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A Randomized Phase 2 Study of Axitinib Dose Titration in Patients With Advanced Renal Cell Carcinoma (RCC): Preliminary Pharmacokinetic and Ambulatory Blood Pressure (BP) Monitoring Results

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Background: Axitinib is a potent, selective, second-generation inhibitor of VEGFR-1, 2, and 3. Previous studies indicate that axitinib drug plasma exposure and treatment-emergent diastolic BP (dBP) $\geqslant$90 mmHg are independently associated with efficacy. It is hypothesized that in a subset of patients (pts) who tolerate the standard 5 mg BID starting dose, subsequent dose titration may increase plasma exposure and improve efficacy. As a part of a double-blind, placebo-controlled, randomized phase 2 study that prospectively evaluated the safety and efficacy of axitinib dose titration from 5 mg twice daily (BID) to a maximum of 10 mg BID in pts with advanced RCC, this analysis compares axitinib exposure and BP profile in pts who were eligible for titration to those not eligible for titration.
Methods: All pts initially received the lead-in axitinib dose of 5 mg BID for 4 weeks. Pts with BP $\leqslant$150/90 mmHg, no grade 3/4 axitinib-related toxicities, no dose reduction, and $\leqslant$2 antihypertensive medications during the lead-in period (Group 1) were randomized to receive axitinib 5 mg BID plus dose titration with either axitinib or placebo. The remaining pts who were not eligible for dose titration (Group 2) continued with axitinib $\leqslant$5 mg BID. In a subset of pts, 24-hr ambulatory BP monitoring was performed at baseline, Day 4, and Day 15, as well as serial pharmacokinetic sampling on Day 15 of the lead-in period, prior to randomization to dose titration or not.
Results: Preliminary analyses of data obtained prior to the decision of dose titration showed that the mean axitinib drug exposure was lower for Group 1 (AUC_{24}=198 ng·h/mL; n = 28) compared to Group 2 (AUC_{24}=467 ng·h/mL; n = 23) ($P < 0.0001$, unpaired t-test). Mean systolic BP (sBP) was also lower for Group 1 (130 mmHg) versus Group 2 (141 mmHg); similar BP trends were observed for dBP and mean change in dBP from baseline (ΔdBP).
Conclusions: Pts eligible for dose titration had lower axitinib plasma exposures and lower mean BP while receiving the starting axitinib dose compared to pts not eligible for dose titration. Thus, the clinical parameters for dose titration may be useful for selecting pts with low axitinib plasma exposures for whom drug exposure may be optimized through dose titration.

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Phase II Trial of the Oral Multikinase Inhibitor Regorafenib (BAY 73–4506) as First-line Therapy in Patients With Metastatic or Unresectable Renal Cell Carcinoma (RCC)

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Background: Regorafenib (BAY 73–4506) is a novel oral multikinase inhibitor of angiogenic (VEGFR1−3, TIE2), stromal (PDGFR-β, FGFR), and oncogenic kinases (KIT, RET, RAF). In preclinical models, regorafenib has shown a broad spectrum of antitumour activity. Regorafenib 160 mg once daily (o.d.) in repeating cycles of 3 weeks on/ 1 week off was determined as recommended dose. Regorafenib was investigated in a multicenter, open-label, Phase II study in previously untreated patients with metastatic or unresectable RCC (ClinicalTrials.gov ID: NCT00664326, sponsored by Bayer). Data presented here are updates of previously presented efficacy and safety data.
Methods: Patients ($\geqslant$ 18 years old) with previously untreated, unresectable or metastatic, predominantly clear cell RCC were enrolled. Other inclusion criteria were ECOG performance status 0−1, low/intermediate risk (MSKCC score), measurable disease according to RECIST v1.0, and adequate bone marrow and organ function. Treatment consisted of regorafenib 160 mg o.d. on a 3 weeks on/ 1 week off schedule. Study objectives were evaluation of antitumour response and safety. The primary efficacy end point was response rate (RECIST).
Results: Patient accrual was completed in October 2008 and as of February 2011, 49 patients (27 male, 22 female; median age 62 years [range 40−76]) received $\geqslant$1 dose of regorafenib. Of 48 evaluable patients, confirmed partial response was observed in 40% and stable disease in 42% of patients. Median duration of response was 17.6 months (n = 19); median progression-free survival was 11.0 months (ITT population, n = 49). All patients were evaluable for safety. Common treatment-related adverse events (AE) ($\geqslant$25% of patients, all grades) were hand-foot skin reaction (HFSR) 71%, fatigue 53%, hypertension 51%, alopecia 45%, diarrhea 45%, mucositis (symptomatic) 43%, rash 39%, voice changes 35%, anorexia 29% and nausea 27%. Grade 3/4 treatment-related AEs ($\geqslant$5% of patients) were HFSR 33%, diarrhea 10%, renal failure 10%, fatigue 8%, hypertension 8%, rash 6%, anorexia 6%, hyponatremia 6% and lipase increase 6%. Renal failure occurred only in patients who continued taking study medication despite inadequate fluid intake and/or diarrhea. Eight (16%) patients remain on treatment.
Conclusions: These data demonstrate substantial antitumour activity of regorafenib as first-line treatment of patients with metastatic/unresectable clear cell RCC. AEs were typical of the drug class and were manageable.

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Toxicity and Use of Granulocyte Colony-stimulating Factor Prophylaxis in a Randomized Phase II Trial of Intensive Induction Chemotherapy (CBOP/BEP) and Standard BEP in Poor Prognosis Germ Cell Tumours (MRC TE23, CRUK 05/014, ISRCTN53643604)

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Background: Up to 50% of patients with advanced metastatic non-seminoma will die. BEP (bleomycin, etoposide and cisplatin) chemotherapy has remained standard for many years, but several trials now suggest a possible benefit from treatment intensification. One of these was a randomized phase II trial evaluating a new intensive chemotherapy regimen, CBOP/BEP, whilst also establishing current BEP response rates (RR). Primary results have been presented. Here, we consider toxicity and use of granulocyte colony-stimulating factor (GCSF).
Materials and Methods: Patients with IGCCCG poor prognosis characteristics were randomized to standard 4xBEP (12 weeks (Wks)) or CBOP/BEP (Wks 1 and 3: Cisplatin 50 mg/m^2 D1&2; vincristine 2 mg D1; bleomycin 15000iu D1. Wks 2 and 4: cisplatin 40 mg/m^2, vincristine 2 mg, carboplatin AUC3, all D1; bleomycin 15000iu D1−5. Wks 5 and 6: vincristine 2 mg D1; bleomycin 15000iu D1. Wks 7−15 3xBEP with bleomycin 15000iu weekly). Outcomes were RR (primary), toxicity, progression-free survival (PFS) and overall survival. 60% favourable RR was anticipated with BEP. Assuming 80% RR with CBOP/BEP, 44 patients were needed to exclude a RR < 60% with 90% power (1-sided $\alpha = 5\%$). An equal number were randomised to BEP to benchmark the RR but the trial was not powered to compare arms. GCSF prophylaxis, initially optional, became mandatory in both arms mid-way through the study (data monitoring committee recommendation).
Results: From 2005 to 2009, 89 patients (43 CBOP/BEP) were randomized; all have >6 (median 33) months follow-up. 50 received GCSF prophylaxis (from wks 1−2 BEP, wks 5−6 CBOP/BEP). 81 (40 CBOP/BEP) completed treatment. CBOP/BEP toxicity, largely haematological, was high (95% had CTC grade $\geqslant$3, 63% BEP). Neutropenic sepsis occurred in 30% CBOP/BEP and 15% BEP, similar regardless of use of GCSF prophylaxis. Pulmonary toxicity was similar in the two arms (grade $\geqslant$3 in 9% CBOP/BEP, 7% BEP). Sensory neuropathy was more common with CBOP/BEP but was grade $\leqslant$2 in all but one patient. RRs were 74% with CBOP/BEP, 61% with BEP (90% CIs (61%, 85%) and (48%, 73%)). 1-year PFS was 65% and 43% respectively (hazard ratio 0.6, 95% CI (0.33, 1.07)).
Conclusions: The trial met its primary outcome with a 90% CI for CBOP/BEP excluding RRs <61%, and supportive PFS data. CBOP/BEP was more toxic than BEP, particularly in terms of haematological toxicity and there was no clear impact of GCSF prophylaxis on rates of neutropenia, although an impact on the duration of such events cannot be ruled out. In choosing between different approaches to treatment intensification, toxicity and cost considerations will be important.