Clovis Oncology's CO-1686 Demonstrates Encouraging Results from Ongoing Phase I/II Study in EGFR-mutant Non-Small Cell Lung Cancer

June 3, 2013 7:30 AM ET

- **Four RECIST partial responses observed in heavily pretreated T790M+ patients**
- **Three of four evaluable T790M+ patients treated at 900 mg BID achieved partial responses**
- **CO-1686 appears well-tolerated; no evidence of wild-type EGFR inhibition**
- **Activity correlates with higher drug exposure**
- **Phase II dose not yet defined; MTD not yet reached**

BOULDER, Colo.--(BUSINESS WIRE)--Jun. 3, 2013-- Clovis Oncology (NASDAQ:CLVS) today announced initial findings from the Phase I portion of its ongoing Phase I/II clinical study of CO-1686, the Company's novel, oral, targeted covalent (irreversible) inhibitor of mutant forms of the epidermal growth factor receptor (EGFR) for the treatment of non-small cell lung cancer (NSCLC) in patients with initial activating EGFR mutations as well as the dominant resistance mutation T790M. Initial results from the Phase I dose-escalation portion of this Phase I/II study are being presented for the first time on Tuesday, June 4 at a poster session during the American Society of Clinical Oncology (ASCO) Annual Meeting 2013 in Chicago. Four RECIST partial responses in T790M positive patients have been observed to date, and the maximum tolerated dose (MTD) has not yet been reached.

"The oncology community has been working to develop successful treatments for EGFR mutant patients with acquired resistance to erlotinib or gefitinib for several years without significant progress," said Dr. Lecia V. Sequist of the Massachusetts General Hospital Cancer Center and Associate Professor of Medicine at Harvard Medical School, Boston. "It has been exciting and quite hopeful to observe that patients are responding to CO-1686 and that the side effect profile has been so mild. A drug that works effectively for EGFR acquired resistance would be welcomed by the lung cancer community."

"There are no approved treatment options for patients with non-small cell lung cancer who have developed the T790M resistance mutation," said Patrick J. Mahaffy, President and CEO of Clovis Oncology. "We are extremely encouraged by these initial results which suggest that CO-1686 is well-tolerated and offers clear evidence of meaningful activity in a heavily pre-treated patient population, despite not yet having established our MTD. We look forward to continuing dose-escalation with our improved tablet formulation in our Phase I/II trial, with the goal of identifying the dose to proceed into the expansion cohorts in our target patient populations and our registration studies."

The Phase I dose escalation portion of the study is being conducted in the United States and France in patients with metastatic or unresectable recurrent NSCLC and a documented EGFR mutation. Patients were not required to be T790M positive for the Phase I portion of the study but had to have progressed on prior EGFR-directed tyrosine kinase inhibitor (TKI) therapy (prior chemotherapy was also allowed). Study objectives were typical for a Phase I trial: determining safety and tolerability, evaluating the pharmacokinetic profile, maximum tolerated dose (MTD) and recommended Phase II dose (RP2D), as well as identification of preliminary efficacy signals.

Forty-two patients have been treated with CO-1686 as of May 2013, mostly in once-daily (QD) and twice-daily (BID) dosing cohorts up to 900mg QD and 900mg BID. Dose-escalation will continue with an improved formulation in the third quarter as the MTD has not yet been reached.

Key data from the study presented at ASCO include:

Evidence of Activity

Objective responses have been observed in heavily pretreated T790M+ patients who are resistant to erlotinib. Additionally, metastasis shrinkage has been observed at multiple organ sites, including both brain and liver metastases.

Included in the poster are six T790M+ patients, including four with RECIST (v1.1) partial responses (PRs) and two patients with tumor shrinkage of greater than 20 percent. Details on each patient follow:

- One patient with a del19/T790M+ tumor had progressed on erlotinib immediately before beginning CO-1686 therapy. The patient, enrolled in the 300 mg BID cohort, is currently in cycle 6 of CO-1686 therapy, with a confirmed PR

- One patient with an L858R/T790M+ tumor had received six previous lines of therapy, including two previous TKIs, dacomitinib and erlotinib, and had most recently progressed on a combination of erlotinib and gemcitibine immediately before beginning CO-1686 therapy. This patient has demonstrated tumor shrinkage in brain metastases (present at baseline), as well as lung and liver tumors. The patient, enrolled in the 900mg BID cohort, exhibited a PR in cycle 4 of CO-1686 therapy; treatment is ongoing
- One patient with a del19/T790M+ tumor had received two previous lines of therapy. This patient exhibited a PR in cycle 2 and is currently being dosed in cycle 3 at 900mg BID
- One patient with a del19/T790M+ tumor had received two lines of prior cytotoxic chemotherapy and had also progressed on erlotinib treatment. This patient exhibited a PR in cycle 2 and is currently in cycle 3, receiving 900mg BID
- Two additional T790M+ patients have achieved greater than 20 percent target lesion shrinkage with stable non-target lesions

A total of six patients have been treated in the 900mg BID cohort (the highest dose evaluated to date): one of these patients is not evaluable for response and one patient is T790M-negative. Three of the four remaining patients achieved PRs, as described above, and the fourth has stable disease at the end of cycle 2.

Safety and Tolerability

CO-1686 appears to be well-tolerated with no evidence of dose-related diarrhea or rash. There were 26 patients (62%) with treatment-related adverse events. The most common adverse events attributed to CO-1686 therapy include fatigue (19%), nausea (17%), diarrhea (14%), muscle spasms (10%), and anemia (10%). These were all grade 1/2 in severity and did not lead to study drug discontinuation. There have been two dose limiting toxicities (DLTs):

- One event of hypoglycemia in the 150 mg QD cohort in a diabetic patient who took oral hypoglycemic agents while fasting
- One acute illness in the 900 mg BID cohort on day three of dosing with anorexia and asthenia (grade 3), abnormal liver function tests (grade 3) and diarrhea (grade 2)

The incidence of adverse events did not increase with dose escalation and does not appear to be dose dependent. These data offer no evidence of dose-related adverse events related to wild-type EGFR inhibition by CO-1686.

Pharmacokinetics

The activity and safety data presented at ASCO, using the free base capsule formulation, demonstrated that plasma exposure of CO-1686 increases with dose and activity appears to correlate to drug exposure. Non-clinical data suggested that maintenance of trough concentrations over 200ng/mL for >12-18 hours was associated with optimal efficacy. In the Phase I portion of the Phase I/II study, T790M+ patients for whom Cmin levels of 200 ng/mL or greater were maintained for 16 hours or more demonstrated improved progression-free survival (PFS) compared to those with inferior exposures. Objective responses were observed exclusively in the higher-exposure group as well:

- For T790M+ patients with Cmin greater than 200 ng/mL for 16 hours or longer, median PFS was 194 days; 50 percent had a 10% or greater tumor shrinkage;
- For T790M+ patients with Cmin greater than 200 ng/mL for fewer than 16 hours, median PFS was 72.5 days; 8 percent of patients had a 10 percent or greater shrinkage

The ASCO poster also presented data with the hydrobromide salt tablet form of CO-1686 from a separate Phase I study in healthy human volunteers, which showed improved exposure and reduced PK variability compared with the current free base capsule formulation, which is being used in the Phase I study in patients with NSCLC. Specifically, in the ongoing Phase I study in healthy volunteers, the tablet form of CO-1686 demonstrated a 2 to 3-fold improvement in absorption and a 4-fold reduction in exposure variability relative to the free base capsule formulation.

As previously stated, the Company intends to transition development of CO-1686, including dose escalation in the ongoing Phase I study, to the tablet formulation in the third quarter of 2013. The Company plans to use the tablet formulation in all future clinical studies of CO-1686.

Poster Presentation

The poster, titled “First-in-human evaluation of CO-1686, an Irreversible, Selective, and Potent Tyrosine Kinase Inhibitor of

EGFR T790M", is being presented on Tuesday, June 4, 8:00 a.m.-12:00 p.m. CDT, in Room E450a at McCormick Place in Chicago. The poster will also be available at www.clovisoncology.com.

The poster will be discussed at the associated discussion session with Dr. David Carbone of Ohio State's Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute serving as discussant. The discussion session will be held on Tuesday, June 4, 11:30 a.m.-12:30 p.m. CDT, with Dr. Carbone scheduled to speak from 11:54 a.m.–12:06 p.m. in Room E354b.

About CO-1686

CO-1686 is a novel, oral, targeted covalent (irreversible) inhibitor of the cancer-causing mutant forms of epidermal growth factor receptor (EGFR) currently being studied for the treatment of non-small cell lung cancer (NSCLC). CO-1686 was designed to selectively target both the initial activating EGFR mutations as well as the T790M resistance mutation, while sparing wild-type, or "normal" EGFR at anticipated therapeutic doses. Accordingly, it has the potential to treat NSCLC patients with EGFR mutations both as a first-line or second-line treatment with a reduced toxicity profile compared to current EGFR inhibitor therapies. The Phase I/II study is currently in the dose escalation phase, being conducted in the U.S. and France. Following the establishment of an appropriate dose, the Company intends to study CO-1686 in a Phase II expansion cohort of NSCLC patients with activating EGFR mutations who have failed initial EGFR-directed therapy and have developed the T790M mutation, as well as a second expansion cohort of first-line mutant EGFR NSCLC patients.

About Clovis Oncology

Clovis Oncology, Inc. is a biopharmaceutical company focused on acquiring, developing and commercializing innovative anti-cancer agents in the U.S., Europe and additional international markets. Clovis Oncology targets development programs at specific subsets of cancer populations, and simultaneously develops diagnostic tools that direct a compound in development to the population that is most likely to benefit from its use. Clovis Oncology is headquartered in Boulder, Colorado, and has additional offices in San Francisco, California and Cambridge, UK.

To the extent that statements contained in this press release are not descriptions of historical facts regarding Clovis Oncology, they are forward-looking statements reflecting the current beliefs and expectations of management made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. Such forward-looking statements involve substantial risks and uncertainties that could cause our clinical development programs, future results, performance or achievements to differ significantly from those expressed or implied by the forward-looking statements. Such risks and uncertainties include, among others, the uncertainties inherent in the initiation of future clinical trials, availability of data from ongoing clinical trials, expectations for regulatory approvals, and other matters that could affect the availability or commercial potential of our drug candidates. Clovis Oncology undertakes no obligation to update or revise any forward-looking statements. For a further description of the risks and uncertainties that could cause actual results to differ from those expressed in these forward-looking statements, as well as risks relating to the business of the company in general, see Clovis Oncology's Annual Report on Form 10-K for the year ended December 31, 2012 and its other reports filed with the Securities and Exchange Commission.

Source: Clovis Oncology

Clovis Oncology
Anna Sussman, 303.625.5022
asussman@clovisoncology.com
or
Breanna Burkart, 303.625.5023
bburkart@clovisoncology.com