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Tragara Pharmaceuticals' Apricoxib Reverses EMT, a Key Process for Cancer Progression and Metastasis

San Diego – May 26, 2011 – Tragara Pharmaceuticals, Inc. announced today that apricoxib (Capoxigem[®], TG01), its novel COX-2 inhibitor in development for select cancer types, demonstrated reversal of the epithelial-mesenchymal transition (EMT) in xenograft models of several types of solid tumors. These data results were presented at the 2011 American Society for Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium and the 2011 American Association for Cancer Research (AACR) Annual Meeting and demonstrate that apricoxib potently inhibits the activity of COX-2 and COX-2 derived prostaglandin E₂ (PGE₂), which in turn mediates EMT and the associated progression and metastasis of solid tumors.

“Reversal of EMT may provide several clinical benefits to patients with non-small cell lung cancer and pancreatic cancer,” stated Sara Zaknoen, M.D., chief medical officer, Tragara Pharmaceuticals, Inc. “Patients may experience longer survival due to effects of EMT reversal on metastases and the cancer stem cell, and benefit from the reversal of resistance to drugs such as erlotinib.”

Tragara has completed two phase II clinical trials of apricoxib. Results from the APRiCOT-L trial, a biomarker-based, phase II, randomized, placebo-controlled study of apricoxib in combination with erlotinib in non-small cell lung cancer, will be presented on June 6th at the ASCO meeting in Chicago. A second phase II study of apricoxib in combination with gemcitabine and erlotinib has completed enrollment and is currently being analyzed.

“COX-2 has been implicated in EMT, so we were gratified to see robust reversal of EMT resulting from apricoxib treatment in xenograft models of pancreatic, colon, and head and neck cancers,” stated Francis Burrows, Ph.D., head of oncology biology, Tragara Pharmaceuticals, Inc. “This effect was associated with profound inhibition of metastasis in orthotopic cancer models but, interestingly, apricoxib-mediated EMT reversal also reduced proliferation and survival of tumor cells in the primary lesion, perhaps due to a reduction in levels of cancer stem cells which are thought to arise via EMT.”

The Capoxigem posters, originally presented earlier in 2011 and available on the [Tragara](#) company website, are:

2011 AACR 102nd Annual Meeting (April 4, 2011)

“Inhibition of COX-2 with Apricoxib Enhances the Efficacy of Standard Therapy in Preclinical Models of Human Pancreatic Cancer”, Amanda R. Kirane, Ph.D., University of Texas Southwestern Medical Center, Dallas.

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2011 ASCO Gastrointestinal Cancers Symposium (January 22, 2011)

“Preclinical Antitumor Activity and Mechanisms of Action of Apricoxib, a Clinical Cox-2 Inhibitor”, Francis Burrows, Ph.D., Tragara Pharmaceuticals, Inc., San Diego.

About Epithelial-Mesenchymal Transition (EMT) and COX-2

The epithelial-mesenchymal transition (EMT) is a developmental program resulting in a cellular shift from an epithelial phenotype to a motile, mesenchymal form that is essential for embryogenesis, tissue remodeling and tumor progression. Under the influence of oncogenic factors such as inflammatory cytokines, polarized epithelial cancer cells detach from their underlying basement membrane and progressively lose lineage-specific markers such as E-cadherin and acquire mesenchymal markers (e.g. vimentin) and the ability to invade and metastasize to new sites. Both EMT and hyperactivity of the COX-2 pathway are associated with poor prognosis in a range of solid tumor types. Many of the properties of solid tumor cells that have undergone EMT, including apoptosis resistance and heightened angiogenic and metastatic capacity, are also associated with chronic inflammation and overexpression of COX-2 and its catalytic product prostaglandin E₂ (PGE₂). Activation of the MAP kinase pathway by PGE₂ induces the master regulators of EMT, the transcriptional repressors Snail and ZEB1 and also enhances TGFβ-dependent EMT by blocking Smad signaling, suggesting that COX-2 derived PGE₂ is a major driver of EMT in human cancer.

About Capoxigem[®] (apricoxib, TG01)

Capoxigem (apricoxib, TG01) is an oral, once-daily selective COX-2 inhibitor. It is being evaluated separately for the treatment of inflammation-related pain and cancer. In inflammation-related pain, Capoxigem modulates the cyclooxygenase pathway, reducing the production of inflammatory prostaglandins. A large phase IIa Proof-of-Concept and dose finding study in inflammation-related pain has been completed in the United States. Superiority to placebo and an active comparator was demonstrated; safety was comparable to the active comparator.

As an anti-cancer treatment, Capoxigem affects a number of different oncogenic signaling pathways, including the HIF-1, VEGF, VEGF-R and PDGF systems for angiogenesis; the EGFR, HER2/neu, Bcr/Abl for growth control and differentiation; the intrinsic and extrinsic pathways for apoptosis; and the integrin and metalloproteinase systems for tissue invasion and metastasis. Capoxigem also potently inhibits COX-2-derived PGE₂ production, reversing the PGE₂-dependent epithelial-mesenchymal transition (EMT) process and the associated progression and metastasis of solid tumors. In pre-clinical cancer models, Capoxigem has shown superiority to compounds with similar mechanisms of action and synergy in combination with cisplatin, trastuzumab, and pemetrexed.

Capoxigem added to erlotinib therapy in a clinically relevant subset of biomarker-selected patients with advanced refractory non-small cell lung cancer significantly prolonged time to progression, progression-free survival and overall survival in a phase II proof-of-concept study (APRiCOT-L). In clinical studies to date, Capoxigem has been well tolerated with a manageable side effect profile.

In addition to the APRiCOT-L study, a phase II study of Capoxigem in pancreatic cancer recently completed enrollment and an investigator initiated study of Capoxigem in NSCLC in combination with chemotherapy is currently underway in the United States.

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About Tragara

Tragara Pharmaceuticals, Inc. is a privately held pharmaceutical company based in San Diego. The company is focused on the clinical and commercial development of proprietary medicines for the treatment of cancer and inflammation. Tragara's lead therapeutic program, Capoxigem[®] (apricoxib, TG01), is currently in phase II clinical development in lung and pancreatic cancers and has completed a phase IIa study in inflammation/pain. A second therapeutic program, TG02, is an oral multi-kinase inhibitor that targets the major signaling pathways involving ERK5, JAK2, FLT3 and several important cyclin-dependent kinases (CDKs). TG02 is currently in phase I clinical development. The Company is also developing a "theranostic" product: ProGEM[™], a proprietary diagnostic kit for the biomarker being evaluated in the Capoxigem clinical trials. Tragara is managed by a team of entrepreneurs with both Big Pharma and Biotech experience in the development and commercialization of oncology therapeutics. Its investors include: Domain Associates, Mitsubishi International Corporation, Morganthaler Ventures, Oxford BioScience Partners and ProQuest Investments.

Tragara strives to provide much-needed therapies that will contribute to patient health through better survival and an increase in the quality of life. For more information, visit www.tragarapharma.com.

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