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## **Next-generation PI3 Kinase Inhibitor Demonstrated Early Efficacy, Safety**

- The drug GDC-0032 demonstrated a favorable safety profile in a phase I clinical trial.
- The agent showed promising activity in PI3 kinase alpha-mutant tumors.

WASHINGTON, D.C. — GDC-0032, a potent, next-generation PI3 kinase inhibitor, demonstrated early signs of efficacy for patients with cancers driven by mutations in the PI3 kinase alpha gene, according to first in-human results presented at the AACR Annual Meeting 2013, held in Washington, D.C., April 6-10.

“We’ve shown that this novel agent is well tolerated,” said Dejan Juric, M.D., lead investigator of the study at the Termeer Center for Targeted Therapies at Massachusetts General Hospital in Boston. “We’ve shown that the safety profile is favorable and that the side effects are predictable. Early results show that the drug has very promising activity, particularly in tumors that have activating mutations in PI3 kinase alpha.”

GDC-0032, which is being developed by Genentech, a member of the Roche Group, targets a family of molecules called PI3 kinases. The drug is distinguished by its enhanced in-vitro activity against the mutant form of the family member called PI3 kinase alpha, which is known to be present in approximately 40 percent of hormone receptor-positive breast cancers.

“We currently have no approved therapies that directly target this critically important component of cancer cells,” Juric said.

This phase Ia, multicenter, open-label study included 34 patients with locally advanced or metastatic solid tumors who received a once-daily dose of GDC-0032. Researchers tested five dosing cohorts: 3 mg, 5 mg, 8 mg, 12 mg and 16 mg.

The drug was well tolerated, and side effects consisted of hyperglycemia, diarrhea, fatigue and nausea. The only study-related grade 4 adverse event was hyperglycemia in the 16-mg dose cohort, according to Juric.

“Those are very common and predictable side effects,” he said. “In particular, hyperglycemia is a so-called ‘on-target’ side effect because PI3 kinase alpha plays an important role in glucose metabolism. All agents that effectively block PI3 kinase alpha lead to some level of glucose elevation.”

The results also showed that four of six patients with breast cancers driven by a PI3 kinase alpha mutation had a partial response according to RECIST criteria, which is an objective measure of tumor shrinkage, according to Juric. In addition, the researchers observed a partial response in one patient with lung cancer driven by a PI3 kinase alpha mutation, as well as objective tumor shrinkage in a patient with HER2-amplified breast cancer.

“This trial is an important step forward in getting us closer to developing an agent that shuts down PI3 kinase alpha effectively,” Juric said. “It is impressive how frequently PI3 kinase alpha mutations are found in human cancers. This is one of the first agents to have shown selectivity and encouraging signs of efficacy when we target that particular mutation.”

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Founded in 1907, the American Association for Cancer Research (AACR) is the world’s first and largest professional organization dedicated to advancing cancer research and its mission to prevent and cure cancer. AACR membership includes more than 34,000 laboratory, translational and clinical researchers; population scientists; other health care professionals; and cancer advocates residing in more than 90 countries. The AACR marshals the full spectrum of expertise of the cancer community to accelerate progress in the prevention, biology, diagnosis and treatment of cancer by annually convening more than 20 conferences and educational workshops, the largest of which is the AACR Annual Meeting with more than 17,000 attendees. In addition, the AACR publishes eight peer-reviewed scientific journals and a magazine for cancer survivors, patients and their caregivers. The AACR funds meritorious research directly as well as in cooperation with numerous cancer organizations. As the scientific partner of Stand Up To Cancer, the AACR provides expert peer review, grants administration and scientific oversight of team science and individual grants in cancer research that have the potential for near-term patient benefit. The AACR actively communicates with legislators and policymakers about the value of cancer research and related biomedical science in saving lives from cancer. For more information about the AACR, visit [www.AACR.org](http://www.AACR.org).

**Abstract Number:** LB-64

**Presenter:** Dejan Juric, M.D.

**Title:** GDC-0032, a Beta Isoform-Sparing PI3K Inhibitor: Results of a First-in-Human Phase 1a Dose Escalation Study

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**Background:** GDC-0032 is an orally bioavailable, potent, and selective inhibitor of Class I PI3K alpha, delta, and gamma isoforms, with 30 fold less inhibition of the PI3K beta isoform relative to the PI3K alpha isoform. Preclinical data show that GDC-0032 has increased activity against PI3K alpha isoform (PIK3CA) mutant and HER2-amplified cancer cell lines.

**Methods:** A Phase 1a, multicenter, open-label study was conducted to evaluate the safety and pharmacokinetics (PK) of GDC-0032 administered once daily in patients with locally advanced or metastatic solid tumors. Preliminary assessment of the anti-tumor activity of GDC-0032 was also performed. The study consisted of 3+3 dose-escalation cohorts with a 35-day window to evaluate dose-limiting toxicity (DLT).

**Results:** As of August 1, 2012, 34 patients were enrolled in this study. Five dosing cohorts ranging from 3 to 16 mg QD were tested (3, 5, 8, 12, and 16 mg), and dose escalation has been completed. Two DLTs (Grade 4 hyperglycemia and Grade 3 fatigue) were observed in two patients from the 16 mg cohort. Adverse events (AEs) assessed by the investigator as related to GDC-0032 in  $\geq 10\%$  of patients, were diarrhea, hyperglycemia, fatigue, nausea, decreased appetite and vomiting. The only Grade 4 treatment-related AE (hyperglycemia) occurred in the 16 mg cohort. GDC-0032 PK was approximately dose proportional and time independent with a mean  $t_{1/2}$  of 40 hours. Paired pre-treatment and on-treatment tumor biopsies of a patient in the 3 mg cohort showed pharmacodynamic inhibition of the PI3K pathway as assessed by reverse phase protein array. Metabolic partial responses via FDG-PET ( $\geq 20\%$  decrease in mSUVmax) were observed in 7 out of 13 patients assessed (54%). Clinical partial responses (PRs) were observed in 5 patients treated at doses of GDC-0032 ranging from 3-12 mg QD. Consistent with GDC-0032 preclinical data, 3 PRs (2 confirmed) were observed out of 5 patients with PIK3CA mutant breast cancer (RECIST -30% to -70%). One cPR has been observed in a patient with PIK3CA mutant NSCLC, and 1 uPR in a patient with HER2-positive, PIK3CA wildtype, breast cancer.

**Conclusion:** GDC-0032 is a PI3K inhibitor with dose-linear PK and expected in-class toxicities. Pharmacodynamic inhibition of the PI3K pathway has been observed in tumor biopsies and FDG-PET imaging. Clinical partial responses observed in patients with PIK3CA mutant and HER2+ tumors suggest that GDC-0032 may have increased anti-tumor activity in diagnostically defined subpopulations.