

Tracking Trends From Web-based Sources, Translational Research, the FDA, and Patient Registries

FDA Grants Fast Track to RENCAREX[®] for

Adjuvant Therapy of Clear Cell Renal Cell Carcinoma

MUNICH—WILEX AG has announced that RENCAREX[®] has been granted Fast Track designation by the FDA. The drug is undergoing the pivotal phase 3 trial ARISER (Adjuvant RENCAREX Immunotherapy trial to Study Efficacy in non-metastasised Renal cell carcinoma) for the adjuvant treatment of patients with non-metastatic clear cell renal cell carcinoma (ccRCC) at high risk of relapse after surgery. WILEX has signed a licencing agreement for RENCAREX[®] with US partner Prometheus Laboratories.

"We are pleased with this decision from the FDA. No drug has been approved to date by the FDA or EMA [European Medicines Agency] for the adjuvant therapy of non-metastatic ccRCC. RENCAREX[®] was granted Orphan Drug status in the United States and in Europe and is of major relevance for those patients with this aggressive type of cancer," said Paul Bevan, PhD, Head of R&D and Member of the Executive Management at WILEX AG.

RENCAREX[®] is based on the antibody girentuximab, which binds to the tumor-specific antigen CA IX an antigen overexpressed in ccRCC. The therapeutic antibody makes the tumor visible to the endogenous immune system, recruiting natural killer cells that can destroy any existing cancer cells. RENCAREX[®] should inhibit the further growth and recurrence of ccRCC. ARISER is an international, multi-center, randomized phase 3 trial that examines the efficacy of the antibody RENCAREX[®] in comparison to placebo in the treatment of ccRCC patients following complete or partial surgical removal of the affected kidney in patients with no detectable metastases.

The ARISER trial involves 864 patients, who received the study medication in once-weekly infusions over a period of 24 weeks. The last patient completed treatment in February 2009. Following the occurrence of the 100th relapse, the first interim analysis for futility was carried out in late 2007. The Independent Data Monitoring Committee (IDMC) recommended that the trial be continued because it will probably deliver a significant result. The process of the interim analysis for efficacy has been started in the first quarter of 2011.

Early Blood Test Stratifies Renal Cell Carcinoma Patients for Progression-Free Survival on 2 Therapies

BROOMFIELD, CO—Data presented at the 10th International Kidney Cancer Symposium in Chicago showed that the pretreatment blood-based test, VeriStrat, was able to stratify patients with renal cell carcinoma (RCC) treated with a combination of 2 targeted therapies, sunitinib (Sutent[®]) and erlotinib (Tarceva[®]), by survival outcomes. Patients who tested VeriStrat Good had significantly longer progression free survival (PFS) and overall survival

(OS) when treated with the combination therapy compared with patients who tested VeriStrat Poor.

The study retrospectively, and in a fully blinded fashion, applied the VeriStrat test to a subset of the patient population from a phase 1/2 clinical trial of erlotinib plus sunitinib in RCC patients. VeriStrat analysis was performed on all available serum samples. Thirty-seven of 46 patients were classified as either VeriStrat Good or VeriStrat Poor based on the VeriStrat algorithm developed for non-small cell lung cancer.

VeriStrat Good patients had a significantly longer PFS and OS versus VeriStrat Poor patients (PFS: median 12.3 vs 4.7 months, and OS: median 38.4 vs 11.6 months). There was a statistically significant correlation between VeriStrat classification and Heng prognostic criteria, but not MSKCC (Memorial Sloan Kettering Cancer Center) classification. VeriStrat showed the potential to further refine current grouping of RCC patients, separating MSKCC intermediate patients into VeriStrat Good and VeriStrat Poor subgroups with statistically significantly different PFS (log-rank $P = .030$).

Heinrich Roder, PhD, Chief Technology Officer of Biodesix said, "This data set shows that our test, VeriStrat, may be helpful in identifying specific and useful disease characteristics in RCC. It is also exciting to see that our test is showing utility across multiple solid tumors. Oncologists currently do not have a simple serum test that can be used across multiple tumor types. We are continuously engaging in additional studies to further explore the full clinical utility of VeriStrat."

Abstracts from the European Society of Medical Oncology and the European Multidisciplinary Cancer Congress, Stockholm, September 23-27, 2011

The European Multidisciplinary Cancer Congress reported an attendance of almost 16,000 from 116 countries, according to the European Society of Medical Oncology (ESMO). Notable abstracts in RCC included the following.

Abstract 7103

Escudier B, Loomis AK, Kaprin A, et al. Association of Single Nucleotide Polymorphisms in VEGF Pathway Genes With Progression-Free Survival and Blood Pressure in Metastatic Renal Cell Carcinoma in the Phase 3 Trial of Axitinib Versus Sorafenib (AXIS Trial)

In the randomized, open-label, phase 3 AXIS trial in second-line metastatic renal cell carcinoma (mRCC; clinicaltrials.gov NCT00678392), axitinib demonstrated a statistically significant improvement in progression-free survival (PFS) compared with sorafenib (median 6.7 vs 4.7 months; hazard ratio 0.665, $P < .0001$). This study also explored potential associations between germline single nucleotide polymor-

(continued on page 93)

MEDICAL INTELLIGENCE

(continued from page 82)

phisms (SNPs) in VEGF pathway and genes with PFS and blood pressure (BP)-related endpoints.

DNA samples (n = 263, 36% of patients) from blood were genotyped using Taqman allelic discrimination. Potential associations between SNPs in VEGF pathway genes (*VEGF-A*, *VEGFR1*, *VEGFR2*, *HIF1*) and PFS were evaluated in the white subpopulation only (n = 249), as well as between SNPs in *VEGF-A*, *VEGFR1*, and *VEGFR2* with hypertension (Grade 3 or greater) and high BP (at least one diastolic BP [dBP] reading of ≥ 90 mmHg).

Differences in PFS were seen with *VEGF-A* SNPs rs1570360 (adjusted $P = .127$; Cox regression interaction test), rs699947 ($P = .058$), and rs833061 ($P = .058$). Log-rank tests indicated that potential associations between PFS and genotype for these 3 SNPs are driven more by differences in PFS among genotypes in the axitinib arm than in the sorafenib arm. For example, the median PFS for *VEGF-A* rs699947 A/A in axitinib-treated patients was 52 weeks (vs 28 weeks for other genotypes; adjusted $P = .16$), while no difference in PFS among these genotypes was noted in sorafenib-treated patients (adjusted $P = .95$). After adjusting for multiple testing, no statistically significant correlations were observed between SNPs and hypertension or high dBP using logistic regression analysis.

Three *VEGF-A* SNPs were potentially associated with PFS. None of the VEGF pathway SNPs examined was associated with axitinib-related hypertension or dBP. These results support previously reported associations of

rs1570360 and rs699947 with overall survival in a trial of a bevacizumab-based regimen (Schneider et al. *J Clin Oncol*. 2008;26:4672), and association of germline SNPs with efficacy for pazopanib (Xu et al. *ASCO GU*. 2011:303). These exploratory data suggest that specific SNPs might help to explain some of the observed interpatient variability in PFS for the RCC patients who received axitinib therapy. Moreover, germline SNPs might be important tools in the future to guide selection of VEGF

Abstract 1006

Motzer RJ, Escudier B, Bukowski R, et al. Prognostic Factors for Progression-Free Survival, Overall Survival), and Long-Term Overall Survival With Sunitinib in 1059 Patients, Treated on Clinical Trials, With Metastatic Renal Cell Carcinoma

With the advent of multiple targeted therapies for metastatic renal cell carcinoma (mRCC), further information on factors that affect prognosis facilitates both clinical decision making and trial design for evaluation of new therapies. The researchers report on a retrospective analysis of prognostic factors for progression-free survival (PFS), overall survival (OS) and long-term overall survival (LT-OS) of at least 30 months in patients with mRCC treated with sunitinib in 6 clinical trials (NCT00054886, NCT00077974, NCT00083889, NCT00338884, NCT00137423, NCT00267748; Pfizer).

Analyses used pooled data from 1059 patients treated with single-agent sunitinib on the approved 50 mg/day 4-week-on/2-week-off schedule (n = 689; 65%) or 37.5 mg continuous once-daily dosing (n = 370; 35%), in the first-

(n = 783; 74%) or second-line (n = 276; 26%) setting. Baseline variables were analyzed for prognostic significance using a Cox proportional hazards model, with each factor investigated in univariate and then multivariate analyses using a stepwise algorithm.

Multivariate analysis of PFS and OS identified 9 and 10 independent predictors, respectively (Table, below). Overall, 215 patients (20%) survived at least 30 months. An analysis of baseline characteristics of these long-term survivors showed differences between these patients and non-long-term survivors, including risk status based on the published Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic criteria (Motzer, 2002; $P < .0001$). For example, 70% of the long-term survivors had favorable risk

features compared with 31% of non-long-term survivors. In contrast, 42% and 5% of the non-long-term survivors had intermediate and poor risk features compared with 28% and 0% of long-term survivors, respectively. Additional characteristics associated with LT-OS will be presented.

These analyses validated use of clinical risk factors previously reported from MSKCC (*J Clin Oncol.* 2002;20:286) and by Heng and colleagues (*J Clin Oncol.* 2009;27:5794). These factors were predictive for shorter PFS as well. In addition, patients with bone metastases had shorter OS to sunitinib. Favorable MSKCC risk status was associated with higher likelihood of achieving LT-OS. Continued progress requires incorporation of RCC tumor-specific biology. **KCJ**

Variable	PFS HR (95% CI)	P-value ^a	OS HR (95% CI)	P-value ^a
Ethnic origin (white vs non-white)	0.598 (0.459, 0.781)	.0002	0.730 (0.535, 0.996)	.0474
ECOG PS ^b (≥ 1 vs 0)	1.250 (1.043, 1.498)	.0159	1.505 (1.218, 1.859)	.0002
Time from diagnosis to treatment [†] (≥1 vs <1 year)	0.814 (0.680, 0.975)	.0252	0.666 (0.541, 0.820)	.0001
Bone metastases (yes vs no)	-	-	1.535 (1.250, 1.886)	< .0001
Baseline hemoglobin ^b (≤ LLN vs > LLN)	1.384 (1.144, 1.675)	.0008	1.548 (1.245, 1.925)	< .0001
Baseline lactate dehydrogenase ^b (> 1.5xULN vs ≤ 1.5xULN)	1.664 (1.201, 2.305)	.0022	1.571 (1.103, 2.238)	.0123
Baseline corrected calcium ^b (> 10 vs ≤ 10 mg/dL)	1.374 (1.080, 1.747)	.0096	2.208 (1.722, 2.832)	< .0001
Baseline neutrophils (≤ ULN vs > ULN)	0.629 (0.483, 0.821)	.0006	0.681 (0.508, 0.915)	.0107
Baseline platelets (≤ ULN vs > ULN)	0.607 (0.469, 0.785)	.0001	0.670 (0.505, 0.889)	.0055
Prior cytokine (yes vs no)	1.342 (1.085, 1.659)	.0066	1.387 (1.094, 1.759)	.0068

^aWald Chi-Square Test; ^bFactor included in MSKCC prognostic model.