Dasatinib first-line treatment in GIST
Multicenter phase II trial of the SAKK (SAKK 56/07)

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SAKK
Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung
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1 GIST - Background

- Tyrosine kinase inhibitors standard of care in advanced GIST
- 1st-line Imatinib:
  - mPFS: 18-23mo mOS: 45-55mo
  - CR+PR: KIT ex11= 64% WT=38% All=45%
- 2nd-line Sunitinib:
  - mPFS: 6mo mOS: 17mo
  - PR+SD: 65%
- Can we stop progression?

2nd-Gen TKI, HSPI, pathway inhibitors, antibodies, combinations etc.

Demetri et al. JCO 2006, Blanke et al JCO 2008; Heinrich et al. JCO 2008; MetaGist JCO 2010

2 Dasatinib - Background

- oral 2nd-Gen multi-target kinase inhibitor
- inhibits BCR-ABL, SRC, PDGFR, KIT
- inhibits Imatinib-resistant PDGFRA D842V mutants[1]
- Dasatinib in GIST after Imatinib failure (SARC 009 trial)[2]
  - N= 47 (80% also sunitinib failure)
  - PR= 22%
  - PFS= 2months (PDGFRA subgroup PFS=10 months; n=3)
  - OS= 19months

1) Dewaele et al. Clin Cancer Res 2008
2) Trent et al ASCO 2011

3 Early FDG-PET* in GIST - Background

- allows early response prediction [3]
- predicts later CT responses[3,4]
- PET response precedes CT by 2-6 months[3,5]
- PET response predicts PFS[3,6] and OS[6]
- Recommendations for PET use exist (EORTC[7]; NCI[8])

(* 18-F-FluoroDeoxyGlucose -Positron Emission Tomography)

3) Stroobants et al. Eur J Cancer 2003; 4) Antoch et al. J Nucl Med 2004; 5) Gobbstein et al Oncology 2005;
6) Goerres et al. Eur J Nucl Med Mol Imaging 2005; 7) Young et al. EJC 1999; 8) Shankar et al J Nucl Med 2006
Van den Abbeele et al. Eur J Cancer 2002; Gayed et al. J Nucl Med 2004; Choi et al. AJR 2004

4 Objectives

- Primary objective
  - Efficacy of dasatinib assessed by fusion PET/CT-scan
- Secondary objective(s)
  - Efficacy and safety of dasatinib in GIST
  - Correlation of dasatinib efficacy with mutational status

5 Dasatinib Trial - Overview

- Starting dose is 70 mg BID (one cycle = 4weeks)
  - Dose level -1 50mg BID
  - Dose level -2 100mg QD
- Continue until progression, unacceptable toxicity and up to 2years
- After 2 years, decision of the physician (continue or switch)
- Elective Surgery is allowed after 6 cycles if SD or better
  - Adjuvant Treatment to be considered
- Interim analysis (response + toxicity) after n=17pts
  If > 9 / 17 pts respond @ PET 4weeks → proceed
- «Promising» Response Rate (CR+PR) = 70% or better

6 Main Inclusion Criteria

- Histologically proven diagnosis of GIST
- Positive baseline PET/CT with [18F]-fluorodeoxyglucose
- Measurable disease by conventional scans (CT or MRI)
- WHO performance status 0-2
- Age ≥ 18 years
- Adequate hematological and organ function values
- Written informed consent before registration.

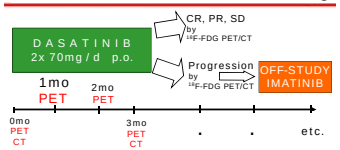
7 Main Exclusion Criteria

- Previous therapy against GIST with TKI
- Previous malignancy within 5 years
- Clinically significant cardiovascular disease
- Concurrent medical condition, incl. pleural or pericardial effusion, coagulation or platelet function disorder, ongoing significant gastro-intestinal bleeding, nausea, vomiting or malabsorption syndrome
- Avoid / not permitted:
  - Antacids – PPI, H-2 blockers
  - IV bisphosphonates
  - CYP 3A4 inducers/inhibitors
  - Medications that prolong QT

8 Central Review

- Pathology
  - Central Pathology Review and Mutational Analysis
- PET
  - Center Qualification before Trial Participation
  - Monitoring of Center Qualification/Calibration during Trial
  - Central PET Review within 3 working days

9 Dasatinib 1st-Line in GIST - Trial Design



Elective surgery allowed after month 6

10 Trial Population

- Trial open from 17.01.2008 – 30.11.2011 (early closure, slow accrual)
- 47 pts included (of 52 pts initially planned)
- 4 pts not eligible
  (n=1 not GIST; n=2 baseline PET negative on central review; n=1 no baseline CT)
- 43 pts treated in 13 centres in 4 European countries
- Total 320 cycles administered (median 5, min 1, max 25)
- Median Follow-Up 12.4 months

11 Patient Characteristics

Parameter	Variable	N	%
Gender	Female	19	44
	Male	24	56
Performance Status	0	30	70
	1	13	30
Mutation at Diagnosis	Kit Exon 11	20	46.5
	Kit Exon 9	1	2
	Wild-Type	7	16
	N.A.	15	35
Localisation at Diagnosis	Gastric	11	26
	Small Intestine	14	33
	N.A.	18	42
Disease Extension at trial start	Localized	4	9
	Metastatic	33	77
	N.A.	6	14

12 Safety / Toxicity

- Treatment was interrupted in 28 patients (65%)
- Dosage was reduced in 9 patients (21%)
- Treatment was stopped due to toxicity in 4 patients (9%)
- 38% of pts experienced a G3, 5% a G4 toxicity
- 3 deaths occurred
  - Clinical deterioration
  - GIST tumor bleeding
  - Cardiac arrest (hospitalised due to an intestinal occlusion (CT confirmed non-progression) and resolved prior death; no autopsy)

13 Adverse Events per Patient

Adverse Event / Grade	1	2	3	4
ALL	**251**	**115**	**30**	**2**
Pulmonary	16	23	4	1
Cough	5	2	0	0
Dyspnea	6	10	1	1
Pleural Effusion	2	11	2	0
Capillary Leak	0	0	1	0
Voice Changes	3	0	0	0
Gastrointestinal	51	25	13	0
Anorexia	8	2	1	0
Dehydration	0	0	1	0
Diarrhea	10	10	5	0
Ileus	0	0	3	0
Nausea	6	8	2	0
Vomiting	6	3	1	0
Fatigue	19	12	1	0
Thrombosis / Embolism (Vascular access)	0	0	0	1

(Shown are all, all G3/4, and frequent GI/Pulm adverse events)

14 PET Response (Primary Endpoint)

- 18-F-fluorodeoxyglucose-PET at 4 weeks compared to baseline
- EORTC criterita (Young et al EJC 1999)
-

	CR	PR	SD	PD	N.A.
All	14 (33%)	17 (40%)	7 (16%)	3 (7%)	2 (5%)
Kit Exon 11	6 (30%)	10 (50%)	2 (10%)	0	2 (10%)
Wild-Type	3 (43%)	1 (14%)	2 (29%)	1 (14%)	0

- **PET Response Rates (CR+PR) (95% CI)**
  - Overall 72% (56 – 85%)
  - KIT Exon 11 80% (56 – 94%)
  - Wild-Type 57% (18 – 90%)

15 Survival (Secondary Endpoint)

- Median Follow-Up 12.4 months
  - On trial 15 pts (35%)
  - Off-trial 28 pts (65%)

Progression	Elective Surgery	Toxicity	Death	Decision Local PI	2 years completed
13	**6**	**4**	**3**	**1**	**1**

- Median PFS 11.1 months
- Median OS not reached

16 Summary

- This multicenter Phase II trial of the Swiss Group for Clinical Cancer Research SAKK investigated first-line Dasatinib, starting dose 70mg BID, in TKI-naïve patients with GIST
- FDG-PET response at 4 weeks compared to baseline was the primary endpoint
- PET qualification per center and regular calibration were mandatory
- PET was centrally reviewed within 3 working days
- 43 eligible patients were evaluated for safety and the primary endpoint
- 38% of pts experienced Grade 3 and 5% Grade 4 toxicity.
- Responses (CR+PR) were 72% overall, 80% in pts with a KIT Exon 11 mutation, and 57% if Wild-Type GIST.
- Median PFS is 11.1 months, overall survival not reached yet.
- Dasatinib shows promising efficacy in this small group of patients.

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