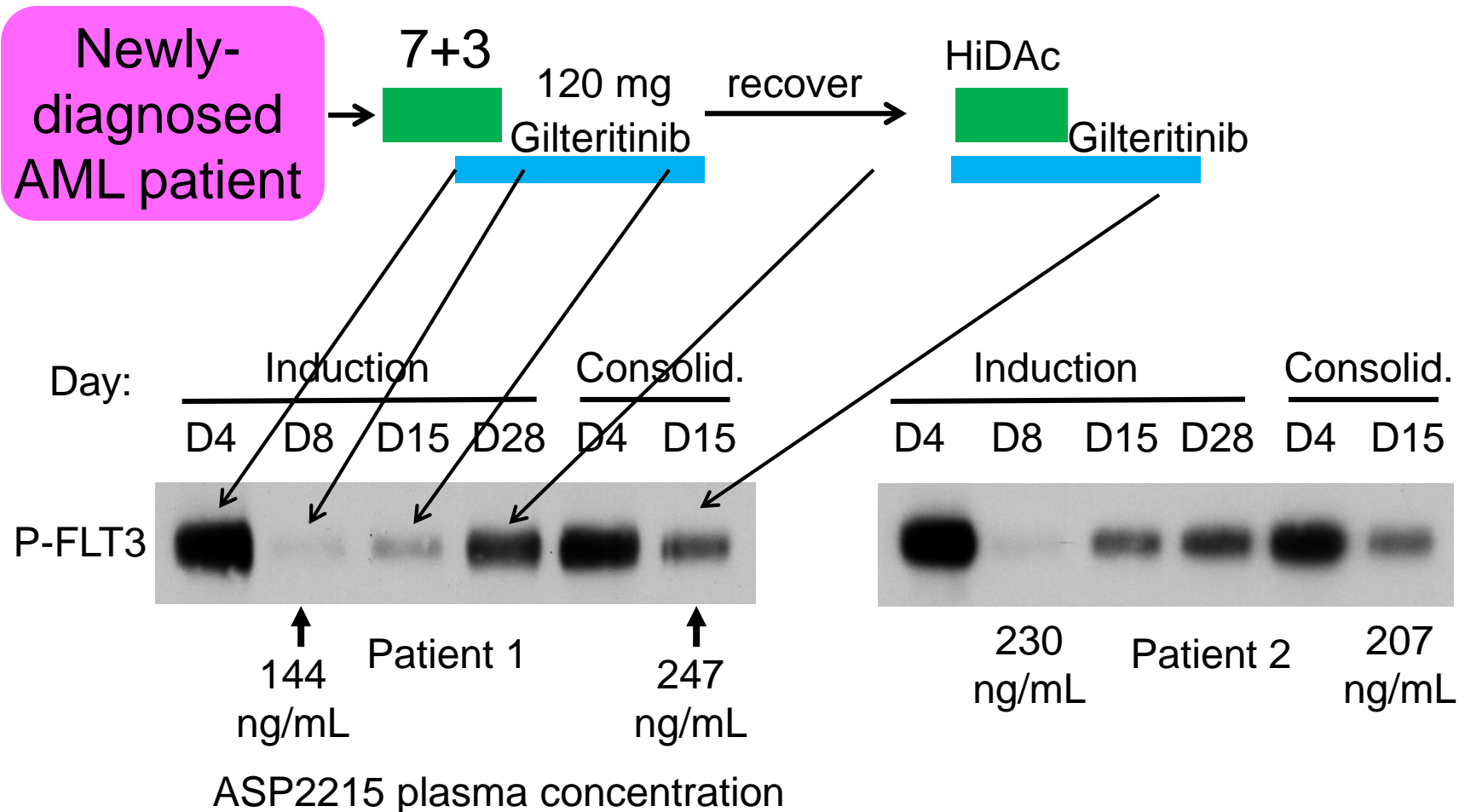
Salvage



Maintenance



A Study of ASP2215 in Combination With Induction and Consolidation Chemotherapy in Patients With Newly Diagnosed Acute Myeloid Leukemia (NCT02236013)



Inhibition of FLT3 by 120 mg/day Gilteritinib: Monotherapy versus post-chemotherapy

Monotherapy

Pre D8_{pre} D8_{post} D15

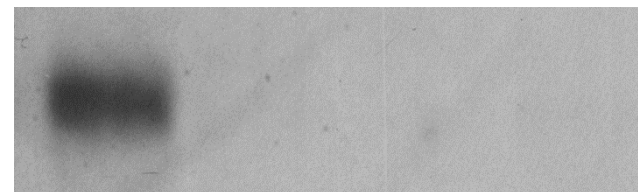
P-FLT3



P-FLT3



P-FLT3



P-FLT3



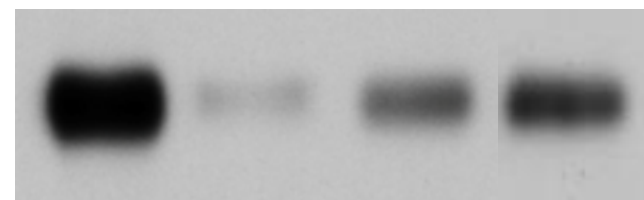
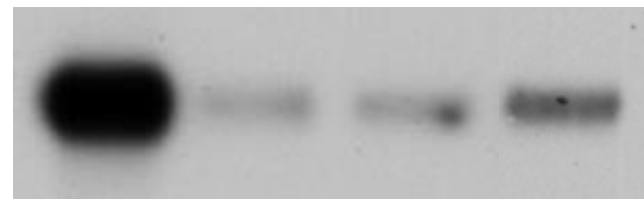
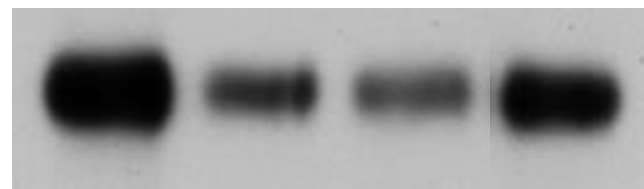
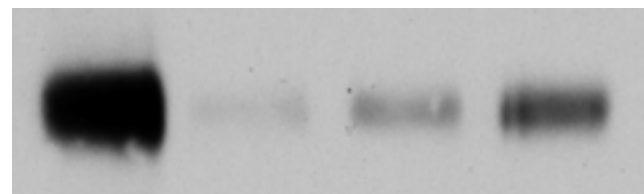
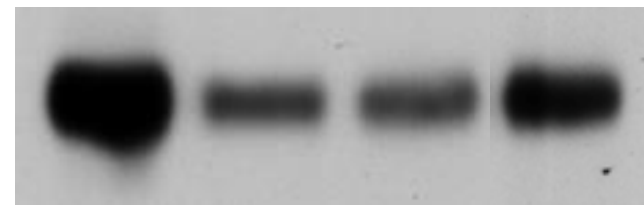
P-FLT3



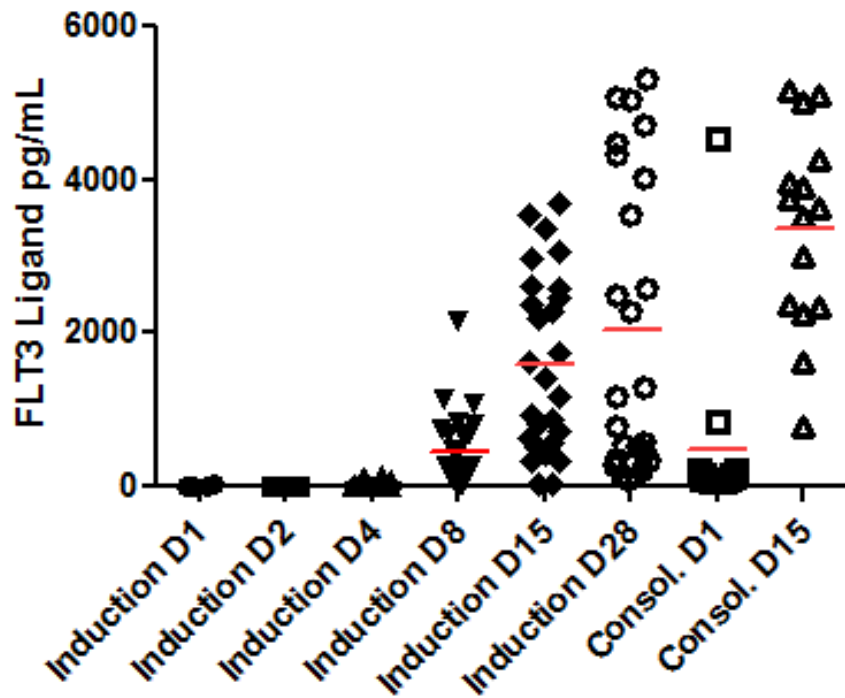
Induction

D4 D8 D15 D15

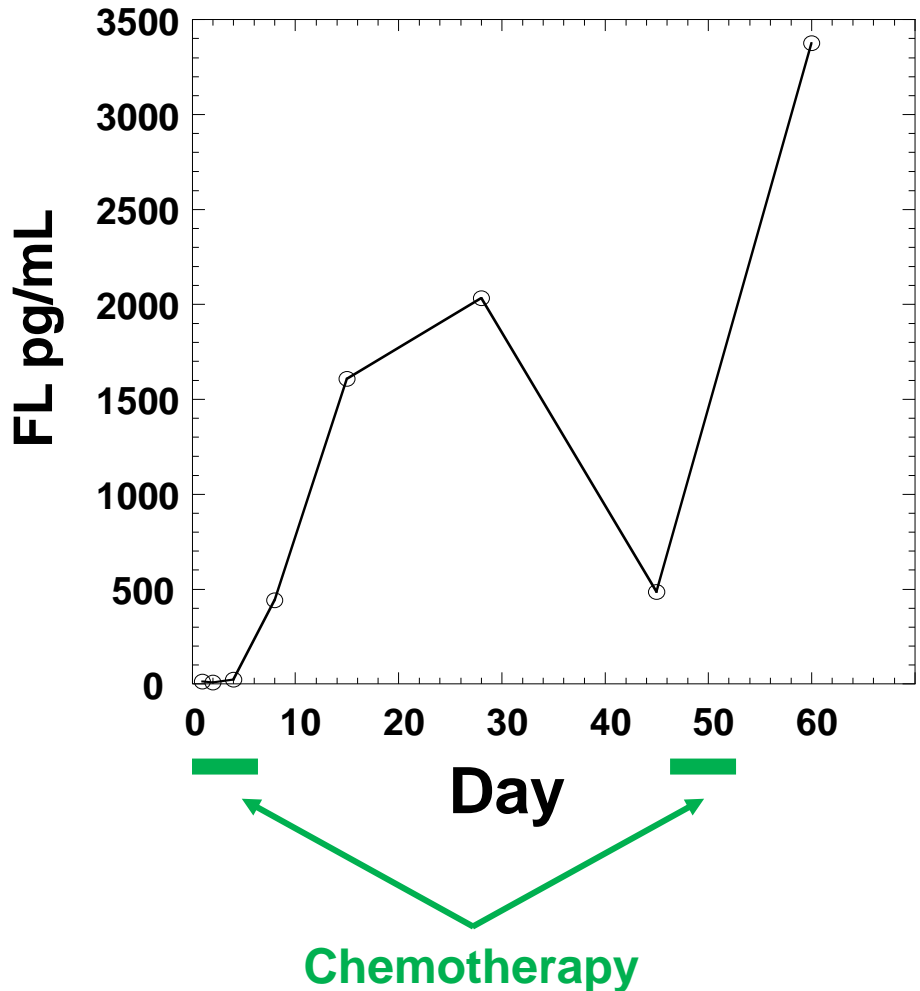
Consolid.



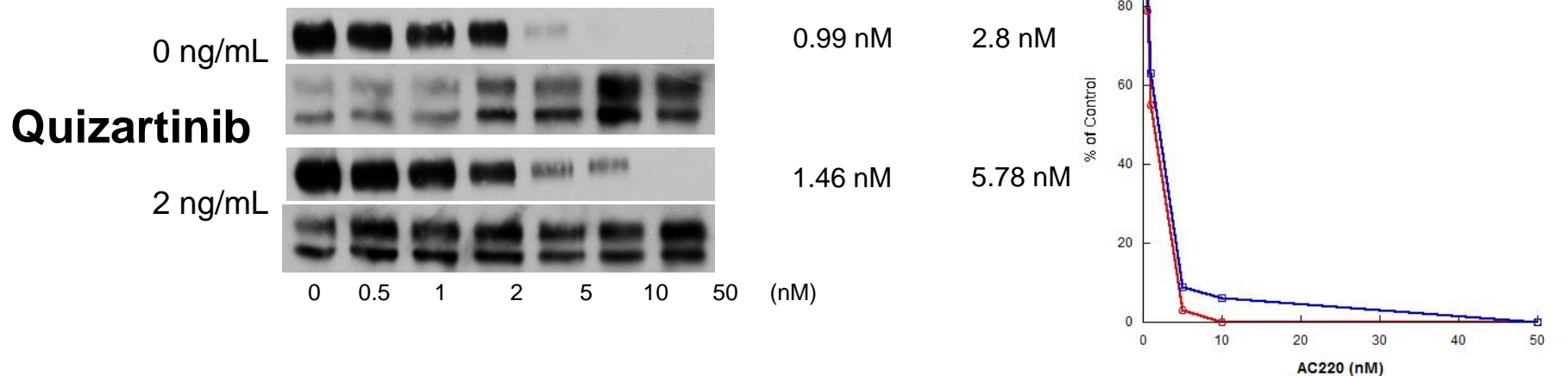
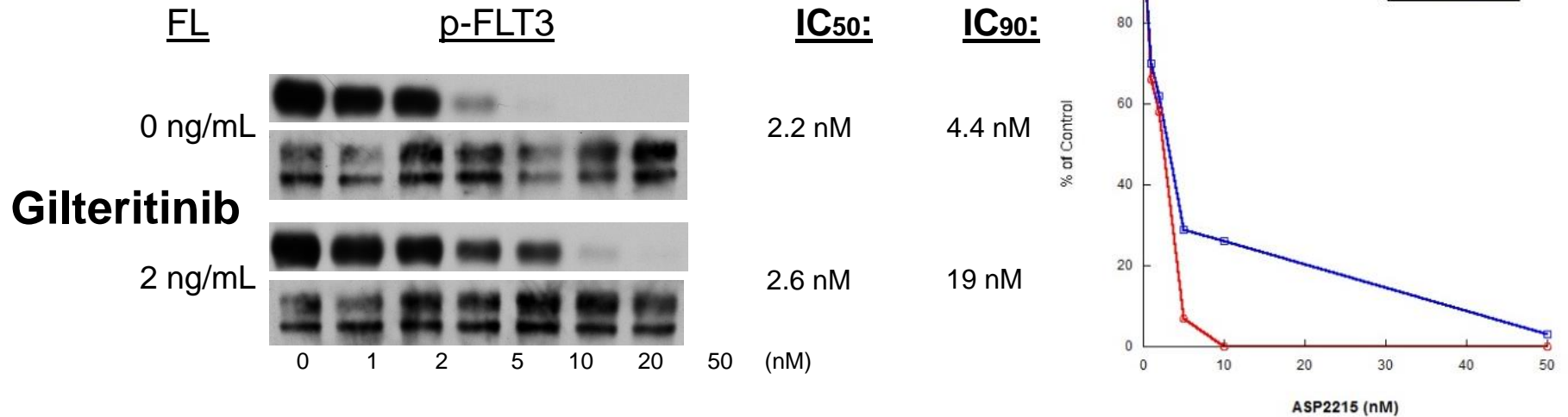
FLT3 ligand (FL) levels rise during chemotherapy-induced aplasia in 2215-CL-0103



Mean FL levels during induction and consolidation



FLT3 Ligand impedes the efficacy of FLT3 inhibitors



Gilteritinib

- Type 1 FLT3 inhibitor
- High response rate in relapsed/refractory FLT3-mutated AML
 - Approved in Japan September 21, 2018
 - Filed for approval in U.S.
- Strengths
 - Active against both ITD and TKD mutations
 - Very well tolerated
 - No c-Kit inhibition
 - Longer duration of response
- Weaknesses
 - Potency?
 - Expect dose increases from 120 mg/day to 160-200 mg/day



JOHNS HOPKINS

M E D I C I N E

**THE SIDNEY KIMMEL
COMPREHENSIVE CANCER
CENTER**

