

SELECT Shows Best Candidates for High Dose IL-2 Treatment

Clear cell histology may help select renal cell carcinoma (RCC) patients likely to respond to high-dose aldesleukin (HD IL-2) treatment, according to results of the SELECT trial, conducted by the Cytokine Working Group. Patients with metastatic or unresectable, histologically confirmed clear cell RCC had a 30% major response rate to HD IL-2 which is significantly greater than the historical 14% major response and durable remission rate seen in the phase 2 trials that led to FDA approval of the agent in 1992.

"We anticipate that from this trial, we will improve patient selection to ensure that more patients who would respond can actually receive treatment," said lead investigator David McDermott, MD, Department of Cell Biology, Harvard School, Boston, MA. "We don't want to treat more patients with IL-2. Our goal is to treat more responders to IL-2."

SELECT was a multicenter, prospective study including 128 adults with RCC enrolled between November 2007 and July 2009. All had histologically confirmed RCC, an Eastern Cooperative Oncology Group Performance Status (ECOG PS) Scale score of 0 or 1 and adequate organ function. Patients provided archived tumor tissue for risk classification by pathology, carbonic anhydrase IX staining, and tissue microarray. At baseline, 99% had undergone prior nephrectomy, 96% had clear cell histology, 72% had an ECOG PS score of 0, and 71% were classified as intermediate risk on the Memorial Sloan-Kettering Cancer Center (MSKCC) scale. Patients received up to 28 doses of intravenous HD IL-2 at 600,000 U/kg every 8 hours on days 1 to 5 and days 15 to 19 every 12 weeks.

A major response was seen in 35 of the 120 evaluable patients and included 7 patients with complete remission (CR) and 28 with a partial response for a major response of 29% which was significantly better than the historical 14% major response rate (95% confidence interval [CI] = 21%-38%, $P = .0009$). Twenty patients continued to be responders (4 to 35 months) and progression free survival (PFS) was 4.4 months. A major response was observed in 35 of the 115 patients with clear cell histology for a response rate of 30% (95% CI = 22%-40%, $P = .004$). However, there was no response to HD IL-2 among the 5 patients with non-clear cell histology, 8 patients with a high UCLA Survival After Nephrectomy and Immunotherapy score.

There were no unanticipated treatment toxicities and 2 treatment-related deaths during the study. Dr. McDermott said that tumor analysis and blood based predictive markers from patients participating in the SELECT study is ongoing and may further improve the selection of patients most likely to respond to treatment with HD IL-2.

Temsirolimus, Bevacizumab Combination Fails in Phase 2 Trial

Combining the standard treatment agents temsirolimus and bevacizumab does not increase efficacy and significantly raises toxicity when used as first line treatment in patients with metastatic RCC. Although full doses of each agent were used in combination in a phase 1 trial with promising results, this contrasting data from the phase 2 TORAVA trial caused ASCO attendees to question the continuation of a similar, nearly complete phase 3 study using the combination.

"Based on this phase 2, the combination cannot be recommended for first line metastatic kidney cancer patient treatment," said Bernard Escudier, MD, Immunotherapy Unit, Institut Gustave Roussy, Villejuif, France. "There is a large phase 3 ongoing that might change our feeling but the chance of positive phase 3 results is obviously low." Dr. Escudier added that had the phase 2 results been known at the time, the phase 3 trial would have been designed differently.

TORAVA was an open label, noncomparative trial including 171 untreated patients with metastatic RCC, an ECOG PS of 0 to 2 with measurable disease. Patients with papillary renal cancer were excluded. They were randomized 2:1:1 to receive temsirolimus 25 mg intravenously (IV) and bevacizumab 10 mg/kg every 2 weeks ($n = 88$), oral sunitinib 50 mg daily for 4 week cycles with 2 weeks between cycles ($n = 42$), or bevacizumab 10 mg/kg every 2 weeks plus alpha interferon 9 MU subcutaneously 3 times a week ($n = 41$). Temsirolimus dose reductions of 15 mg or 20 mg were permitted but no dose adjustments were allowed for bevacizumab. Patients in all 3 arms were treated until disease progression or unacceptable toxicity occurred. The predetermined primary endpoint for the group receiving combined temsirolimus and bevacizumab was the nonprogression rate at 48 weeks. Secondary endpoints were toxicity, response rate, and survival.

The overall median follow up in TORAVA was 14.7 months. Treatment was stopped before 48 weeks due to toxicity in 43% of patients in the temsirolimus and bevacizumab combination group with 26% having a grade 3 adverse event, 12.5% having a grade 4 adverse event, and 3 deaths occurring. Premature treatment discontinuation due to toxicity was required for 12% of those in the sunitinib arm and 23% of those receiving bevacizumab plus alpha interferon. In the sunitinib arm grade 3 adverse events occurred in 12% of patients, grade 4 events were reported in 2.4%, and there were no deaths. Grade 3 events occurred in 20% of patients in the bevacizumab and alpha interferon group and grade 4 events occurred in 7.5%; no deaths occurred. "Toxicity certainly seemed to be synergistic [in the temsirolimus-bevacizumab group] rather than just additive," said discussant Marc Michaelson, MD, Massachusetts General Hospital, Boston, MA. He pointed out that the toxicity rate in the experimental group was much higher than is normally expected with either agent alone.

The nonprogression rate was significantly lower in the temsirolimus and bevacizumab arm. An intent-to-treat analysis of patients with a median 43-week follow up showed 31% nonprogression in the combination group compared with 40.5% in the sunitinib group and 65.9% in the bevacizumab and alpha interferon arm. Best response rates were 27% in the temsirolimus and bevacizumab group including 2% with complete response and 25% with partial response, 24% (all partial responders) in the sunitinib group, and 39% in the bevacizumab and alpha interferon group comprised of 2% complete response and 37% partial responses. Progression free survival was 8.2 months in both the temsirolimus-bevacizumab combination and sunitinib groups, and 16.8 months in the bevacizumab plus alpha interferon group. "The toxicity profile of temsirolimus and bevacizumab was higher than expected and lead to a high drop-out rate. The results do not suggest any evidence of a synergistic or additive efficacy with this combination," Dr. Escudier said.

Tivozanib Offers Most Benefit to Clear Cell, Nephrectomy Patients

Patients with clear cell RCC who underwent nephrectomy experienced significantly increased PFS according to a subgroup analysis of a previously reported phase 2 randomized discontinuation trial of tivozanib, an inhibitor of vascular endothelial growth factor receptor (VEGFR)-1, 2, and 3 kinases. Median PFS among these patients was 14.8 months versus 11.8 months for the overall cohort, reported Pankaj Bhargava, MD, Vice President of Clinical Research for AVEO Pharmaceuticals and an instructor at Harvard Medical School, Boston, MA.

There were 272 patients with RCC enrolled in the phase 2 trial including 83% with clear cell histology, 73% who had undergone nephrectomy, and 46% who had failed previous treatment with cytokines or chemotherapy. The median duration of tivozanib treatment was 8.5 months ranging from 0.03 months to 23.8 months. Researchers reported that the overall response rate was 25.4% for all patients, 27% among those with clear cell histology, 28.1% in patients with prior nephrectomy, and 29.6% for those having both clear cell histology and nephrectomy. Median PFS was 11.8 months in all patients, 12 months for both clear cell histology and nephrectomy, and 14.8 months for those having both ($P = .02$). In addition, PFS was similar among patients who were treatment naïve and those who had failed previous therapy, Dr. Bhargava said.

Adverse events were as expected and included hypertension in 54.4% of patients and dysphonia in 21%. Fatigue occurred in 9.9% of patients, diarrhea in 10.7%, somatitis in 3.7%, and hand-foot syndrome in 3.3%. Dose reduction due to adverse events was required by 8.5% of patients, and 2.9% required treatment interruption because of adverse events.

Phase 2 Immunotherapy Results Promising

Interim data from a phase 2 trial of AGS-003 in patients with newly diagnosed, advanced RCC in combination with sunitinib show a median PFS of 12.5 months among those with poor or intermediate prognostic scores, reported Asim Amin, MD, Carolinas Medical Center, Charlotte, NC. The potential autologous immunotherapy targets patients' specific cancer cells using monocyte-derived dendritic cells which are electroporated with the patients' amplified tumor and synthetic CD40L RNA.

The phase 2 trial enrolled 25 patients with newly diagnosed clear cell RCC who had undergone nephrectomy. They received sunitinib in 4-week cycles with 2 weeks off between cycles and concomitant AGS-003 injections of 5 doses every 3 weeks and then every 3 months until disease progression or the end of the study. The intent-to-treat population included 22 patients, 16 of whom were evaluable. Three patients dropped out before the first dose of AGS-003 and 8 discontinued treatment during the trial due to disease progression. Of the 16 evaluable patients, 13 were classified MSKCC intermediate risk and 3 were MSKCC poor risk. Dr. Amin reported that there was an overall clinical benefit rate of 81% (13 of 16 patients). All 3 of the patients classified as poor risk experienced progression-free intervals of > 3.7 months, and 11 of the 13 intermediate risk patients achieved progression-free intervals of > 10.6 months. "Most patients have progression-free intervals longer than what would be

expected for sunitinib treatment alone," he said.

Treatment was well-tolerated and there were no serious adverse events or grade 3 or 4 adverse events associated with the combination of AGS-003 and sunitinib and 10 patients continue treatment. Updated PFS results are expected in late 2010, Dr. Amin said.

TKI Discontinuation Following Complete Remission

Up to 65% of patients remain in CR when treatment with a tyrosine kinase inhibitor (TKI) is discontinued, according to results of a retrospective study of the French Kidney Cancer Group reported by Laurence Albiges, MD, Institut Gustave Roussy, Villejuif, France. Furthermore, researchers found that CR occurs with TKI treatment alone or in combination with local treatment, regardless of the number or location of metastatic sites and prognostic risk group.

The French Kidney Cancer Group performed a multicentric, retrospective analysis of 65 patients with metastatic RCC who developed CR while being treated with sunitinib or sorafenib alone, or in combination with local treatment consisting of surgery, radiotherapy, or radiofrequency ablation. Tumor histology, prior treatment, the number and location

of metastatic sites, prognostic group according to French Classification, duration of TKI treatment, the type and date of local treatment, and follow up after CR were analyzed.

Of the 64 patients achieving CR, 61 had clear cell histology, 64 had a previous nephrectomy, 61 were treated with sunitinib, and 4 were treated with sorafenib. Thirty nine patients achieved CR with TKI therapy alone and 26 had additional local treatments. Twenty seven of the CR patients had 1 metastatic site, 23 had 2 metastatic sites, and 15 had metastases to 3 or more sites. Prognostic risk classification was favorable for 22 patients, intermediate for 39 patients, and poor for 4 patients.

Of the 39 patients developing CR with TKI treatment alone, 27 discontinued TKI therapy an average of 1 month after CR was obtained and of these, 17 (63%) remained in CR at a median follow up of 291 days. Among the 26 patients achieving CR with TKI combined with local therapy, 23 stopped TKI treatment and 15 (65%) remained in CR at a median follow up of 322 days. Although CR is uncommon with TKI treatment for metastatic RCC, it may occur and subsequent interruption of TKI treatment is possible, Dr. Albiges concluded. **KCJ**