

RAD001 More Than Doubles Time Without Tumor Growth After Failure of Standard Treatment in Patients With Advanced Kidney Cancer

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- - RECORD-1 trial shows RAD001 reduces risk of disease progression by 70%
- - RAD001 is first and only drug to show significant benefit after failure of approved therapies Sutent(R) or Nexavar(R),** with potential to address unmet medical need
- - Once-daily oral RAD001 directly targets and continuously inhibits mTOR, a protein that controls tumor cell division and blood vessel growth
- - RAD001 is currently being studied in multiple types of cancer including neuroendocrine, breast, gastric, lung, and lymphoma

EAST HANOVER, N.J., May 19 /PRNewswire/ -- New data show RAD001 (everolimus) may provide an important new treatment option for patients with advanced kidney cancer who have failed standard therapies.

The interim study findings demonstrated that RAD001 significantly extended the time without tumor growth from 1.9 to 4 months and reduced the risk of cancer progression by 70% (hazard ratio = 0.30 with 95% CI 0.22 to 0.40; p- value < 0.0001). The study, RECORD-1 (REnal Cell cancer treatment with Oral RAD001 given Daily), will be presented at the 44th annual meeting of the American Society of Clinical Oncology (ASCO) in Chicago, Illinois, US on Saturday, May 31, 2008.

Earlier this year, an independent data monitoring committee stopped the RECORD-1 trial after interim results showed that patients receiving RAD001 experienced a significantly longer time without their cancer worsening compared to patients receiving placebo. The trial included patients whose cancer had stopped responding to approved treatments for renal cell carcinoma (RCC), such as Nexavar® (sorafenib) or Sutent® (sunitinib), or both.

RAD001 is a once-daily oral therapy that may offer a new approach to cancer treatment by continuously inhibiting the mTOR protein, a central regulator of tumor cell division and blood vessel growth in cancer cells.

"This is the first study to show clinical benefit in patients with advanced kidney cancer who have experienced treatment failure with the most commonly used first-line therapies," said Robert J. Motzer, MD, attending physician, Memorial Sloan-Kettering Cancer Center, New York, and principal investigator of the RECORD-1 trial. "The results show RAD001 extended progression-free survival in patients regardless of their prior treatments, risk status, age, or gender."

During the second half of 2008, the interim results from RECORD-1 will be used to submit a new drug application for RAD001 as a treatment for metastatic renal cell carcinoma.

"As we will see in presentations at the upcoming meeting, RAD001 has the potential to benefit patients living with a variety of cancers including neuroendocrine, breast, gastric, and lung," said David Epstein, CEO and President of Novartis Oncology. "We look forward to updates from trials in pancreatic neuroendocrine tumors before year-end."

RECORD-1 results

RECORD-1 is the largest Phase III clinical trial investigating the effects of an oral mTOR inhibitor in metastatic RCC. It is a randomized, double-blind placebo-controlled multicenter trial of more than 400 patients with RCC whose cancer worsened despite prior treatment, including Nexavar or Sutent, or both. In addition, prior therapy with Avastin, interferon, and interleukin-2 was allowed.

The primary endpoint of RECORD-1 was progression-free survival (PFS) assessed via a blinded, independent central review and defined as the amount of time between randomization and first documented disease progression or death due to any cause. Results of the study demonstrated a statistically significant improvement in PFS for RAD001 compared to placebo (hazard ratio = 0.30 with 95% CI 0.22 to 0.40; p-value < 0.0001; median PFS 4 months vs. 1.9 months, respectively).

Secondary endpoints included comparison of overall survival, objective response rate, quality of life, safety, and pharmacokinetics. There was no significant difference in overall survival between the RAD001 and placebo groups (hazard ratio = 0.83 with 95% CI 0.50 to 1.37; p-value = 0.23). The study design allowed patients to be unblinded at the time of radiological disease progression; patients receiving placebo were allowed to cross over to receive RAD001. There was no significant difference in objective response rate between the RAD001 and placebo groups (1% vs. 0% of responders). However, in a central review among patients evaluable for best percentage change in target lesions (223 and 107 in RAD001 and placebo arms, respectively), tumor shrinkage was observed in 50% of patients receiving RAD001 during the double-blind portion of the study versus 8% of patients receiving placebo. Quality of life measurements taken throughout the study showed no significant difference between the RAD001 and placebo groups.

Safety findings in the study were consistent with those seen in prior Phase II studies. The most frequent adverse events in patients who took RAD001 included mouth sores (40%), feelings of weakness (37%), and rash (25%). There was a low incidence of grade 3 or 4 drug-related adverse events (greater than or equal to 1% of patients listed): mouth sores (3%), lung inflammation (3%), infection (3%), tiredness/feelings of weakness (4%), diarrhea (1%), mucosal inflammation (1%), and difficulty breathing (1%). The trial had a low rate of adverse drug reactions leading to discontinuation among patients who took RAD001 (6%).

About renal cell carcinoma (RCC)

In the United States, kidney cancer accounts for approximately 3% of all adult cancers. RCC, the most common type of kidney cancer, accounts for approximately 90% of malignant kidney tumors. In RCC, cancer cells develop in the lining of the kidney's tubes and grow into a tumor.

About RAD001

RAD001, an oral inhibitor of mTOR, is an investigational drug being studied in multiple tumor types. In cancer cells, RAD001 inhibits mTOR, a protein that acts as a central regulator of tumor cell division, cell metabolism, and blood vessel growth. RAD001 is a once-daily oral therapy that provides continuous inhibition of mTOR.

In addition to RCC, RAD001 is presently being evaluated in neuroendocrine tumors, lymphoma, other cancers, and tuberous sclerosis as a single agent or in combination with existing cancer therapies.

As an investigational compound, the safety and efficacy profile of RAD001 has not yet been established in oncology. Access to RAD001 is available only through carefully controlled and monitored clinical trials. These trials are designed to better understand the potential benefits and risks of the compound. Because of the uncertainty of clinical trials, there is no guarantee that RAD001 will ever be commercially available for oncology indications anywhere in the world. Everolimus is approved under the trade-name Certican® for the

prevention of organ rejection in heart and kidney transplant recipients. Certican was first approved in the EU in 2003 and is available in more than 60 countries.

Disclaimer

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