Two phase 1 studies of MPC-6827, a novel vascular disrupting agent (VDA), in patients with advanced solid tumors and CNS metastases.

R. Kurzrock1 MD, W. Akerley2 MD, D. Hong1 MD, C. Ng1 MD, T. Warren1, K. Zavitczak PhD, C. McCage3 PhD, M. Laughlin3 MD and L.H. Camacho1 MD.

1Phase 1 Program, Division of Cancer Medicine, M.D. Anderson Cancer Center, Houston TX. 2Dept. of Oncology, Huntsman Cancer Institute, Salt Lake City, UT and 3Myriad Pharmaceuticals, Inc. Salt Lake City, UT.

MPC-6827 Background

- MPC-6827 (Antaxym) is a novel competitive inhibitor of tubulin polymerization via the alpha/gamma tubulin binding site.
- MPC-6827 functions as a highly potent novel vascular disrupting agent and a novel vascular disrupting agent (VDA).
- MPC-6827 inhibits tubulin polymerization and blocks microtubule function.
- MPC-6827 is not a substrate for multidrug resistance pumps and reach high CSF concentrations (14 X plasma).
- MPC-6827 toxicity consists of optimal chemotherapeutic windows arising of microtubule dysfunction.

Objectives

- To determine the safety and tolerability of MPC-6827 administered as a 3-week dose-finding study.
- To evaluate the maximum tolerated dose (MTD) of MPC-6827 as a single agent.
- To characterize the pharmacokinetics (PK) of MPC-6827 (1 hour for infusion).
- To determine if there is evidence of radiologic activity of MPC-6827 in treatment of a variety of solid tumor types with CNS involvement.

Study Design

- Phase 1, 1 dose, 3 cycles
- Dosing schedule weekly X 3 in a 4-week cycle
- Safety assessments weekly and every 3 weeks
- Study assessments after each cycle
- MTD assessed by DLTs (grade > 2 in > 30% patients, grade > 4 in > 10% patients)

Subject Eligibility

- Patients with advanced or refractory solid tumors, or have refractory cancer metastatic to the brain despite prior treatment.
- Karnofsky score > = 60%
- Performance Status (Karnofsky Score) > = 60%
- Be age > = 18
- Women of non-childbearing potential (nec) or hormonal contraception for 12 weeks.
- Childbearing potential.

Safety Assessments

- Physical Examination and Neurological Assessment
- Hematology
- Liver Function Tests
- Electrocardiogram
- Performance Status (Karnofsky Score)

Efficacy Assessments

- Tumor Assessment
  - Adenocarcinoma Survival Rate
  - Brain Tumor Survival Rate
  - Head CT Scan
  - MRI of the Head

Results: Safety

- No serious adverse events observed by RECIST criteria

Conclusions

- MPC-6827 behaves predictably and clinically as a vascular disrupting agent (VDA).
- The dose limiting toxicity was acute coronary syndrome which was observed in 16 subjects at 3.9 mg/m2 and in 26 patients at 4.5 mg/m2.
- The maximum tolerated dose is 3.3 mg/m2, where 24 of 47 patients have been treated for up to 14 months without evidence of acute coronary syndrome.
- No effect on QTc-interval was observed.
- There is a transient increase in BP during infusion and for a few hours post-inflation.

- MPC-6827 is proceeding into Phase 2 in a number of primary tumor types with CNS involvement.

References