Ponatinib, a pan-BCR-ABL inhibitor, potently inhibits key activating and drug-resistant KIT mutants found in GIST

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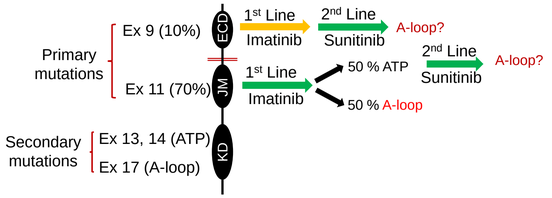
Ponatinib

- Ponatinib (Iclusig™) was designed as a highly potent inhibitor of native BCR-ABL as well as the T315I gatekeeper mutant that is resistant to all approved therapies for chronic myeloid leukemia (CML)
- Ponatinib recently (2012) received accelerated approved by the FDA for the treatment of adult patients with CML and Ph+ ALL who are resistant or intolerant to prior TKI therapy
- Ponatinib potently (IC_{50}<20 nM) inhibits the *in vitro* kinase activity of several mutationally activated kinases (e.g. KIT, RET, FLT3, FGFR and PDGFR)

GIST

- Approximately 80% of gastrointestinal stromal tumors (GIST) contain primary activating KIT mutations, the majority of which cluster in exon 11
- Imatinib & sunitinib are approved as 1st line and 2nd line treatments of GIST. However, patients commonly relapse due to the acquisition of secondary resistance mutations located in the ATP-binding pocket or the activation (A)-loop
- Since KIT A-loop mutations remain a therapeutic challenge, we explored the ability of ponatinib to inhibit a variety of KIT mutants

KIT mutation spectrum and treatment regimen



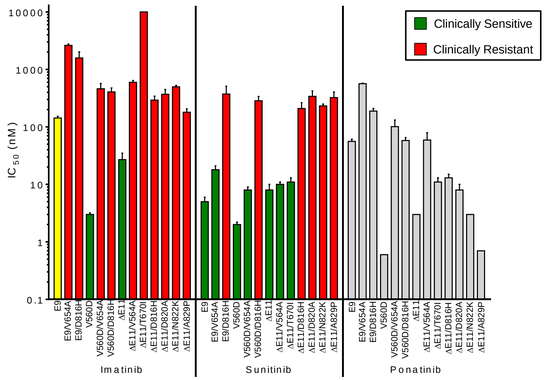
Generation of Ba/F3-KIT cell lines

Primary Mutations	Location	Secondary	Location	Designation
Exon 9 Ins (502-503 AY)	Ex9 (ECD)	-	-	E9
		V654A	Ex13 (ATP binding)	E9/V654A
		D816H	Ex 17 (A-loop)	E9/D816H
V560D	Ex11 (JM)	-	-	V560D
		V654A	Ex13 (ATP binding)	V560D/V654A
		D816H	Ex 17 (A-loop)	V560D/D816H
Del 557-558	Ex11 (JM)	-	-	ΔE11
		V654A	Ex13 (ATP binding)	ΔE11/V654A
		T670I	Ex14 (Gatekeeper)	ΔE11/T670I
		D816H	Ex 17 (A-loop)	ΔE11/D816H
		D820A	Ex 17 (A-loop)	ΔE11/D820A
		N822K	Ex 17 (A-loop)	ΔE11/N822K
		A829P	Ex 17 (A-loop)	ΔE11/A829P

Ponatinib inhibits a spectrum of KIT mutants

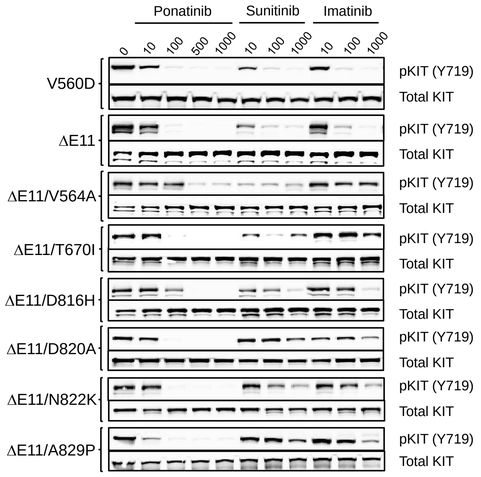
Ponatinib inhibits primary and secondary KIT mutants

Inhibition of KIT-driven cell viability

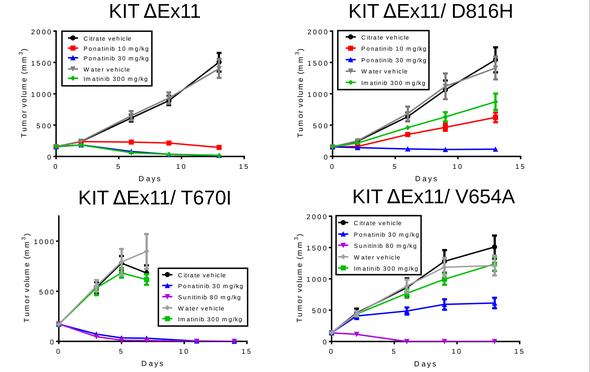


Ponatinib potently inhibits KIT activity

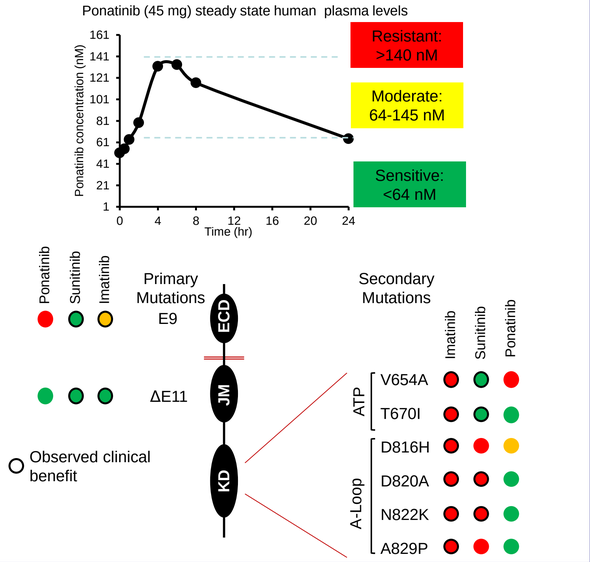
Inhibition of KIT phosphorylation



Ponatinib is efficacious in mutant KIT mouse models



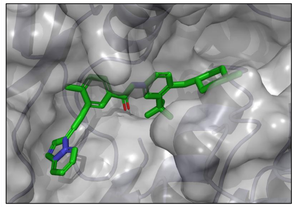
Ponatinib PK profile predicts its ability to inhibit KIT mutants



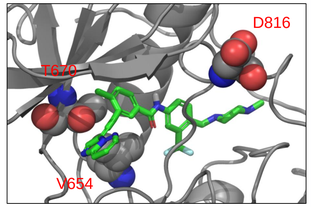
Structural

Ponatinib binding is uniquely tolerant of KIT mutations

Ponatinib/ KIT co-crystal structure



Ponatinib binds the inactive conformation deep in the ATP binding pocket



Ponatinib binding can tolerate key KIT resistance mutations

Summary

- Ponatinib potently inhibits a broad spectrum of GIST-relevant primary and secondary KIT mutants including a variety of A-loop mutations
- Ponatinib either regresses or significantly inhibits tumor growth in KIT ΔE11, KIT ΔE11/V654A , KIT ΔE11/T670I and KIT ΔE11/D816H mouse models
- The ponatinib/ KIT co-crystal structure demonstrates that ponatinib binds the inactive (DGF-out) conformation of KIT in an analogous manner to its binding to ABL
- Ponatinib possesses potent activity versus the major clinically relevant KIT mutants, inhibiting their activity with IC_{50}s that fall within clinically achievable plasma concentrations
- The above data support the evaluation of ponatinib in patients with GIST and a phase 2 study of ponatinib in drug resistant-GIST is being initiated

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