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.

1138 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 $\geqslant$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 $\leqslant$ 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 $\geqslant$2 and PFS and OS showed statistical significance. Baseline neutrophil and platelet counts < median and baseline hemoglobin $\geqslant$ 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)	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 = 164)	Gr <2 (n = 252)		$\geqslant$/< Gr 2	$\geqslant$/< Gr 2
TTP	9.2	5.3	0.0003	0.585 (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 $\leqslant$1 (n = 374)		>/$\leqslant$ Gr 1	>/$\leqslant$ 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)					
	$\leqslant$ LLN (n = 315)	> LLN (n = 85)		$\leqslant$/> LLN	$\leqslant$/> 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.

1139 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-alfa (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.

1140 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.