survival (PFS) and objective response rate (ORR) over interferon alfa (11 vs. 5 mo and 47% vs. 12%, respectively; P < 0.000001) with a median overall survival of more than 2 years (26.4 mo) as first-line mRCC therapy in a randomized phase III trial (Figlin et al. ASCO '08). The purpose of the current multicenter phase II trial (clinicaltrials.gov: NCT00338884; sponsor: Pfizer) is to assess sunitinib, given at 37.5 mg on a continuous once-daily dosing schedule, in first-line mRCC patients.
Material and Methods: Treatment-naïve patients with histologically confirmed mRCC with a clear cell component were enrolled in this open-label, multicenter, phase II trial. Eligibility criteria include measurable disease, Eastern Cooperative Oncology Group performance status 0 or 1, and adequate organ function. Patients receive oral sunitinib 37.5 mg continuously once-daily in the morning without regard to meals. The primary endpoint is RECIST-defined objective response. A sample size of 120 patients is required to detect a 37% ORR with a 95% 2-sided confidence interval (CI) with a 9% half width.
Results: The study has completed enrollment with 120 patients of whom 119 have received treatment and are included in the safety analysis. The mean age is 57.5 years (range, 24−78), 76% are male and 42% Asian. As of March 2009, 34 of the 119 treated patients (29%) had completed 1 year of therapy per protocol and 7 (6%) remained on study; 78 patients (66%) had discontinued with 43 (36%) due to disease progression/relapse and 11 (9%) due to treatment-related adverse events (AEs). Median treatment duration was 22.4 weeks (range, 1.1−53.9). 37 of 115 efficacy evaluable patients had a partial response, yielding an ORR of 32.2% (95% CI: 23.8, 41.5). Median PFS was 9.2 months (95% CI: 7.2, 12.5). The most commonly reported grade 3/4 treatment-related AEs were hand-foot syndrome (13%), neutropenia (11%), anemia (8%), asthenia, diarrhea and thrombocytopenia (all 7%), and fatigue (6%).
Conclusions: Continuous once-daily dosing of sunitinib 37.5 mg shows activity with a manageable safety profile as first-line mRCC therapy. This is a feasible alternate dosing regimen in mRCC patients. A randomized phase II trial in mRCC patients comparing sunitinib 50 mg on schedule 4/2 vs. 37.5 mg continuous dosing has completed accrual with results expected in 2010.

7123 POSTER

First-line bevacizumab + reduced-dose interferon-alpha2a in patients (pts) with metastatic renal cell carcinoma (mRCC): an update on overall survival

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Background: The randomised, double-blind, phase III trial, AVOREN (BO17705F), demonstrated that bevacizumab (BEV, Avastin®) significantly improves duration of progression-free survival (PFS) when combined with interferon-alpha2a (IFN) in pts with untreated mRCC compared with IFN + placebo [Escudier, Lancet 2007]. A previous retrospective subgroup analysis showed that BEV + lower-dose (LD) IFN improved tolerability and maintained PFS [Melichar, Ann Oncol 2008]. We report overall survival (OS) and tolerability in this subgroup of pts based on longer follow-up from the final data cutoff for OS.
Methods: Between June 2004 and October 2005, 649 nephrectomised pts with clear cell mRCC were randomised to IFN at a recommended dose of 9 MIU 3×/week for up to 52 weeks + BEV 10 mg/kg q2w or placebo until disease progression. The protocol specified that IFN should first be withheld and the dose then lowered to 6 or 3 MIU for grade ⩾3 adverse events (AEs) attributable to IFN that did not resolve within 28 days or for other investigator-defined reasons.
Results: IFN dose was reduced in 131 and 97 pts in the BEV and placebo arms, respectively. Baseline characteristics, including MSKCC score, were similar in pts who reduced the dose of IFN compared with the overall population. Median OS in pts who received BEV + reduced doses of IFN (26.0 months) was consistent with the total BEV + IFN population (23.3 months). With longer follow up, no new safety signals were observed. A lower incidence of grade ⩾3 IFN-related events, including fatigue, asthenia, influenza-like illness, pyrexia and malaise, was observed during the 6 weeks after IFN dose reduction (18%) than during the 6 weeks prior to dose reduction (44%) in pts treated with BEV + reduced doses of IFN.
Conclusions: The OS benefit of BEV + reduced doses of IFN (median 26 months) is comparable to that of the overall BEV + IFN population. These data suggest that reducing the dose of IFN used in combination with BEV is an effective measure to manage toxicity and improve tolerability without compromising efficacy.
Trial sponsored by F. Hoffmann-La Roche, Ltd.

7124 POSTER

Association between time to disease progression (TDP) endpoints and overall survival (OS) in patients with metastatic renal cell carcinoma (mRCC)

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Background: The establishment of TDP endpoints (progression free survival [PFS], time to progression [TTP], or event-free survival) as valid surrogates for OS in pivotal studies in mRCC may expedite access to safe and effective novel therapies. Although the suitability of TDP endpoints as surrogates for OS has been established in other cancers, it has not been rigorously examined in patients with mRCC. We assessed the association between treatment effects on TDP endpoints and treatment effects on OS in controlled trials of patients with mRCC.
Materials and Methods: A systematic literature search was conducted (Medline, conference abstracts, references of retrieved studies/systematic reviews) to identify studies that met the following criteria: controlled trials in mRCC of IL-2, IFN-α, sunitinib, sorafenib, pazopanib, bevacizumab, temsirolimus, or everolimus; English language; publication date ⩾1997; median TDP (PFS or TTP) and OS reported for ⩾2 treatment groups or hazard ratios for TDP and OS reported for ⩾1 treatment comparison. For each treatment group comparison, treatment effects were measured in terms of differences in median failure times and relative risk reduction (RRRs) for TDP and OS. The associations between treatment effects on TDP and treatment effects on OS were analyzed using weighted ordinary least-squares (OLS) regression.
Results: A total of 28 studies representing 8,770 patients, 69 treatment groups, and 38 comparisons of median failure times or RRRs for TDP and OS were identified. The average difference in median TDP was 1.53 months (range: −1.1 to 7.13). The average difference in median OS was 2.76 months (range: −8.0 to 13.0) (Pearson correlation coefficient = 0.69). In weighted OLS regression, a 1-month increase in the difference in median TDP was associated with a 1.29-month increase in the difference in median OS ($P < 0.0001$, adjusted R-sq = 0.46). Each 10% increase in RRR for TDP was associated with a 4.2% increase in RRR for OS ($P = 0.0010$, adjusted $R^2 = 0.28$). The association between treatment effects on TDP and treatment effects on OS was strongest when TDP was measured by PFS, in studies that did not allow cross-over after disease progression, and in studies published before 2005.
Conclusion: Treatment effects on TDP endpoints are strongly associated with treatment effects on OS in controlled trials of treatments for mRCC.
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7125 POSTER

Tolerability and adverse events of sunitinib in Japanese patients with advanced renal cell carcinoma

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Background: Sunitinib is an oral, multitargeted tyrosine kinase inhibitor (TKI) that inhibits vascular endothelial growth factor receptor, platelet-derived growth factor receptor, stem cell factor receptor, and colony-stimulating factor-1 receptor. It has been suggested that efficacy and safety of TKIs may differ according to races. We evaluated the adverse events and tolerability of sunitinib in Japanese patients with metastatic renal cell carcinoma (mRCC).
Materials and Methods: Twenty-seven patients with mRCC who were treatment-naïve or previously treated with cytokine therapy or other TKI received sunitinib 50 mg/day in 6-week cycles (4 weeks on, then 2 weeks off treatment). The level and frequency of adverse events and the rate of patients that completed the first treatment course were evaluated.
Results: The most frequently occurring drug-related adverse event (any grade) was neutropenia (81.5%), followed by thrombocytopenia (70.4%), hypertension (59.3%), fatigue (59.3%), anemia (55.6%) and diarrhea (51.9%). Hypertension, Hypothyroidism (48.1%), hand-foot syndrome (48.1%) and rash (40.7%) occurred more frequently than reported in the phase III study conducted in Europe and America. The occurrence of grade 3 or 4 thrombocytopenia (44.4%) and neutropenia (33.3%) were also obviously frequent. Eighteen patients (66.7%) failed to complete the first four-week cycle of sunitinib because of drug-related adverse events;