INTRODUCTION/BACKGROUND

Figure 1. Western blot analyses of PDGFRA D842V-transduced Ba/F3 cells after treatment with imatinib, nilotinib, sorafenib, and sunitinib for 90 min.

Currently available TKIs like imatinib, sunitinib, sorafenib, and nilotinib have little to no in vitro activity against the D842V mutated PDGFRα RTK.

The most common PDGFRα mutation is the D842V mutation (encoded by exon 18). This gain-of-function mutations results in auto-phosphorylation and constitutive activation of PDGFRα kinase. As a result, PDGFRα autophosphorylated and phosphorylates downstream pathways that mediate cell proliferation, motility, survival, and angiogenesis.

In a total of 33 documented cases of patients with the PDGFRA D842V mutation in international clinical trials, none responded to treatment with imatinib or sunitinib. Similarly, other trials have also shown that patient with the D842V mutation do not respond to treatment with nilotinib or sorafenib.

Clinically, D842V mutation is associated with reduced responsiveness to standard of care TKIs. The median progression-free survival of patients harboring PDGFRA D842V mutation is much shorter than the median survival of imatinib-sensitive GIST patients which is greater than 3 years.

METHOD

Crenolanib is an orally administered, benzimidazole compound that is a highly selective and potent inhibitor of both PDGF receptors (PDGFRα and PDGFRβ) and has shown good oral bioavailability, a favorable toxicity profile, and achievable serum concentrations at high 2000 nM.

Crenolanib (CP-868,596), a Highly Potent PDGFR Inhibitor, Inhibits Phosphorylation of the Imatinib-Resistant PDGFRα

Drug: Crenolanib is an orally bioavailable, highly potent and selective PDGFR TKI. Crenolanib is a benzimidazole compound that has IC

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0.05 nM for PDGFRα and PDGFRβ, respectively. Phase I trials of crenolanib have shown good oral bioavailability, a favorable toxicity profile, and achievable serum concentrations at high 2000 nM.

Methods: Western blot analyses were performed by transfection of Chinese Hamster ovary cells. The transfected cells were treated with various concentrations of standards before preparation of protein extracts. Protein extracts were prepared after treatment with PDGFRα phospho-specific antibodies by immunoprecipitation, followed by sequential immunoblotting for phospho-PDGFRA (using anti-phosphotyrosine antibody) or total PDGFRA (anti-PDGFRA monoclonal antibody).

RESULTS:

An international survey of GIST referral centers, documented that none of the nineteen assessable patients with the PDGFRA D842V mutation had an objective response to treatment with imatinib. In the B222 phase II trial, none of the three patients with PDGFRA D842V mutation responded. In the EORTC phase III trial, 4 patients with known PDGFRA D842V mutation had no response.

In the US phase III study, none of the 4 patients with PDGFRA D842V mutation responded to imatinib treatment.

In the D842V phase I trial, there were no patients with PDGFRA D842V mutation who had a partial response (PR) or complete response (CR) within 90 days after treatment.

Crenolanib is an orally administered, benzimidazole compound that has a favorable toxicity profile, and achievable serum concentrations at high 2000 nM.

Crenolanib (CP-868,596) is a unique TKI that blocks phosphorylation of D842V mutant PDGFRα at clinically achievable concentrations.

Crenolanib may provide the first effective systemic therapy for GIST patients with the PDGFRA D842V mutation as this activating mutation is clinically resistant to imatinib, sunitinib, and other commercially available tyrosine kinase inhibitors.

CONCLUSION/DISCUSSION

Crenolanib is a benzimidazole compound that is a highly selective and potent inhibitor of both PDGF receptors (PDGFRα and PDGFRβ) and has shown good oral bioavailability, a favorable toxicity profile, and achievable serum concentrations at high 2000 nM.

Inhibition of phosphorylation of exon 18, PDGFRα mutation, D842V

Figure 2. Flow cytometric analysis of PDGFRα D842V-transduced Ba/F3 cells after treatment with imatinib, sorafenib, sunitinib, and nilotinib. None of the tested drugs had any effect on the phosphorylation of the mutant PDGFRα. (Adapted from Diksic et al. 2008; and Heinrich et al. 2008).