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.
Acknowledgment: This study is supported by Novartis Pharmaceuticals Corporation.

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;

of these, thrombocytopenia and neutropenia occurred in fourteen patients (77.8%).
Conclusions: Japanese patients with mRCC treated with sunitinib (50 mg/day in 6-week cycles) frequently experienced severe levels of thrombocytopenia and neutropenia. Most patients were unable to tolerate the present dose and subsequently failed to complete the four-week because of drug-related adverse events. Dose modification of sunitinib may be required for tolerable treatment.

Adverse events	All grades	Grade 3 and 4 (%)
Neutropenia	81.5	33.3
Thrombocytopenia	70.4	44.4
Hypertension	59.3	18.5
Fatigue	59.3	11.1
Anemia	55.6	3.7
Diarrhea	51.9	3.7
Hypothyroidism	48.1	7.4
Hand-foot syndrome	48.1	7.4
Rash	40.7	

7126 POSTER

What is the impact of subsequent antineoplastic therapy on overall survival (OS) following first-line bevacizumab (BEV)/interferon-alpha2a (IFN) in metastatic renal cell carcinoma (mRCC)? – Experience from AVOREN

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Background: BEV (Avastin®) directly inhibits VEGF, the key mediator of angiogenesis. The phase III AVOREN trial (BO17705F) compared 1st-line BEV + IFN with IFN + placebo in patients (pts) with mRCC. The duration of OS, the primary endpoint, was increased in pts receiving 1st-line BEV + IFN compared with IFN + placebo (Escudier et al ASCO 2009). Given the recent availability of four new agents, sequencing of therapy in mRCC is of interest. We analysed OS data in subgroups of pts who received $\geqslant$1 dose of subsequent therapy following initial study medication.
Methods: Nephrectomised pts with clear cell mRCC, KPS of $\geqslant$70%, no CNS metastases and adequate organ function received IFN ($\times$3/week at a recommended dose of 9 MIU for up to 1 year) plus BEV (10 mg/kg q2w) or placebo until PD. Use of subsequent therapies was recorded and OS calculated in these subgroups.
Results: Between 06/04 and 10/05, 649 pts (641 treated) were randomised to BEV + IFN (n = 327) or IFN + placebo (n = 322). Post-protocol therapy was received by 180 (55%) pts in the BEV + IFN and 202 (63%) in the IFN + placebo arm; the majority (148 and 171) received 1 or 2 subsequent therapies. Pt characteristics, including MSKCC score, were similar in pts who received subsequent therapy and the overall population. The results of sequencing with different post-protocol therapies are shown below.

Median OS

	IFN + placebo (n)	BEV + IFN (n)	IFN + placebo (months)	Bev + IFN (months)	HR (95% CI)
All pts	322	327	21.3	23.3	0.86 (0.72–1.04)
TKI*	120	113	33.6	38.6	0.80 (0.56–1.13)
Sunitinib*	92	83	39.7	43.6	0.88 (0.58–1.35)
Sorafenib*	50	60	30.7	38.6	0.73 (0.44–1.20)
2nd-line TKI**	81	96	33.2	38.6	0.77 (0.51–1.15)

*Subsequent therapy defined as more than one treatment given as post-protocol therapy, any line; **2nd-line TKI therapy given for one-line only immediately after study therapy

Conclusions: Although the AVOREN trial was not designed to examine the effect of 2nd-line therapy on OS, this retrospective exploratory analysis suggests a potential improvement in OS (greater than 30 months) in pts who receive BEV + IFN followed by subsequent therapies such as TKIs. The overall sequence of therapies should be considered when selecting 1st-line therapy for pts with mRCC, but prospective studies are required to confirm these findings.
Trial sponsored by F. Hoffmann-La Roche, Ltd.

7127 POSTER

Results from additional analyses of patient reported outcomes in RECORD-1 – a randomized trial of everolimus with metastatic renal cell carcinoma patients

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Background: Phase III trial of everolimus in metastatic renal cell carcinoma (mRCC) patients demonstrated reduced risk of disease progression or death compared to placebo (hazard ratio [HR] = 0.33, 95% confidence interval [CI] = 0.25−0.43, p < 0.001). Patient-reported outcomes (PRO) were also assessed in this trial. Main results, in terms of time to deterioration compared between groups of patients defined by best overall response, were analyzed and presented previously.
Materials and Methods: Patients with mRCC were randomized (n = 416) to receive everolimus or placebo plus best supportive care. Patients completed the FACT-Kidney Symptom Index-Disease Related Symptoms (FKSI-DRS) and EORTC-QLQ C30 at baseline and monthly during treatment. Deterioration was defined as a decrease from baseline of at least 3 points for FKSI-DRS and at least 10% for EORTC Physical Function (PF) and Global Quality of Life (QL) scales. This analysis considered as deterioration events a composite end-point including tumor progressions or deaths occurring prior to deterioration or censoring date. The impact of baseline and early changes in PRO scores on progression-free survival (PFS) was evaluated. Comparisons were made using stratified log-rank tests and Cox proportional hazard models.
Results: Regardless of treatment arm, patients whose tumors did not progress on study experienced delayed time to deterioration, compared to patients whose tumors did progress, in FKSI-DRS (HR = 0.41, 95% CI = [0.27, 0.63]; p < 0.001) and QL (HR = 0.68, 95% CI = [0.47, 0.97]; p = 0.033) scores. This comparison was not statistically significant for PF scores (HR = 0.69, 95% CI = [0.47, 1.01]; p = 0.053). For the composite endpoint a 55% risk reduction for progression or deterioration in FKSI-DRS was observed for the everolimus arm compared to placebo (HR = 0.45, 95% CI = [0.33, 0.61]; p < 0.001). A similar benefit was observed for PF (HR = 0.54, 95% CI = [0.40, 0.73]; p < 0.001) and QL (HR = 0.57, 95% CI = [0.42, 0.77]; p < 0.001). Baseline PRO scores were not predictive of PFS. However, patients whose FKSI-DRS scores worsened by at least 3 points during the first month had significantly shortened PFS compared to patients whose scores improved or remained stable (p = 0.021). Early changes in PF or QL were not predictive of PFS.
Conclusions: Compared to placebo, everolimus delayed progression of disease-related symptoms. The PFS benefit demonstrated for everolimus is associated with a corresponding delay in the worsening of symptoms.

7128 POSTER

PREDICT (Patient characteristics in Renal cell carcinoma and Daily practice Treatment with Nexavar) global non-interventional study: first interim results

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Background: Sorafenib was shown to be effective for the treatment of metastatic renal cell carcinoma (mRCC) in randomized controlled trials (RCT). Because pts treated under daily-practice conditions have heterogeneous characteristics that may differ from RCT populations, the PREDICT (Patient characteristics in RENal cell carcinoma and Daily practICe Treatment with Nexavar) non-interventional study was undertaken to record baseline characteristics of mRCC pts and their potential influence on the efficacy and safety of sorafenib in community practice settings. PREDICT is ongoing in 14 countries throughout Europe, Latin America, and Asia, and thus encompasses a broad multi-ethnic population. Results of the first analysis (cutoff: Feb 25, 2009) categorizing the baseline characteristics and adverse events (AEs) of this population are compared to those in the pivotal Phase 3 TARGET study (Escudier, *N Engl J Med* 2007).
Methods: Clinicians follow mRCC pts, for whom they have prescribed sorafenib, for the length of therapy, up to 12 months. Baseline characteristics are recorded and at pts' normally scheduled follow-up visits, tumor status, pt status, and adverse events (AEs) are noted.