

recruited to the study (1997–2010). Patients were divided according to histological types in two major groups: epidermoid NSCLC (n=61) and non-epidermoid NSCLC (n=95). DNA was extracted from peripheral-blood samples. The *MMP-9* Q279R was genotyped by Real-Time PCR. Overall survival (OS) was the endpoint of this analysis and was calculated from the date of diagnosis to date of death of the patient. Survival data were analyzed according to *MMP-9* polymorphisms' genotypes.

Results: The *MMP-9* Q279R polymorphism was significantly associated with overall survival in the non-epidermoid subgroup. Patients with genotypes carrying the G allele (AG/GG) had a statistically significant diminished survival when compared with patients with AA genotype (18.5 months and 28.7, respectively; $P=0.019$).

Conclusion: Our results suggest that *MMP-9* Q279R polymorphism is associated with a decreased overall survival in non-epidermoid NSCLC patients. In the era of pharmacogenomic profiles and directed therapies, it would be important to conduct further functional studies are to clarify the role of this polymorphism in *MMP-9* expression and how it conditions tumour progression, in order to better understand the observed effect.

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POSTER

Neutropenia as a Biomarker of Sunitinib Efficacy in Patients (Pts) With Gastrointestinal Stromal Tumour (GIST)

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Background: KIT is key to hematopoietic cell growth and development, and potent inhibitors of KIT signaling are likely to exhibit some degree of myelotoxicity through on-target mechanisms. We retrospectively investigated the association between myelosuppression and efficacy endpoints in sunitinib-treated pts with GIST from four clinical trials (RTKC-0511–013, NCT00075218, NCT00137449 and NCT00372567; Pfizer).

Materials and Methods: Analyses included data from a total of 416 pts with GIST, of whom 325 received sunitinib on an intermittent schedule (283 at 50 mg/day on a 4-week-on/2-week-off schedule) and 91 received sunitinib at 37.5 mg on a continuous daily dosing schedule. Median TTP, PFS and OS were estimated by Kaplan–Meier (KM) methods and compared between pt subgroups using the log-rank test. Multivariate and time-dependent covariate analyses were performed, the latter to address potential bias from longer drug exposure. Myelosuppression was graded using CTCAE v 3.0.

Results: In KM and multivariate analyses, neutropenia grade ≥ 2 during treatment was associated with significantly longer TTP, PFS, and OS (Table 1). Thrombocytopenia grade >1 was associated with significantly longer TTP and PFS. Hemoglobin $\leq$ the lower limit of normal (LLN) during treatment was significantly associated with longer TTP and showed a similar trend for longer PFS in KM analysis; both were significant in multivariate analysis. However, in time-dependent covariate analysis, only the associations between neutropenia grade ≥ 2 and PFS and OS showed statistical significance. Baseline neutrophil and platelet counts $<$ median and baseline hemoglobin $\geq$ median were associated with significantly longer OS in KM analysis only (data not shown). Analyses of safety endpoints associated with hematologic parameters will be presented.

Table 1. Association between myelosuppression and efficacy outcomes

Efficacy endpoint	Median time to progression/survival event (mo)	P	Multivariate analysis, HR (P*)	Time-dependent covariate analysis, HR (P*)
Neutropenia during treatment (AE data)				
	Gr ≥ 2 (n = 164)	Gr < 2 (n = 252)	$\geq / <$ Gr 2	$\geq / <$ Gr 2
TTP	9.2	5.3	0.0003 (0.0001)	0.812 (0.108)
PFS	14.7	10.6	< 0.0001 0.523 (< 0.0001)	0.768 (0.036)
OS	25.2	15.7	< 0.0001 0.598 (0.001)	0.599 (0.0006)
Thrombocytopenia during treatment (AE data)				
	Gr > 1 (n = 42)	Gr ≤ 1 (n = 374)	$> / \leq$ Gr 1	$> / \leq$ Gr 1
TTP	10.8	6.7	0.001 0.457 (0.001)	0.710 (0.160)
PFS	10.1	6.2	0.001 0.505 (0.001)	0.782 (0.279)
OS	28.1	19.0	0.088 0.690 (0.141)	0.829 (0.429)
Hemoglobin during treatment (lab data)				
	$\leq$ LLN (n = 315)	$>$ LLN (n = 85)	$\leq / >$ LLN	$\leq / >$ LLN
TTP	7.8	6.7	0.047 0.655 (0.003)	0.897 (0.401)
PFS	6.9	6.2	0.059 0.674 (0.004)	0.942 (0.636)
OS	20.1	19.7	0.301 0.801 (0.231)	1.241 (0.175)

Gr: grade; *Wald chi-square test

Conclusions: Neutropenia may be a previously unrecognized biomarker of sunitinib efficacy significantly associated with improved TTP, PFS and OS in pts with GIST. These results require validation in prospective trials. Hematologic parameters should be monitored closely during sunitinib treatment.

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POSTER

Asthenia and Fatigue as Potential Biomarkers of Sunitinib Efficacy in Metastatic Renal Cell Carcinoma

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Background: Asthenia and fatigue (A/F) are commonly reported adverse events in patients with metastatic renal cell carcinoma (mRCC) treated with sunitinib. In a randomized phase III trial of treatment-naïve mRCC patients, sunitinib showed superior progression-free survival (PFS) over interferon- α (11 vs. 5 months; $P < 0.001$), with a median overall survival (OS) of 26.4 months (Motzer, 2009). This established sunitinib as a reference standard of care for advanced RCC. Effective management of patients' adverse events may help maximize clinical benefit.

Materials and Methods: We retrospectively investigated correlations between A/F and efficacy endpoints using pooled data from 770 sunitinib-treated mRCC patients from five clinical trials (NCT00054886, NCT00077974, NCT00083889, NCT00338884, NCT00137423; Pfizer). Patients received sunitinib 50 mg/d on a 4-weeks-on-2-weeks-off schedule (n = 544; 71%) or 37.5 mg continuous daily dosing (n = 226; 29%). Adverse events were recorded regularly and graded according to CTCAE v 3.0. Median time to tumour progression (TTP), PFS and OS were estimated using Kaplan–Meier methods and compared between patients with and without A/F using a log-rank test. Multivariate analysis was performed using age, gender, race, baseline Eastern Cooperative Oncology Group performance status, time from diagnosis to treatment, relative dose intensity, lactate dehydrogenase, serum hemoglobin, corrected serum calcium, and baseline blood pressure as covariates. Time-dependent covariate analysis was performed to address potential bias from longer drug exposure. Landmark analyses were used to compare outcomes in patients with or without A/F after 6 and 12 weeks of treatment.

Results: Of 770 patients, 583 (76%) developed A/F of any grade, compared with 187 (24%) who did not. Patients who developed any-grade A/F had significantly better TTP (11.1 vs. 6.5 months), PFS (10.9 vs. 6.4 months), and OS (26.2 vs. 15.0 months) than patients who did not develop A/F (all $P < 0.0001$). Multivariate analysis showed that sunitinib-associated A/F was a significant predictor of improved outcome for all endpoints ($P < 0.0001$). However, these results were not confirmed statistically in time-dependent covariate or landmark analyses. Analyses investigating the impact of A/F severity on outcome are in progress.

Conclusions: In patients with mRCC, sunitinib-associated A/F seems significantly and independently associated with improved clinical outcomes (TTP, PFS and OS). Since time-dependent covariate and landmark analyses supported the hypothesis that A/F may develop in patients who have longer drug exposure, the value of A/F as an early predictor of efficacy requires further analysis. This is the first reported link between drug-associated A/F and efficacy, and validation in prospective studies is warranted.

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POSTER

Asthenia and Fatigue as Predictors of Sunitinib Efficacy in Gastrointestinal Stromal Tumour (GIST)

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Background: Sunitinib is an established treatment for imatinib-resistant/intolerant GIST. Asthenia and fatigue (A/F) are commonly reported side effects of sunitinib that may lead to dose reduction, potentially affecting patient outcome. Identification of a significant association between A/F and efficacy could have implications for patient management.

Materials and Methods: We retrospectively investigated associations between A/F and efficacy endpoints using data from 416 patients (pts) with GIST from four trials (RTKC-0511-013, NCT00075218, NCT00137449 and NCT00372567; Pfizer). Pts received sunitinib either on an intermittent schedule (n=325; 283 of whom received sunitinib at a starting dose of 50 mg/day on a 4-week-on/2-week-off schedule) or a continuous daily dosing schedule (37.5 mg/day; n=91). Adverse events were recorded regularly using CTCAE version 3.0. Median time to tumour progression (TTP), progression-free survival (PFS) and overall survival (OS) were estimated using Kaplan–Meier (KM) methods and compared between pts with and without A/F using the log-rank test. Multivariate analysis was performed using age, gender, race, baseline Eastern Cooperative Oncology Group performance status, time from diagnosis, relative dose intensity, duration of prior imatinib treatment, baseline tumour volume, baseline granulocyte count, baseline hemoglobin, and baseline blood pressure as covariates. Time-dependent covariate analysis was performed to address potential bias from longer drug exposure, and landmark analyses were used to compare outcomes in pts with or without A/F after 6 and 12 weeks of treatment.

Results: Of 416 pts, 311 (75%) developed A/F of any grade, compared with 105 (25%) who did not. TTP and PFS were significantly longer in pts who developed A/F on sunitinib: median TTP was 7.8 vs 5.8 months and median PFS was 7.7 vs 5.1 months for pts with vs without A/F, respectively ($P \leq 0.004$). There was a trend for improved OS in pts with A/F (median OS: 20.1 vs 18.1 months; $P=0.135$). Multivariate analysis showed that sunitinib-associated A/F was a significant predictor of improved outcome for all endpoints ($P \leq 0.013$). However, these results were not confirmed statistically in time-dependent covariate and landmark analyses. Analyses investigating the impact of A/F severity on outcome are in progress.

Conclusions: In pts with GIST, sunitinib-related A/F was significantly associated with improved TTP and PFS in KM analysis and was a significant predictor of TTP, PFS and OS in multivariate analysis. Since time-dependent covariate and landmark analyses supported the hypothesis that A/F may develop in pts who have longer drug exposure, the value of A/F as an early predictor of efficacy requires further analysis. This is the first reported link between drug-associated A/F and efficacy, and prospective studies are needed to validate these results.

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POSTER

Neutropenia and Thrombocytopenia During Treatment as Biomarkers of Sunitinib Efficacy in Patients With Metastatic Renal Cell Carcinoma (mRCC)

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Background: Baseline neutrophils, thrombocytes and hemoglobin have been validated as prognostic factors in mRCC. We retrospectively studied the correlation between these hematologic variables during treatment and efficacy endpoints in sunitinib-treated mRCC patients from 5 clinical trials (NCT00054886, NCT00077974, NCT00083889, NCT00338884, NCT00137423; Pfizer).

Materials and Methods: Analyses included pooled data from 770 mRCC patients who received sunitinib 50 mg/d on a 4-wk-on-2-wk-off schedule (n=544; 71%) or 37.5 mg/d continuous dosing (n=226; 29%). Median PFS, TTP and OS were estimated by Kaplan–Meier methods and compared between subgroups using log-rank test. Multivariate and time-dependent covariate analyses were performed, the latter to address potential bias from longer drug exposure. Myelosuppression was graded using CTCAE v 3.0.

Results: In multivariate analyses, neutropenia grade ≥ 2 and thrombocytopenia grade >1 were associated with significantly longer TTP, PFS and OS (Table). Within the time-dependent covariate analysis, neutropenia grade ≥ 2 was significantly associated with all three efficacy endpoints; there was a trend for improvement in the endpoints with thrombocytopenia grade >1 . Baseline neutrophil count $\leq$ ULN and baseline thrombocyte count $\leq$ ULN were associated with significantly longer TTP, PFS and OS in multivariate analysis. Baseline and on-treatment hemoglobin data will be presented at the meeting.

Conclusions: Neutropenia and thrombocytopenia during treatment may be previously unrecognized biomarkers of sunitinib efficacy, significantly associated with improved TTP, PFS and OS in mRCC patients. These data require validation in prospective trials. Hematologic parameters should be monitored closely with sunitinib treatment.

Table: Association between myelosuppression and efficacy outcomes

Efficacy endpoint	Median time to progression/survival event (mo)		P	Multivariate analysis, HR (P*)	Time-dependent covariate analysis, HR (P*)
Neutropenia during treatment (AE data)					
	Gr ≥ 2 (n = 366)	Gr < 2 (n = 404)	<0.0001	$\geq < Gr 2$	$\geq < Gr 2$
TTP	13.7	7.8	<0.0001	0.553 (<0.0001)	0.775 (0.0073)
PFS	13.6	7.1	<0.0001	0.520 (<0.0001)	0.759 (0.0032)
OS	35.6	15.8	<0.0001	0.415 (<0.0001)	0.467 (<0.0001)
Baseline neutrophil count (lab data)					
	$\leq$ ULN (n = 69)	$>$ ULN (n = 74)		$\leq > ULN$	$\leq > ULN$
TTP	10.8	3.9	<0.0001	0.469 (<0.0001)	NA
PFS	10.7	3.2	<0.0001	0.482 (<0.0001)	NA
OS	24.9	9.1	<0.0001	0.664 (0.0048)	NA
Thrombocytopenia during treatment (AE data)					
	Gr > 1 (n = 101)	Gr ≤ 1 (n = 669)		$\geq < Gr 1$	$\geq < Gr 1$
TTP	13.8	10.1	0.001	0.660 (0.004)	0.765 (0.058)
PFS	13.7	8.8	0.001	0.658 (0.003)	0.767 (0.056)
OS	31.1	21.4	0.014	0.724 (0.038)	0.776 (0.088)
Baseline thrombocyte count (lab data)					
	$\leq$ LN (n = 649)	$>$ ULN (n = 117)		$\leq > ULN$	$\leq > ULN$
TTP	11.0	4.7	<0.0001	0.481 (<0.0001)	NA
PFS	10.8	4.6	<0.0001	0.525 (<0.0001)	NA
OS	24.9	9.1	<0.0001	0.664 (0.0048)	NA

Gr: grade; NA: not applicable; *Wald chi-square test.

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POSTER

Clinical Significance of Macrodissection in Two Different KRAS Tests for Colorectal Cancer: Results From a Multi-center Clinical Trial

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Background: The KRAS mutation is a predictive marker for non-responsiveness to anti-EGFR antibodies for metastatic colorectal cancer. Macrodissection (MD) is currently recommended to enrich tumour cellularity when the ratio of tumour area is less than either 50 or 70%. However, evidence supporting the importance of MD is inadequate. We previously reported that a Luminex[®] KRAS detection kit showed a high concordance rate (99.1%) with direct sequencing (DS) and met our primary endpoint.

Methods: Formalin-fixed paraffin-embedded (FFPE) tissue specimens from 227 patients with colorectal cancer were registered. In total, 212 samples were analyzed as the full analysis set. The percentages of tumour area were blindly determined by independent pathological review and tumours were classified according to the percentages of tumour area ($<50\%$ versus $\geq 50\%$, $<70\%$ versus $\geq 70\%$). DNA from FFPE tumour tissues, with and without MD, were analyzed by both DS and the Luminex method. The results from DS with MD were used as a standard. We investigated the concordance of KRAS status according to the percentages of tumour area. Statistical analysis was performed by binominal tests.

Results: The KRAS mutation ratio detected by DS, with and without MD, was 34.9% and 32.1%, respectively. The KRAS mutation ratio detected by Luminex, with and without MD, was 35.8% and 33.5%, respectively. In the 165 samples with $<70\%$ of tumour area, 6 samples showed a discordance between DS with and without MD, which was statistically significant ($P=0.016$). In the 47 samples with $\geq 70\%$ tumour area, the concordance rate was 100%. On the other hand, 3 samples with $<70\%$ tumour area showed discordance between Luminex without MD and DS with MD ($P=0.125$), while in samples with $\geq 70\%$ tumour area, the concordance rate was 100%. For samples classified with tumour areas between $<50\%$ and $\geq 50\%$, the same trend was observed, but one sample with $\geq 50\%$ area showed discordance between DS with and without MD.

Tumour area (%)	Luminex method				P value	Direct-sequencing method				P value
	True positive	False positive	False negative	True negative		True positive	False positive	False negative	True negative	
<50	38	0	3	81	0.125	36	0	5	81	0.031
50–100	33	0	0	57	1	32	0	1	57	0.5
<70	54	0	3	108	0.125	51	0	6	108	0.016
70–100	17	0	0	30	1	17	0	0	30	0.5