AEs were hypertension (10%), asthenia (9%), HFS (9%), anorexia (8%) and diarrhea (6%). No differences were observed between pts receiving AM vs. PM dosing. RECIST-defined ORR was 20% by investigator assessment, with 43 pts (40%) achieving clinical benefit of ⩾6 mo of stable disease. Median PFS is 8.3 mo. QOL results will be presented.
Conclusions: Sunitinib 37.5 mg/d administered on a continuous dosing schedule has a manageable safety profile and shows promising clinical benefit as second-line therapy in mRCC, with a median PFS similar to that observed on the 4/2 schedule. This regimen may warrant further study for use in combination studies.

4505 ORAL

A population pharmacokinetic/pharmacodynamic (PK/PD) analysis of exposure–response for sunitinib in metastatic renal cell carcinoma (mRCC)

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Background: Sunitinib malate (SU) is an oral, multitargeted tyrosine kinase inhibitor of VEGFRs, and PDGFRs, approved multinationally for the treatment of advanced RCC. SU has previously shown substantial antitumor activity in mRCC [Motzer et al. JCO 2006; Motzer et al. JAMA 2006; Motzer et al. NEJM 2007]. The current analysis used a population PK/PD approach to examine the relationship between SU or total drug (TD; SU+SU12662 [active metabolite]) exposure and response in these studies.
Materials and Methods: PK and efficacy data were collected from 2 prior phase II trials of cytokine-refractory mRCC (N = 148) and phase III trial of treatment-naive mRCC (N = 44). SU starting dose was 50 mg/d, administered in 6-wk cycles (4 wks on followed by 2 wks off treatment), but modifications to 37.5, 25, or 62.5 mg/d were allowed based on tolerability and response. Plasma concentrations of SU and SU12662 were fitted to a 2-compartment population PK model and used to estimate the area under the curve at steady state (AUCss) for SU, SU12662, and TD. AUCss for SU and TD were used in subsequent PKPD analyses to examine the relationship between drug exposure and partial response (PR) rates, time to tumor progression (TTP), overall survival (OS), or tumor volume changes.
Results: For cytokine-refractory pts, the probability of PR increased as exposure to SU or TD increased. The odds-ratio suggested a 2.6-fold increase in PR frequency for each unit increase in AUCss. High SU and TD AUCss were also associated with a trend toward longer TTP and OS. A tumor growth dynamics model was used to describe changes in tumor volume as a function of AUCss for both cytokine-refractory and treatment-naive pts treated with SU. Clinical trial simulations based on this model and assuming perfect pt compliance predicted 62% of pts would achieve a PR with SU 50 mg/day.
Conclusions: For SU-treated pts with advanced mRCC, the probability of PR was significantly correlated with SU and TD AUCss. Elevated exposure was also associated with longer TTP and OS. A tumor growth dynamics model suggested that increased exposure to SU was associated with clinical benefit for pts with either cytokine-refractory or treatment-naive mRCC.

4506 ORAL

A large open-label, non-comparative, phase III study of the multi-targeted kinase inhibitor sorafenib in European patients with advanced renal cell carcinoma

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Background: A phase III trial showed that sorafenib (400 mg twice daily) doubled PFS and produced a 39% improvement (non-significant) in overall survival relative to placebo in previously treated patients with clear cell renal cell carcinoma (RCC). The objectives of the present trial were to make sorafenib available to European patients until regulatory approval and collect safety and efficacy data from a large and unselected study population.
Methods: This non-randomised, open-label study included male and female patients, ⩾18 years of age, with an ECOG PS 0–2 and a life expectancy >2 months. Patients had to be unsuitable for, or have failed, prior cytokine therapy. Controlled, asymptomatic brain metastases were allowed. Patients received continuous therapy with sorafenib 400 mg twice daily until disease progression, intolerable toxicity, or withdrawal of consent. Dose increases were not permitted. Recruitment was planned to continue until regulatory approval of sorafenib for advanced RCC. Study assessments were conducted at baseline and then monthly. Adverse events were graded according to NCI CTCAE v3.0 criteria. Tumour assessment and radiological evaluation were conducted within 28 days prior to the start of sorafenib therapy, and then according to local standards of care, but at least every 3 months.
Results: Over 1,150 patients were recruited in 11 European countries. Approximately 75% of patients were male. Median age at enrolment was 62 years. At baseline, ECOG PS = 0 in 38%, 1 in 45% and 2 in 17% of patients; approximately 73% of patients had tumour lesions in the lungs, 32% in bone, 32% in lymph nodes, 27% in the liver and 23% in the kidneys. Approximately 10% had not had the primary tumour resected. Approximately 24% had no prior therapy and were included because they were unsuitable for cytokine treatment. Tumour histology included clear cell (78%), papillary (11%) and chromophobe (3%). Sarcomatoid features were noted in tumour samples from 6% of the patients. At a median follow up of >10 months, approximately 40% of the patients remained on study drug. In addition to the efficacy and safety data for the study as a whole, subgroup analyses will be performed for prior treatment, performance status, tumour histology and location of metastases.

4507 ORAL

Axitinib (AG-013736; AG) in patients (pts) with metastatic clear cell renal cell cancer (RCC) refractory to sorafenib

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Background: Sunitinib and sorafenib, receptor tyrosine kinase inhibitors (TKIs) of VEGF and PDGF receptors (VEGFR, PDGFR), are FDA-approved treatments for advanced RCC. AG is a potent inhibitor of VEGFR 1, 2 & 3 and showed substantial efficacy in a previous phase II study in pts with cytokine refractory RCC (Rini et al., ASCO 2005). The activity of AG in metastatic RCC patients refractory to prior TKI therapy is of clinical interest.
Methods: Pts with sorafenib-refractory metastatic RCC were enrolled in this multicenter, open-label, phase II study. Eligibility criteria included measurable disease, ECOG performance status of 0 or 1, controlled CNS metastases (if present) and adequate organ function. All pts received a starting dose of AG 5 mg orally BID, titrated according to tolerance. The primary endpoint was RECIST-defined objective response (OR) with a null hypothesis of OR ⩽8% versus ⩾20% under the alternative hypothesis. Pts underwent radiographic staging at baseline and every 8 weeks and were treated until progressive disease or unacceptable toxicity.
Results: All planned 62 pts have been enrolled. Median age of pts was 60 years (range 35–77); 42 pts (68%) were male; 60 pts (97%) had prior nephrectomy. All pts had received prior sorafenib and 14 pts also received prior sunitinib. Median final AG dose was 5 mg (range, 2–10 mg). Partial response (PR) was observed in 9/62 evaluable pts (14%; 95% CI: 7–26%), stable disease in 23 pts (37%), and 15 pts (24%) experienced progressive disease. 51% of patients overall experienced tumor shrinkage. With a median follow-up of 7.4 months (95% CI: 4.7–8.7 months), the median progression-free survival (PFS) was not reached, but preliminary analysis indicates overall median PFS > 7.7 months. One of 14 patients with prior sorafenib and sunitinib treatment had a PR, with median PFS > 6.2 months in this sub-group. Grade 3 and 4 treatment-related adverse events included fatigue (13%), hypertension (11%), hand–foot syndrome (11%), diarrhea (5%) and dyspnea (5%). Overall, 22 pts remain on study.
Conclusions: AG has substantial antitumor activity in pts with sorafenib-refractory metastatic RCC. Toxicity is as expected with a VEGFR TKI and generally manageable.