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 ($P \leqslant 0.004$). 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 ($P \leqslant 0.013$). 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.

1141 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 $\geqslant$2 and thrombocytopenia grade >1 were associated with significantly longer TTP, PFS and OS (Table). Within the time-dependent covariate analysis, neutropenia grade $\geqslant$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 $\leqslant$ULN and baseline thrombocyte count $\leqslant$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 $\geqslant$2 (n = 366)	Gr <2 (n = 404)	<0.0001	$\geqslant$/< Gr 2	$\geqslant$/< 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)					
	$\leqslant$ULN (n = 69)	>ULN (n = 74)		$\leqslant$/> ULN	$\leqslant$/> 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	<0.000	0.664 (0.0048)	NA
Thrombocytopenia during treatment (AE data)					
	Gr >1 (n = 101)	Gr $\leqslant$1 (n = 669)		>/$\leqslant$ Gr 1	>/$\leqslant$ 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)					
	$\leqslant$ LN (n = 649)	>ULN (n = 117)		$\leqslant$/> ULN	$\leqslant$/> 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.

1142 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 $\geqslant$50%, <70% versus $\geqslant$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 $\geqslant$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 $\geqslant$70% tumour area, the concordance rate was 100%. For samples classified with tumour areas between <50% and $\geqslant$50%, the same trend was observed, but one sample with $\geqslant$50% area showed discordance between DS with and without MD.

Tumour area (%)	Luminex method					Direct-sequencing method				
	True positive	False positive	False negative	True negative	P value	True positive	False positive	False negative	True negative	P value
<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