7104 ORAL

Targeted agents in metastatic Xp11 Translocation/TFE3 gene fusion renal cell carcinoma (RCC): a report from the Juvenile RCC Network

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Purpose: Xp11 translocation renal cell carcinoma is a recently recognized subtype of renal cell carcinoma (RCC), which comprises 15% of RCC patients younger than ages 45 years. The benefit of vascular endothelial growth factor (VEGF)-targeted agents and m-TOR inhibitors in metastatic patients remains unknown.
Patients and Methods: Among patients who had Xp11 translocation/TFE3 fusion gene translocation RCC, we retrospectively identified metastatic patients who where treated with VEGF-targeted agents and/or m-TOR inhibitors. Pathology slides were reviewed to confirm the status of TFE3 nuclear immunostaining. Response according to RECIST criteria, progression-free survival (PFS) and overall survival (OS) were analyzed.
Results: Among 53 identified patients, 21 out of 23 metastatic patients were eligible for the study. Median age of patients was 34 years (range, 2−45 years) and sex ratio was approximately 1:1. The overall objective response for VEGF-targeted agents and m-TOR inhibitors was 38%. In first-line setting, 11 patients received sunitinib, and 9 patients cytokine-based regimens; the median PFS were 8.2 months and 2 months, respectively ($p = 0.003$). Beyond first line setting, patients were treated with sunitinib (22%), sorafenib (39%), or m-Tor inhibitors (39%). All patients treated with sunitinib had partial response with a median PFS of 11 months (range, 5−15+ months). Six out of 7 patients treated with sorafenib had stable disease with a median PFS of 7 months (range, 3−29+ months). For m-Tor inhibitors, one patient had a prolonged partial response and 6 patients had a stable disease with a median PFS of 3 months (range, 3−15 months). With a median follow-up of 16 months, median overall survival was 30 months (range, 12−52 months).
Conclusions: Patients who had metastatic Xp11 translocation/TFE3 fusion gene display an aggressive disease. VEGF-targeted agents and m-Tor inhibitors achieved objective responses and prolonged PFS that appear similar to those reported in clear-RCC histology.

7105 ORAL

Phase II trial of the oral multikinase inhibitor BAY 73−4506 as 1st-line therapy in patients with metastatic or unresectable renal cell cancer (RCC)

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Background: Tyrosine kinase inhibitors have considerably changed the treatment of RCC, and several new agents are being evaluated in the search for improved therapy options. BAY 73−4506 is a potent, oral multikinase inhibitor targeting angiogenic, stromal, and oncogenic receptor tyrosine kinases (eg VEGFR, TIE2, PDGFR, FGFR, KIT, and RET). Following promising results in preclinical tumor xenograft models and in a Phase I study (3 weeks on/1 week off schedule), BAY 73−4506 is being investigated in a multicenter, open-label, Phase II study in previously untreated patients with metastatic or unresectable RCC (ID 11726; sponsor Bayer Schering Pharma AG).
Methods: Adult patients with previously untreated, unresectable, or metastatic, predominantly clear-cell RCC were enrolled. Other inclusion criteria were Eastern Cooperative Oncology Group performance status 0−1, low or intermediate risk (Motzer score), measurable disease according to RECIST (Response Evaluation Criteria In Solid Tumors), and adequate bone marrow and organ function. Treatment consisted of BAY 73−4506 160 mg once daily on a 3 weeks on/1 week off schedule. Study objectives were evaluation of antitumor response and safety. The primary efficacy end point was response rate (RECIST).
Results: Patient accrual was completed in October 2008 and as of April 2009, 49 patients (27 male, 22 female; median age 62 years [range 40−76]) have received $\geqslant$1 dose of BAY 73−4506. Of 48 patients evaluable for efficacy, preliminary data indicate a partial response (PR) in 33% (23% confirmed PR) and stable disease in 46% of patients. All patients were evaluable for safety. Common treatment-related adverse events (AE) ($\geqslant$20% of patients, all grades) were hand-foot skin reaction (HFSR) 61%, fatigue 51%, mucositis 45%, hypertension 41%, rash 35%, alopecia 33%, diarrhea 31%, voice changes 29%, and anorexia 24%. Grade 3/4 treatment-related AEs ($\geqslant$5% of patients) were HFSR 18%, fatigue 10%, hypertension 6%, rash 6%, anorexia 6%, and renal failure 6%. Renal failure occurred in patients who continued taking study medication despite having inadequate fluid intake and/or diarrhea. Twenty-six patients remain on treatment.
Conclusions: Current data indicate promising antitumor activity of BAY 73−4506 as 1st-line treatment of patients with metastatic or unresectable RCC. AEs were typical of the drug class and were manageable.

7106 ORAL

Predictive and prognostic factors in a phase III study of pazopanib in patients with advanced renal cell carcinoma (RCC)

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Background: Pazopanib, an oral multikinase angiogenesis inhibitor, has shown clinical efficacy in patients (pts) with advanced RCC. Efficacy and safety of pazopanib was evaluated in a Phase III double blind, placebo-controlled study (VEG105192; NCT00334282; GSK), in pts with advanced RCC. Pazopanib demonstrated a significant improvement in the ITT population in progression-free survival (PFS) vs placebo in the overall study population (9.2 vs 4.2 mos; HR 0.40: $p < 0.0000001$), in the treatment naïve subgroup (11.1 vs 2.8 mos; HR; 0.40; $p < 0.0000001$), and in the cytokine-pretreated subgroup (7.4 vs 4.2 mos; HR: 0.54; $p < 0.001$) [ASCO 2009; #5021]. The current analysis investigated prognostic factors for efficacy in RCC pts who received pazopanib.
Methods: Patients ($N = 435$) with clear cell advanced RCC, measurable disease, and no prior treatment or 1 prior cytokine-based treatment, were stratified and randomized (2:1) to pazopanib 800 mg QD or placebo. The primary endpoint was PFS. Secondary endpoints included overall survival, response rate (RR) and safety. Hazard ratios comparing pazopanib to placebo and log rank tests within the pazopanib arm were calculated for subgroups defined based on hemoglobin (Hgb), age, sex, MSKCC risk group, ECOG PS, number of disease sites, and time from initial diagnosis to treatment. RRs were compared using Fisher's exact test.
Results: PFS treatment effects consistent with the ITT analysis were observed in all subgroups. Within the pazopanib arm, higher RRs were observed in pts with MSKCC favorable vs intermediate (42.5% vs 33.3%, $p = 0.1$), ECOG PS 0 vs 1 (43.9% vs 29.3%, $p = 0.013$), hemoglobin $\geqslant$ lower limit of normal (LLN) vs < LLN (41.0% vs 29.1%, $p = 0.037$) and time from diagnosis to treatment >1 vs $\leqslant$ 1 year (40.0% vs 28.8%, $p = 0.068$). Median PFS was significantly longer for pazopanib-treated pts with MSKCC favorable vs intermediate risk (14.8 vs 5.6 mos, $p = 0.0002$); ECOG PS of 0 vs 1 (14.8 vs 7.4 mos, $p = 0.0287$); Hgb $\geqslant$ LLN vs 1 vs $\leqslant$ year (12.9 vs 7.4 mos, $p = 0.0289$).
Conclusions: MSKCC favorable risk category, ECOG PS 0, hemoglobin $\geqslant$ LLN, number of disease sites 1−2 and time from diagnosis to treatment >1 year were significantly correlated with a longer PFS. With the exception of the number of disease sites, these factors also predict for a higher RR.