4517 POSTER

Sunitinib in patients with cytokine-refractory metastatic renal cell carcinoma (mRCC)

D.J. George[1], M.D. Michaelson[2], J.E. Rosenberg[3], B.G. Redman[4], G.R. Hudes[5], R.M. Bukowski[6], S.T. Kim[7], I. Chen[7], G. Wilding[8], R.J. Motzer[9]. *[1]Duke University Medical Center, Surgery, Durham, USA; [2]Massachusetts General Hospital, Urology, Boston, USA; [3]University of California San Francisco, Medicine, San Francisco, USA; [4]University of Michigan, Internal Medicine, Ann Arbor, USA; [5]Fox Chase Cancer Center, Medical Oncology, Philadelphia, USA; [6]Cleveland Clinic Taussig Cancer Center, Experimental Therapeutics, Cleveland, USA; [7]Pfizer Inc., Global Research and Development, La Jolla, USA; [8]University of Wisconsin, Paul P. Carbone Comprehensive Cancer Center, Madison, USA; [9]Memorial Sloan-Kettering Cancer Center, Genitourinary Oncology Services, New York, USA*

Background: Sunitinib malate is an oral, multitargeted tyrosine kinase inhibitor of VEGFRs, PDGFRs, KIT, RET and FLT3 with antiangiogenic and antitumor activity. In a pivotal, multicenter phase II trial of sunitinib in pts with cytokine-refractory mRCC, 44% of pts achieved an investigator-assessed objective response rate (ORR) [Motzer et al., JAMA 2006; 295: 2516–24]. Sunitinib has also demonstrated statistically significant improvement in progression-free survival (PFS) and ORR in the first-line setting compared to interferon-alfa ($P < 0.001$) [Motzer et al., NEJM 2007; 356: 115–24]. Here we report the efficacy results, including overall survival (OS), for the pivotal phase II trial.
Methods: Pts with mRCC were enrolled in this trial from February through November 2004. Major eligibility criteria included clear-cell histology, prior nephrectomy, measurable metastases, and failure of 1 prior cytokine therapy due to progression. Sunitinib was administered 50 mg orally once-daily in 6-wk cycles (4 wks on, 2 wks off). The primary endpoint was ORR according to RECIST, as assessed by investigators and an independent, third-party laboratory (central review).
Results: Of 106 pts enrolled, 105 were evaluable for efficacy. Median age was 56 yrs (range: 32–79). The median duration of treatment was 9 mo (range: <1–36). ORR was 49% (95% CI: 39–58) by investigator assessment (including 1 complete response for >2 years) and 33% (95% CI: 24–43) by central review, with a median response duration of 14 mo (95% CI: 11–16). Median time to tumor progression and PFS were 11 mo (95% CI: 8–14) and 9 mo (95% CI: 8–13), respectively. The median OS was 24 mo (95% CI: 14–31), and 43 pts remain alive. The most common treatment-related grade 3 adverse events were fatigue (16%), hand–foot syndrome (12%), and stomatitis (7%). Grade 3 neutropenia was observed in 19% of pts, but was not associated with fever or sepsis. A treatment-related grade 3 decrease in left ventricular ejection fraction was reported in 5 pts (5%), but without clinical signs of congestive heart failure.
Conclusions: The results of this pivotal trial demonstrate the exceptional benefit of sunitinib therapy for pts with cytokine-refractory mRCC, with pt survival that compares favorably with historical experience in the second-line setting.

4518 POSTER

First-line bevacizumab improves progression-free survival with lower doses of interferon-α2a in the treatment of patients with metastatic renal cell carcinoma (AVOREN)

B. Melichar[1], P. Koralewski[2], A. Pluzanska[3], A. Ravaud[4], S. Bracarda[5], C. Szczylik[6], C. Chevreau[7], M. Filipek[8], N. Moore[9], B. Escudier[10]. *[1]University Hospital Hradec Králové, Oncology and Radiotherapy, Hradec Králové, Czech Republic; [2]Szpital im. Rydygiera, Krakow, Poland; [3]Klinika Chemioterapii AM, Lodz, Poland; [4]Hôpital Saint André, CHU Bordeaux, Medical Oncology and Radiotherapy, Bordeaux, France; [5]Azienda Ospedaliera, Medical Oncology, Perugia, Italy; [6]Wojskowy Instytut Medyczny, Oncology, Warsaw, Poland; [7]Institut Claudius-Regaud, Medical Oncology, Toulouse Cedex, France; [8]Szpital Wojewodzki im. Sw. Luk, Tarnow, Poland; [9]F.Hoffmann-La Roche, Basel, Switzerland; [10]Institut Gustave Roussy, Medicine, Villejuif, France*

Background: Bevacizumab (BEV, Avastin®) is a humanised monoclonal antibody targeted against vascular endothelial growth factor, the key mediator of tumour angiogenesis. In the first- and second-line treatment settings, BEV provides a clinical benefit to patients with metastatic renal cell cancer (mRCC). The efficacy and safety of BEV in combination with interferon (IFN)-α2a (Roferon®) in the first-line treatment of mRCC was evaluated in multicentre, randomised, double-blind, phase III trial (AVOREN).
Materials and Methods: Nephrectomised patients with clear cell mRCC, Karnofsky performance status ⩾70%, no CNS metastases and adequate organ function received IFN-α2a at a recommended dose of 9 MIU 3×/week plus BEV 10 mg/kg q2w or placebo until disease progression. Tumour assessments were performed every 8 weeks until week 32 and every 12 weeks thereafter. The protocol specified that during treatment, IFN-α2a administration was withheld with the development of a grade 3 adverse event (AE) attributable to IFN-α2a or other investigator reasons. If the reason for dose reduction did not resolve within the first 28 days, IFN-α2a could be restarted at a reduced dose of 6 MIU (3×/week). The dose of IFN-α2a was further reduced to 3 MIU (3×/week) with the development of a subsequent grade 3 AE due to an IFN-α2a-attributable or other event.
Results: Between June 2004 and October 2005, 649 patients were randomised (641 treated) at 101 centres in 18 countries. At the recommended dose of 9 MIU, duration of progression-free survival (PFS) was significantly longer in patients receiving IFN-α2a plus BEV (7.4 months [95% CI: 5.56−10.06]; n = 188) compared with placebo (3.8 months [95% CI: 3.68−5.16]; n = 215). The dose of IFN-α2a was reduced, according to the protocol, to 6 or 3 MIU in the IFN-α2a/BEV (n = 125) and IFN-α2a/placebo (n = 94) treatment groups. In patients who received a reduced dose of IFN-α2a, the duration of PFS was also significantly longer in the BEV (12.4 months [95% CI: 10.36−14.50]) versus placebo (7.7 months [95% CI: 5.59−9.24]).
Conclusions: The addition of BEV improved the duration of PFS in patients who received the recommended doses of IFN-α2a. IFN dose reduction to 6 or 3 MIU (as per protocol) had no impact on the efficacy of BEV.

4519 POSTER

Phase II study of sunitinib in patients (pts) with relapsed or refractory urothelial carcinoma (UC)

D.J. Gallagher[1], M.I. Milowsky[1], S.R. Gerst[2], A. Iasonos[3], M. Boyle[1], J. Riches[1], D.B. Bajorin[1]. *[1]Memorial Sloan-Kettering Cancer Center, Medicine, New York, USA; [2]Memorial Sloan-Kettering Cancer Center, Radiology, New York, USA; [3]Memorial Sloan-Kettering Cancer Center, Biostatistics, New York, USA*

Background: Second-line chemotherapy has limited activity in advanced UC. Pre-clinical evidence demonstrates an important role for angiogenesis in UC biology, thus supporting this study of the novel VEGF targeted agent, sunitinib, in pts with UC.
Materials and Methods: The primary objectives of this single institution phase II trial of sunitinib in pts with UC who have failed prior chemotherapy are: 1) to determine the response rate (RECIST); and 2) to evaluate toxicity. Prior therapy is restricted to ⩽4 chemotherapy drugs. Pts receive sunitinib 50 mg orally daily for 4 weeks followed by 2 weeks off (one cycle). Response is assessed after each of the initial 4 cycles and every other cycle thereafter. The Simon 2-stage design requires ⩾2 responses in the first 21 pts to proceed to maximal accrual of 41 evaluable pts.
Results: 28 pts (22 male, 6 female) with median age of 64 yrs (39−80) and median KPS of 80 (60−90) were enrolled between 9/15/06 and 04/12/07. Primary tumor sites include bladder (16 pts), ureter/renal pelvis (11 pts) and urethra (1). Prior therapy included 17 pts with 1 regimen, 8 with 2 and 3 with 3. 20 pts have metastatic visceral disease [lung (11), liver (8) and bone (1), prostate (1), adrenal (1)], and 8 pts have only lymph node metastases. To date, 23 pts are evaluable for radiographic response after completing at least one cycle of therapy; 4 pts did not complete 1 cycle of treatment and 1 is too early for assessment. One pt experienced a treatment-related death in the first cycle of therapy. Responses include: 2 PR, 8 with SD and 13 with POD. Radiographic regression has been observed in liver, lung, bladder, bone, soft tissue and lymph node metastases. Clinically significant toxicity (Grade 3/4) includes: lymphopenia (n = 7 pts), thrombocytopenia (5), anaemia (2), neutropenia (1), rash (3), infection (2), fatigue (2), anorexia (1), hematuria (1), mucositis (1), diarrhea (1), and abdominal pain (1), cardiac arrhythmia (1), hyponatremia (2), hyperglycaemia (1), hypophosphatemia (1).
Conclusion: Sunitinib has clinical activity in pts with advanced UC. Accrual is ongoing to define further the level of activity, the duration of response, and the time to progression.