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

ARIAD Pharmaceuticals, Inc., Cambridge, MA, USA

A4CR 2013

Ponatinib

- Ponatinib (IC50**10-15 nM) 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 approval by the FDA for the treatment of adult patients with CML and Ph+ ALL who are resistant or intolerant to prior TKI therapy.
- Ponatinib potency (IC50=20 nM) inhibits the in vitro kinase activity of several mutually antagonistic 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.

PK profile predicts its ability to inhibit KIT mutants

Summary

- Ponatinib potently inhibits a broad spectrum of GIST-relevant primary and secondary KIT mutations including a variety of A-loop mutations.
- The ponatinib / Kit 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 IC50s 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.