Abstract

Phase I trial of panobinostat (P) and imatinib (IM) in patients with treatment-refractory gastrointestinal stromal tumors (GIST)

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Background

Gastrointestinal stromal tumors (GIST) is the most common mesenchymal tumor of the GI tract
- Long lasting responses observed in >80% of pts
- Progression in the majority of patients eventually
- HDAC inhibitors inhibit imatinib-resistant bcr-abl
- Long lasting responses with imatinib in >80% of pts
- Primary: Maximum tolerated dose and DLT of Panobinostat (LBH589) is a pan-deacetylase-inhibitor
- Background: Induce apoptosis in BCR/ABL positive leukemia cell lines
- Panobinostat (LBH589) is a pan-deacetylase-inhibitor
- Imidazole of H4K5 and H4K8 (imatinib) and H3K9 (imatinib) increases in GIST patients with lesions

Methods I

- IM was administered at a dose of 400mg qd
- Following a 7-day run-in phase, escalating doses of P were added
- Start dose of 20mg/patient q28 in week 1-3
- Doses were increased by 10mg if no DLT emerged within 4 weeks of the run-in phase

Methods II

- PK and biomarker assessments of IM, N-desmethyl-IM, and Panobinostat using validated RP-HPLC method
- Determination of MTD / DLTs

Trial design

- Patient characteristics
  - N=12 patients, withdrawn consent: 1
  - ECOG 0: 3 patients
  - ECOG 1: 3 patients
  - ECOG 2: 3 patients
  - ECOG 3: 3 patients

- Methods I
  - Dose-level -I: 10mg
  - Wk 1-3, q28
  - Target inhibition seen at MTD
  - Moderate tolerability of panobinostat and imatinib
  - Summary: Imatinib + Panobinostat as treatment for GIST patients

- Methods II
  - PK assessments
    - PK: panobinostat plasma concentrations at 30mg IM in GIST models in vitro and in vivo
    - Imatinib trough levels: 1085ng/ml (without panobinostat)
    - Imatinib terminal half-life: 20.5h (with panobinostat)
    - Imatinib Cmax: 2068ng/ml (without panobinostat)
  - Determination of MTD / DLTs
    - No dose-limiting toxicities emerged within 4 weeks of the core study
    - Most common AE`s: thrombocytopenia, anemia, fatigue
    - 2 dose-limiting toxicities at dose level 2 (30mg):
      - Thrombocytopenia: 1/4
      - Dose level 2 was declared MTD
    - 3 more DLTs?
      - 1
      - 1
      - 0

- Endpoints
  - Primary: basal tied dose and DLT of combined dosing of IM and Panobinostat
  - Secondary: Safety and tolerability

- Determination of MTD / DLTs
  - 2 dose-limiting toxicities at dose level 2 (30mg): Thrombocytopenia: 1/4
    - Dose level 2 was declared MTD
  - Must common: 80% toxicity: thrombocytopenia, neutropenia, nausea, mostly in week 4
  - Most common AE`s: headache, asthenia, fatigue, nausea, vomiting, myalgia, weight loss
  - 4 treatment interruptions in 2 patients at 20mg, 3 interruptions at 30mg

Response evaluation (PET)

- 12 patients evaluable for PET after 3 weeks of combined treatment
- No DLT
- Longest treatment duration: 17 weeks (median); 14 weeks (mean)
- No objective radiological remission
- Stable disease in single lesions

Immunoblots: acetylated histone H3 in PBMNCs of patients at baseline and after treatment (P)

Histone H3 acetylation in PBMNCs

Summary

- Most common AE`s: thrombocytopenia and imatinib
- No objective radiological remission
- Stable disease in single lesions
- Target inhibition seen at MTD
- Limited objective activity in heavily pretreated GIST
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