Abstract
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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) most common mesenchymal tumor of GI tract
- Long lasting responses withimatinib in >80% of pts
- Progression in the majority of patients eventually
- HDAC inhibitors inhibit imatinib-resistant bcr-abl and induce apoptosis in BCR/ABL positive leukemia cell lines

- Panobinostat (LBH589) is a pan-deacetylase-inhibitor
- Inhibition of KIT via inhibition of HSP90 and transcriptional repression of KIT in GIST*
- Strong inhibitory effects in KIT-positive but not KIT-negative imatinib-resistant cell lines
- preclinical activity with additive effects in combination with IM in GIST models in vitro and in vivo

Endpoints

- Primary: Maximum tolerated dose and DLT of escalating doses of LBH589 in combination with IM
- Secondary: Safety and tolerability
  single- and repeated dose PK assessment
  preliminary assessment of activity (PET)
  time to response, time to progression

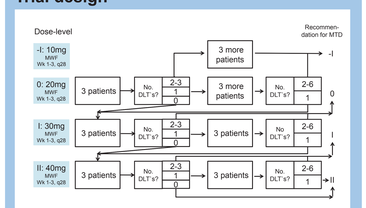
Methods I

- IM was administered at a dose of 400mg qd
- Following a 7 day run-in phase, escalating doses of P were added
- starting dose for P was 20 mg given as a three-times-per-week (MWF schedule) oral dose for 3 out of 4 weeks
- Doses were increased by 10 mg if no dose limiting toxicities emerged within 4 weeks of the core study

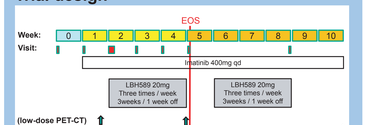
Methods II

- PK and biomarker assessments of IM, N-desmethyl-IM, and Panobinostat using validated RP-HPLC method
- Acetylation of histone A3 from PBMNC as pharmacodynamic marker for P activity
- Metabolic response using PET (EORTC-PET study criteria) on day 7 of IM run-in and after 3 weeks of combined treatment with IM and P

Trial design



Trial design



Cohort (3-6pts/cohort)	Imatinib Day 1 – 28 of each cycle	LBH589 Day 8 – 28 of each cycle
1	400 mg qd po	20 mg given three times a week po
2	400 mg qd po	30 mg given three times a week po
3	400 mg qd po	40 mg given three times a week po

Patient characteristics

- N=12 patients, withdrawn consent: 1
- 8 male, 4 female
- Median age: 56 years
- Median pretreatment: 5 (4-11); IM and SU pretreatment in all patients; nilotinib (n=6), sorafenib (n=6)
- Median ECOG: 0 (0-1)

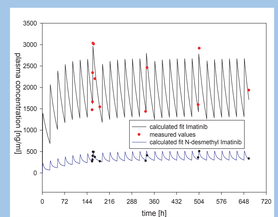
Determination of MTD / DLTs

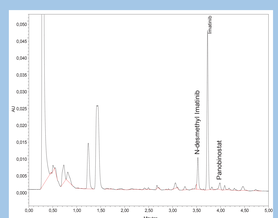
- 2 dose-limiting toxicities at dose level 2 (30mg):
  Thrombocytopenia IV
- Dose level 1 was declared MTD

- Most common III/IV toxicities: thrombocytopenia, neutropenia, nausea, mostly in week 4
- Most common AE`s: thrombocytopenia, anemia, fatigue nausea, emesis, diarrhoea, muscle cramps, weight loss
- 4 treatment-interruptions in 2pts at 20mg, 3 interr. at 30mg

PK assessments

- PK: peak concentration LBH589: 14.8 +/- 9.5 ng/ml (20 mg): equivalent: 42nM
- Imatinib Cmax: 2068ng/ml (without panobinostat)
  (p=0.185) 2564ng/ml (with panobinostat)
- Imatinib terminal half-life: 20.5h (with panobinostat)
- Imatinib trough levels: 1085ng/ml (without panobinostat)
  (p=0.125) 1290ng/ml (with panobinostat)



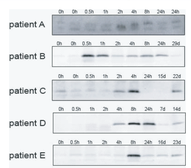


Plasma concentrations of Imatinib, desmethyl-Imatinib and panobinostat were determined in 12 patients for 14 courses of imatinib/panobinostat. A typical chromatogram of a plasma sample is shown

Adverse Events (regardless of causality)

Dose-level	Grade 1	n=	Grade 2	n=	Grade 3	n=	Grade 4	n=
1 (20mg) N= 7	Muscular cramps	3	Anemia	5	Thrombocytopenia	1	Thrombocytopenia	1
	Abdominal pain	3	Fatigue	3	Lymphocytopenia	1	Neutropenia	1
	Vertigo	3	Nausea	2	DVT	1		
	Thrombocytopenia	2	Diarrhea	2	Hypophosphatemia	1		
	Diarrhea	2	Performance status	2	Renal failure	1		
	Nausea	2	Creatinin	2				
	Emesis	2	Weight loss	1				
	Fatigue	2	Bilirubin	1				
	Headache	2	Emesis	1				
	Weight loss	2	Bigeminus	1				
	Xerostomia	2	Cardiac Ischaemia	1				
	Edema	2						
	Mucositis	2						
	Heartburn	1						
	Dysphonia	1						
	Ageusia	1						
	Obstipation	1						
	Leucopenia	1						
	Creatinin	1						
	Dyspnoe	1						
2 (30mg) N=4	Edema	2	Emesis	3	Thrombocytopenia	3	Thrombocytopenia	2
	Epistaxis	2	Anemia	2	Nausea	2	Hypertension	1
	Skin	2	Fatigue	2	Hypothyroidism	2		
	Abdominal pain	1	Creatinin	2	Ventricular arrhythmia	1		
	Dry eyes	1	Weight loss	2		1		
	Hypokalemia	1	Nausea	1		1		
	Fatigue	1	Diarrhea	1		1		
	Creatinin	1	Seizure	1		1		
	Constipation	1	Neutropenia	1		1		
	Diarrhea	1	Muscular cramps	1		1		
	Emesis	1	Lymphocytopenia	1		1		
	Vertigo	1	Leucocytosis	1		1		
	ALT	1	Infection	1		1		
			Headache	1		1		
			Hemorrhage	1		1		

Histone H3 acetylation in PBMNCs

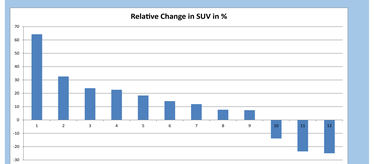


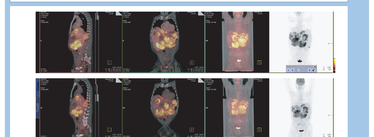
All patients treated with 20mg panobinostat

Immunoblots: acetylated histone H3 in PBMNCs of patients at baseline and after different time points after initiation of panobinostat treatment

Response evaluation (PET)

- 12 patients evaluable for PET after 3 weeks of combination
- 1 had mPR, 8 had mSD and 3 had mPD
- Longest treatment duration: 17 weeks (median: 6wks)
- No objective radiological remission
- Subtle shrinkage in single lesions





Partial metabolic remission according to EORTC-PET-criteria
upper panel: baseline; lower panel: post 3 weeks panobinostat;

Summary

- Moderate tolerability of panobinostat and imatinib combination at 20mg MWF 3weeks on/1wk off schedule
- Target inhibition seen at MTD
- Limited clinical activity in heavily pretreated GIST

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