Drug everolimus does not improve overall survival in patients with advanced liver cancer

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Despite strong preclinical data, the drug everolimus failed to improve overall survival in patients with advanced liver cancer, compared to placebo, according to a study in the July 2 issue of *JAMA*.

Patients with advanced hepatocellular carcinoma (HCC; a type of liver cancer) have a median overall survival of less than l year, largely because of the absence of effective therapies. The drug sorafenib is the only systemic therapy shown to significantly improve overall survival in advanced HCC; however its benefits are mostly transient and modest, and disease eventually progresses. In preclinical models, everolimus prevented tumor progression and improved survival, according to background information in the article.

Andrew X. Zhu, M.D., Ph.D., of the Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, and colleagues randomly assigned 546 adults with advanced HCC whose disease progressed during or after sorafenib or who were intolerant of sorafenib to receive everolimus (n = 362) or placebo (n = 184), both given in combination with best supportive care and continued until disease progression or intolerable toxicity. In this phase 3 study, patients were enrolled from 17 countries between May 2010 and March 2012.

The researchers found no significant difference in overall survival between the two groups: there were 303 deaths (83.7 percent) in the

everolimus group and 151 deaths (82.1 percent) in the placebo group. Median overall survival was 7.6 months with everolimus, 7.3 months with placebo. The disease control rate (the percentage of patients with a best overall response of complete or partial response or stable disease) was 56.1 percent (everolimus) and 45.1 percent (placebo).

"The results from [this study, EVOLVE-1] extend the list of failed phase 3 studies in advanced HCC, highlighting the challenge of developing effective therapies for this cancer," the authors write.

The researchers note that EVOLVE-l and the other failed phase 3 studies have provided several important lessons, including that it is difficult to assess efficacy signals from phase 2 trials; surrogate end points such as time to progression, progression-free survival, and response rate inconsistently predict overall survival in phase 3 trials; and clinical and biologic heterogeneity likely affects the performance of targeted therapies in HCC. "In the absence of well-characterized and validated predictive bio-markers, targeted agents will likely continue to have a high risk of failure if phase 3 trials are conducted in unselected populations."

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