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Original article

Midostaurin in indolent systemic mastocytosis patients: an open-label phase 2 trial.

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Conflict of Interest

The authors declare no relevant conflicts of interest.

Clinical implications

Midostaurin appeared both effective in reducing refractory mediator symptoms and improving quality of life in patients with indolent systemic mastocytosis; cessation of treatment resulted in a rapid relapse.

Capsule summary

This is the first report on a trial using a Kit D816V targeting drug in indolent systemic mastocytosis. The results indicate midostaurin to be effective in reducing symptom severity and improving quality of life.

Key words: midostaurin, ISM, systemic mastocytosis, Phase II trial, MQLQ, MSAF, PKC412

44 **Abbreviations used**

45	CTC	Common Terminology Criteria for adverse events
46	ISM	indolent systemic mastocytosis
47	IQR	interquartile range
48	MQLQ	mastocytosis quality-of-life questionnaire
49	MSAF	mastocytosis symptom assessment form
50	SCORMA	SCORing MAstocytosis Index
51	SM	systemic mastocytosis
52	SD	standard deviation
53	UP	urticaria pigmentosa

To the editor

Indolent systemic mastocytosis (ISM) is the most prevalent form of mastocytosis and characterized by mast cell infiltration of - in particular - the bone marrow, gastrointestinal tract and skin, but – by definition - no resulting organ dysfunction, setting it apart from advanced SM. (1) For most ISM patients the mast cell burden will remain stable throughout a near-normal life expectancy. (2) Over 70% of ISM patients experience an impaired quality-of-life due to refractory symptoms caused by mast cell mediator release, illustrating the large unmet therapeutic need. (3) Midostaurin is a multi-kinase inhibitor capable of inhibiting the kinase activity of both wild-type and D816V mutated *KIT*. (4) Studies in advanced SM demonstrated a rapid response of mast cell mediator symptoms, suggesting a potential use in ISM patients. (5). We therefore conducted an open-label, nonrandomized, single-centre, phase 2 trial to study the efficacy and safety of midostaurin in 20 ISM patients with severe mast cell activation symptoms refractory to anti-histamine medication.

Patients ≥ 18 years were eligible if a diagnosis of *KIT* D816V+ indolent or smoldering systemic mastocytosis according to the World Health Organization criteria was present. (1) Excluded were: pregnant or nursing women, patients diagnosed with advanced SM, patients diagnosed with another malignancy unless they were disease-free for at least 5 years or had a diagnosis of non-melanoma skin cancer. Finally, patients with serious comorbidity expected to

interfere with therapy and follow-up compliance were excluded. This study, registered with Clinical Trials.gov, NCT01920204, was approved by the University Medical Center Groningen Institutional Review Board; all patients gave written informed consent before study entry. All mediator symptom suppressing drugs that patients were taking prior to the study were continued. Midostaurin was supplied by Novartis (Basel, Switzerland) as capsules of 25 mg, and had to be taken orally at the dose of 100 mg twice a day. Patients received midostaurin continuously from day 1. All patients took premedication with anti-emetic 5-HT₃ receptor antagonists two hours before midostaurin intake, which was adjusted after two weeks according to symptoms of nausea and vomiting.

Starting June 2012, 248 ISM and SSM patients were screened on symptom severity using the mastocytosis symptom assessment form (MSAF), available for download online. (3) A detailed patient accrual and trial profile is given in Figure 1 in this article's Online Repository. Between September 2013 and August 2015, twenty ISM patients were included. The mean age of included patients was 49 ± 12 years with an almost even male-female proportion (45-55%) and all but five patients exhibited UP (75%). There were an insufficient number of patients included with episodic vascular collapse to study an effect on anaphylaxis-like symptoms. During the trial (before week 12) three patients dropped out due to nausea-related adverse events.

The primary objective of the study was the symptomatic response rate according to MSAF. After 12 weeks of midostaurin treatment patients showed a statistical

significant median 35% ($P < 0.01$; IQR: 16%-56%) reduction in symptom severity, resulting in an improvement in symptoms for 75% ($n=15$) of the patients.

Symptom severity scores further improved to an average 38% reduction at week 24 (Figure 1); if the analysis was limited to only the initial highest scoring symptoms, this reduction was 45%. The strongest improvement in chronic mediator release symptoms was seen in the symptoms fatigue and musculoskeletal pain, as evidenced by a median 4 point and 3.5 point difference in score on a 0-10 scale after 24 weeks of treatment.

The secondary efficacy endpoint of disease-specific quality-of-life as measured by the MQLQ indicated a statistically significant median 29% ($P < 0.001$, IQR 16% - 47%) improvement after 24 weeks of treatment.(3) The strongest improvement of 39% was found in the domain fatigue. All the changes per domain of the quality-of-life measurement tools are displayed in Figure 2 (Online Repository).

Mast cell load was used as a final secondary efficacy endpoint. Already after 4 weeks all 19 still included patients showed a statistically significant reduction in tryptase levels (from 36.0 to 15.5 $\mu\text{g/l}$, $P < 0.001$) that remained stably reduced for all but 1 patient throughout the study (Figure 2). The increase in tryptase seen in one patient followed an adverse event with associated dosage reduction of midostaurin. A similar rebound effect was observed in most patients during the 2 month wash-out period. At the end of the study, 8 out of 16 histologically assessable bone marrow biopsies showed a reduction in the percentage of mast

cells (from median 7.5% to 4.0%), 2 an increase and 6 no change. Urticaria pigmentosa improved in 12 (80%) of the 15 patients with skin symptoms, resulting in a 40% reduction in median SCORMA score with the strongest effect seen in the intensity of lesions. (6) (Online supplementary Figure 3)

Midostaurin was reasonably well tolerated; the most common adverse events were nausea (n=16, 80%), headache (n=10, 50%), diarrhea (n=7, 35%), all grade 1-2. Midostaurin-related nausea responded well to 5-HT₃ receptor antagonist anti-emetics, but was necessary until the end of the study for all but six patients. In three female patients nausea – although CTC 2 - was uncontrolled by anti-emetics and these patients dropped out. Midostaurin did not induce changes in electrocardiography. There was one SAE, anaphylaxis during lunch with collapse not objectified by tryptase-measurements, deemed to be probably not treatment-related and two additional other grade 3-4 adverse events (syncope and transient elevated ALT). Notably, there were no CTC grade >1 hematological adverse events. The frequencies of grade 1-2 AEs are shown in online repository Table 2.

According to protocol, all patients stopped midostaurin at week 24. Most patients experienced a rapid relapse of symptoms, accompanied by an increase in tryptase levels (Figure 2). Ten patients restarted midostaurin at twice 100 mg and all showed an improvement of symptoms once more, accompanied by a reduction in tryptase in all but two patients (Online repository Figure 5). In the following 12 months, 2 patients were not motivated to continue, and were considered lost to follow-up. In the remaining 8 patients dosage reductions were attempted. Midostaurin dosage was titrated based on mastocytosis symptom severity and serum tryptase. Dosage reductions were successful in 5 patients resulting in less nausea without loss of efficacy. As per December 2016, the average daily dosage of midostaurin was 150 mg.

In conclusion, we find midostaurin to be an effective, fast acting, relatively safe and reasonably tolerable treatment modality for ISM patients with severe mediator release symptoms or skin infiltration. The decrease of tryptase, bone marrow and skin infiltration suggests a beginning of mast cell eradication. On purpose, given the novelty of midostaurin, the size of our trial was small and the selection strict to avoid exposure of too many patients if the drug would not have been effective. One caveat related to our strict patient selection is the possibility of regression to the mean of symptom severity. However, all trial patients had their symptoms scored at least twice before the study at start – during pre-screening and at entry. A post hoc analysis comparing symptom severity between the screening phase and the start of the trial did not show a significant

164 difference in symptom severity over these 6 months. A recent trial of the tyrosine
165 kinase inhibitor masitinib found a significant improvement of symptoms compared
166 to placebo in ISM patients. (7) Direct comparison of efficacy with midostaurin is
167 difficult due to the use of different primary outcome measures and response
168 definitions. Nevertheless, in a post-hoc analysis to facilitate comparison,
169 midostaurin appeared more effective (Appendix 1).

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Figure legends

Figure 1: Percentage change in symptom severity as measured by the
mastocytosis symptom assessment form (MSAF), halfway and after 24 weeks.

Figure 2: Serum tryptase reduction during Midostaurin treatment.

Online repository Figure 1. Patient accrual and trial profile

Online repository Figure 2: Symptom severity as measured by the median mastocytosis symptom assessment form (MSAF) score before and after 24 weeks of treatment with midostaurin, the higher the score, the more severe the symptoms.

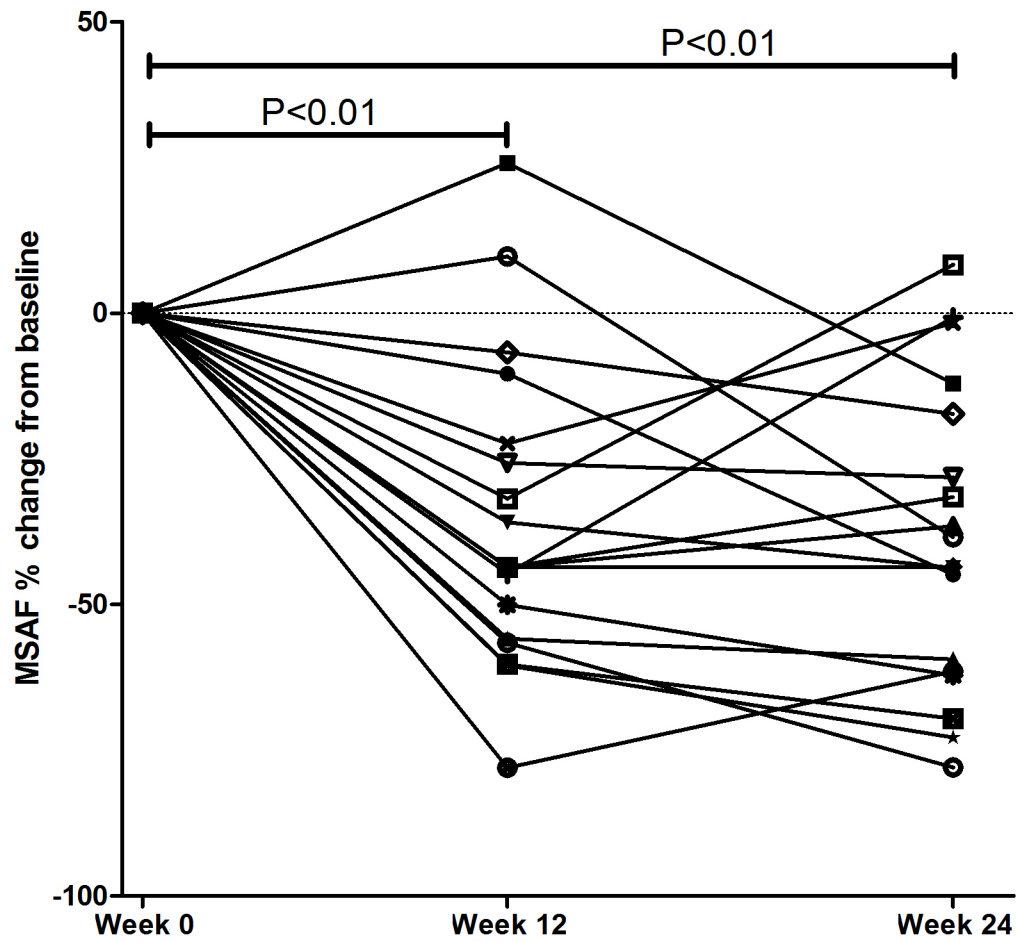
Online repository Figure 3: Response in mast cell infiltration markers after 24 weeks of Midostaurin, each bar represents a single patient

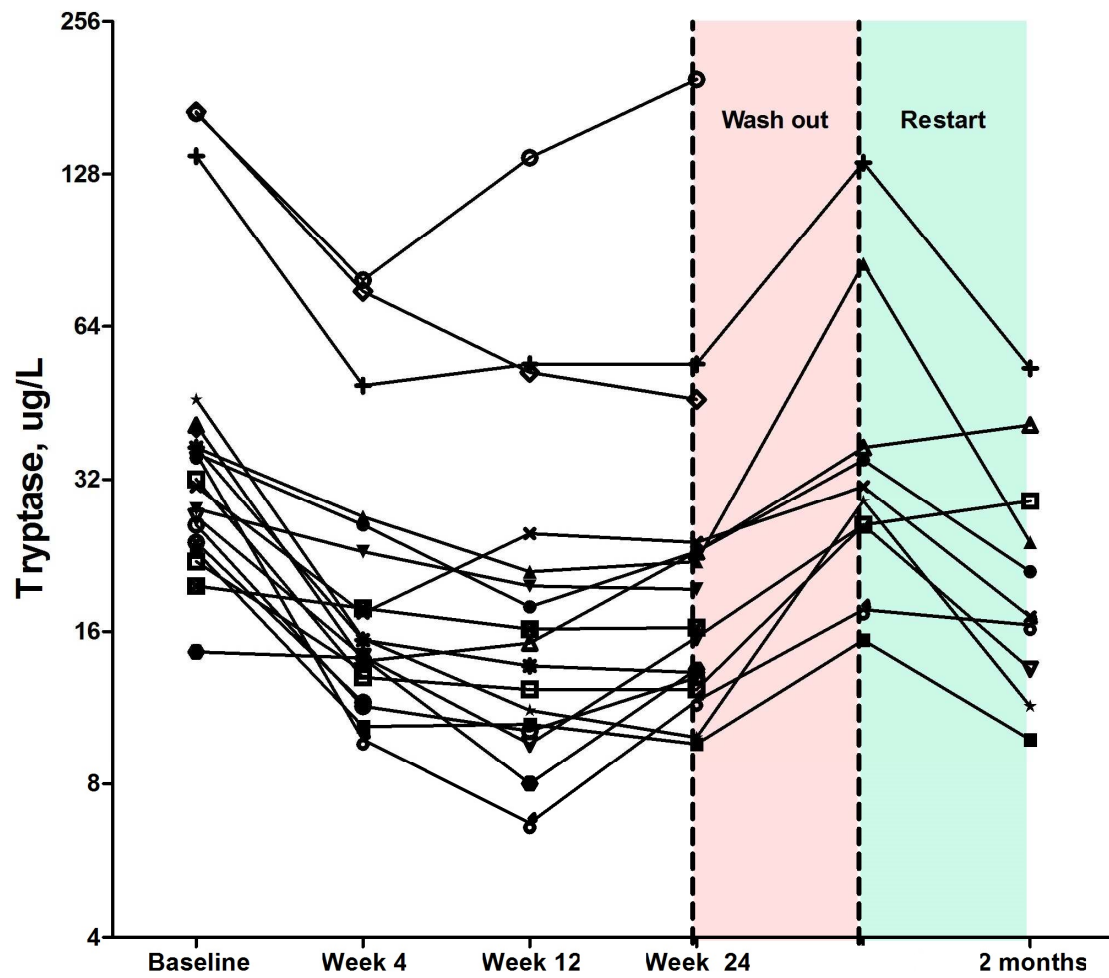
Methylhistamine(MH) and methylimidazole acetic acid (MIMA) were measured in morning urine samples, voided on waking.

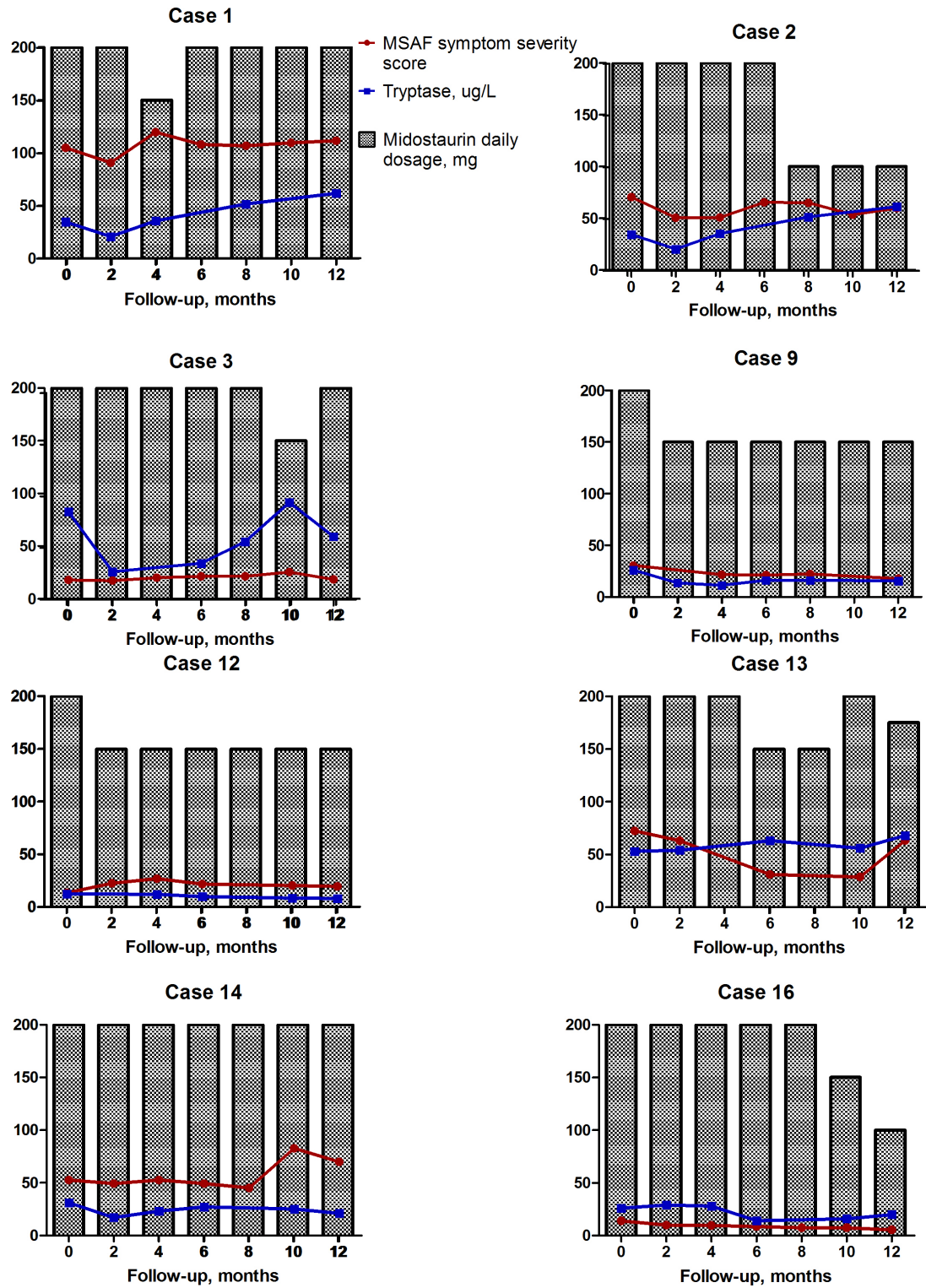
Online repository Figure 4: Median scoring per domain of the disease specific Mastocytosis Quality-of-Life Questionnaire (MQLQ) and the general Short Form Health Survey 36 (SF36) related quality of life, a higher score indicates less burden.

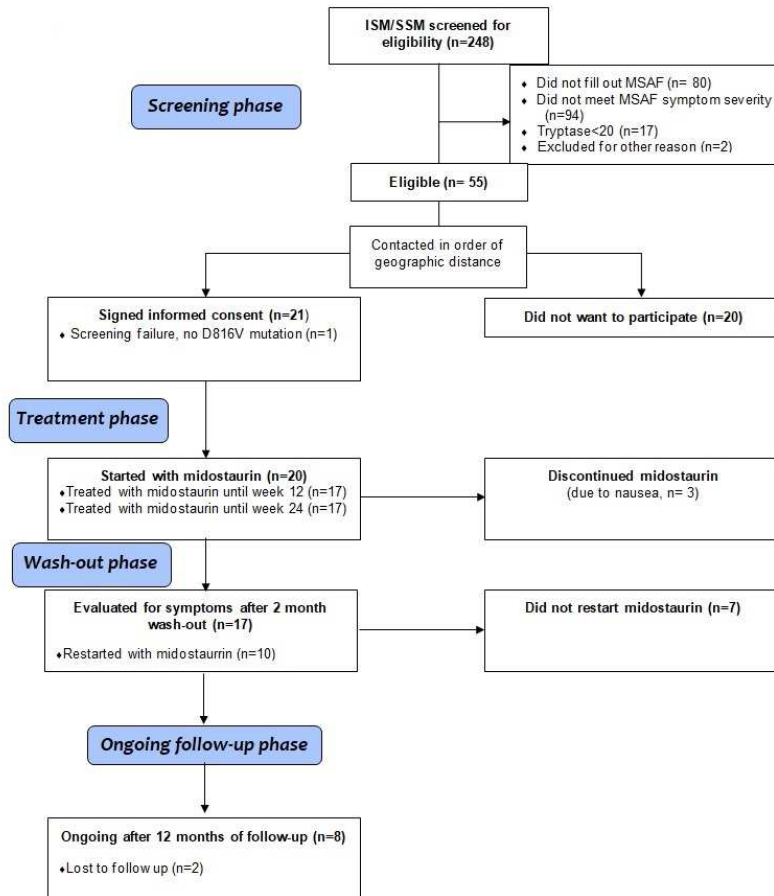
Online repository Figure 5: The effect of midostaurin dosage tapering on tryptase and symptom severity during 12 months of follow-up

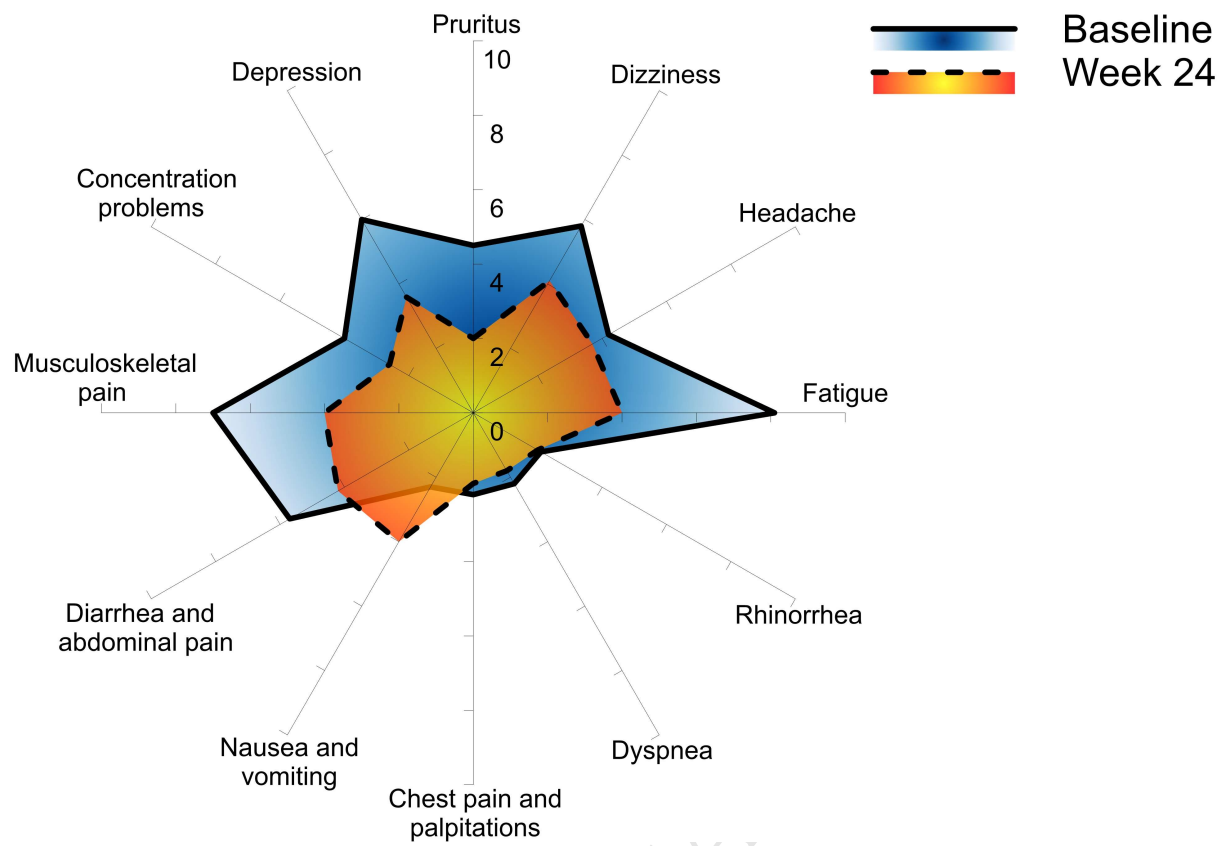
Online repository Table 1. Common adverse events, occurring in >10% of patients or CTC grade >2.

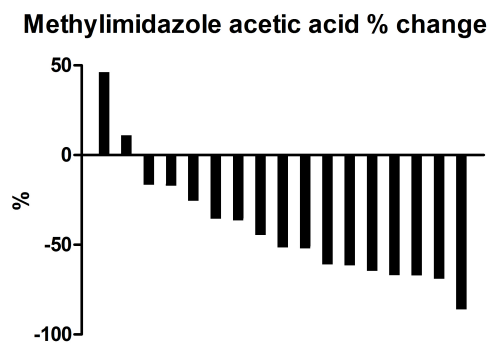
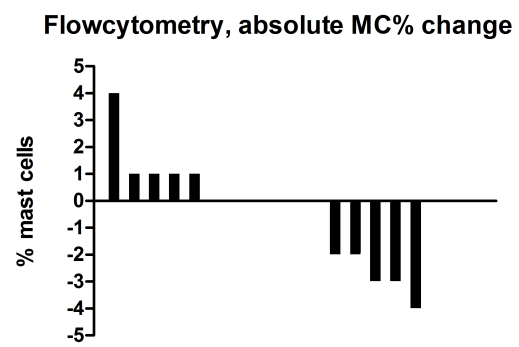
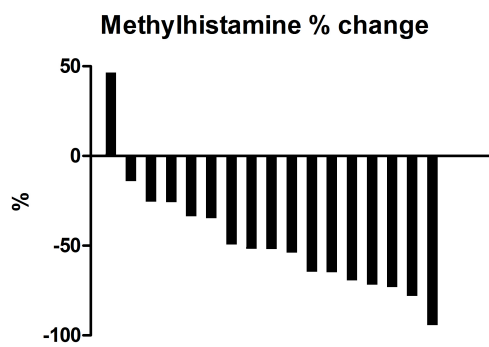
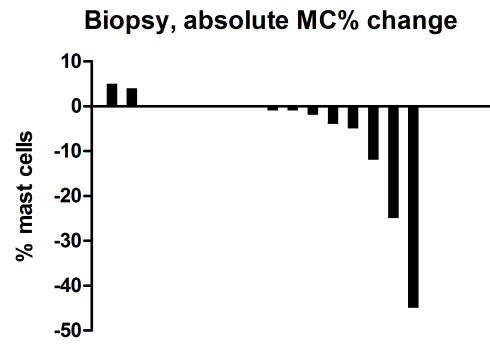
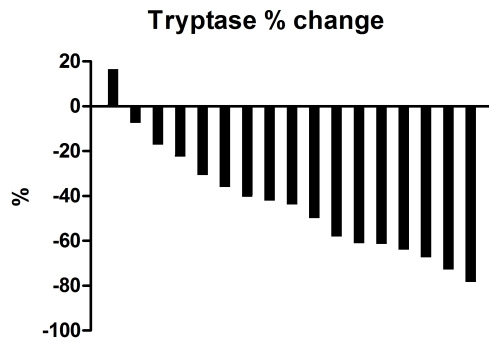


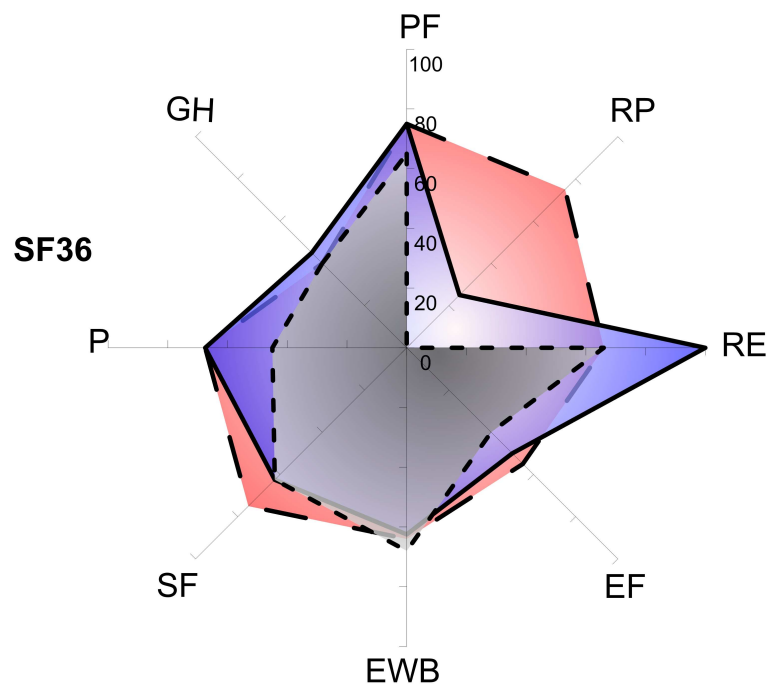
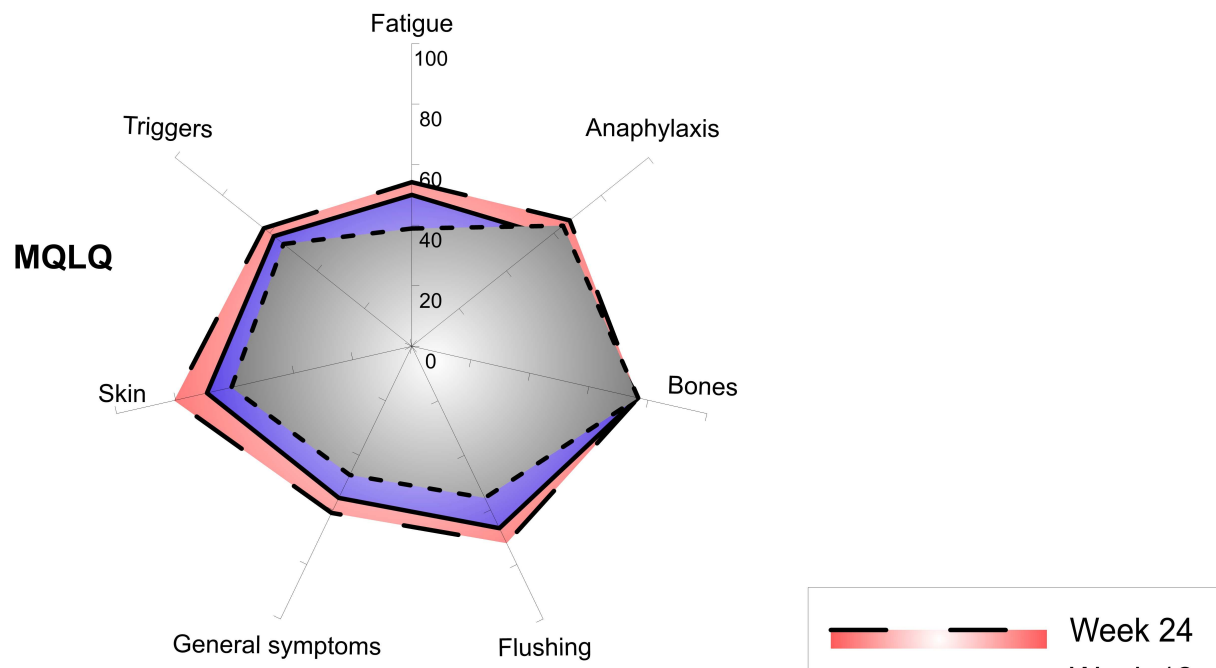












PF: Physical functioning
 RP: Role limitations due to physical health
 RE: Role limitations due to emotional problems
 EF: Energy/fatigue

EWB: Emotional well-being
 SF: Social functioning
 P: Pain
 GH: General Health

Appendix 1: Post Hoc Analysis for comparison with masitinib.

For the post hoc analysis all weekly MSAF scoring forms were re-analyzed following, if possible, the methodology of Lortholary et al. (7) For the 17 patients with data available from week 8 and later severe symptoms at baseline of pruritus, flushing, depression and fatigue symptoms were identified. The definition of severe symptoms was identical to that used in the rest of the paper: in this case depression, fatigue, pruritus score of 4 or flushes 7 or more per week. We defined response following Lortholary et al. as a 75% improvement from baseline for any of these four symptoms and defined cumulative response as the number of responses between weeks 8 and 24, divided by the total number of possible responses over the same treatment period. As an example, a patient with two severe symptoms at baseline filling out weekly MSAF forms during 16 weeks had 32 possible responses.

For the total group of 17 patients there were 607 possible responses, in 181 of these there was an improvement equal or greater than 75%. For example, a baseline MSAF pruritus scoring of 8 reduced to 2 during one week. The cumulative response rate for all 4 symptoms together was 29.8% Pruritus had the highest individual response rate at 56.8%.

Online repository Table 1. Common adverse events, occurring in >10% of patients or CTC grade >2.

Adverse event	CTC grade 1-2	CTC Grade 3
Nausea	16 (80%)	0
Headache	10 (50%)	0
Diarrhea	7 (35%)	0
Elevated transaminases	7 (35%)	1 (5%)
Fatigue	6 (30%)	0
Urinary tract infection	3 (15%)	0
Dizziness	3 (15%)	0
Flu like symptoms	3 (15%)	0
Anemia	3 (15%)	0
Abdominal pain	2 (10%)	0
Arthralgia	2 (10%)	0
Vomiting	2 (10%)	0
Anaphylaxis	0	1 (5%)
Syncope	0	1 (5%)