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

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MPC-6827 Background

- MPC-6827 (Azixa™) is a novel competitive inhibitor of tubulin polymerization via the colchicine binding site[1]
- MPC-6827 functions as a highly potent (1-10nM) cytotoxic agent[1] and as a vascular disrupting agent (VDA)[2]
- MPC-6827 inhibits tumor cell growth and survival *in vitro* and *in vivo*, with activity in xenograft models of mouse melanoma and human cancers of the ovary, breast, prostate, colon and pancreas[1]
- MPC-6827 is not a substrate for multidrug resistance pumps and reaches high CSF concentrations (14 X plasma)[3]
- MPC-6827 acts synergistically with cytotoxic chemotherapeutics in mouse xenograft models[2]

[1]Kasibhatla et al. 2007 Cancer Research, [2]Pleiman et al. 2007 AACR and [3]Jessing et al. 2005 AACR.

Objectives

Primary

- To investigate the safety and tolerability of MPC-6827 administered as a 1-2-hour intravenous (IV) infusion, given once weekly for 3 consecutive weeks, repeated every 28 days in subjects with a variety of refractory solid tumors (study #1) or subjects with refractory brain metastases (study #2)
- To establish the maximum tolerated dose (MTD) of MPC-6827 as a single agent
- To characterize the pharmacokinetics (PK) of MPC-6827 (1-2 hour IV infusion)

Secondary

- To observe for any evidence of antitumor activity of MPC-6827 in treatment of a variety of refractory solid tumors and brain metastases

Study Design

- Phase 1, open label, dose escalation
- Dosing schedule weekly X 3 in a 4 week cycle
- "3 + 3" design, starting dose 0.3 mg/m^2, modified Fibonacci dose escalation for study #1
- "3 + 3" design, intra-subject dose escalation, starting dose 2.1 mg/m^2, modified Fibonacci dose escalation for study #2 (maintained highest dose for subsequent cycles)

Subject Eligibility

Inclusion

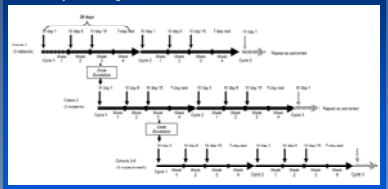
- Have advanced or metastatic cancer, which has progressed despite prior treatment with current standard of care (study #1)
- Or have refractory cancer metastatic to the brain despite prior treatment with standard of care, including but not limited to radiotherapy (study #2)
- Have measurable or evaluable neoplastic disease
- Be age $\geq$ 18
- Have a Karnofsky score $\geq$ 70
- Have a predicted life expectancy of $\geq$ 12 weeks
- Have adequate hematology and organ function

Exclusion

- Have had a prior serious hypersensitivity reaction to Cremophor® EL
- Receive any other anticancer treatment or investigational therapy within 28 days prior to study Day 1 (or within 6 weeks after mitomycin C or nitrosourea)
  - Subjects with advanced prostate cancer may continue to receive LHRH therapy
  - Subjects with breast cancer may continue to receive Herpectin® for systemic control.
- Have pre-existing dementia/cognitive dysfunction

Protocol MPC-6827-04-001: Phase 1 Open Label, Dose Escalating, Multiple Dose Study To Determine The Safety, Tolerability, Maximum Tolerated Dose, And Pharmacokinetics Of MPC-6827 Administered IV Weekly X 3, Repeated Every 28 Days, In Subjects With Refractory Solid Tumors

Study # 1: Design and Treatment Schema



Protocol MPC-6827-04-002: Phase 1 Open Label, Dose Escalating, Multiple Dose Study To Determine The Safety, Tolerability, Maximum Tolerated Dose, And Pharmacokinetics Of MPC-6827 Administered IV Weekly X 3, Repeated Every 28 Days, In Subjects With Refractory Brain Metastases

Study # 2: Progressive Dose Escalation Plan

Cohort number	Dose level (modified Fibonacci series)
Cohort 1	Dose 1 = 1.0 mg/m^2 Dose 2 = 1.5 mg/m^2 Dose 3 = 2.1 mg/m^2 Continuing dose = 2.1 mg/m^2 (provided no DLT)
Cohort 2	Dose 1 = 1.5 mg/m^2 Dose 2 = 2.1 mg/m^2 Dose 3 = 2.7 mg/m^2 Continuing dose = 2.7 mg/m^2 (provided no DLT)
Cohort 3	Dose 1 = 2.1 mg/m^2 Dose 2 = 2.7 mg/m^2 Dose 3 = 3.3 mg/m^2 Continuing dose = 3.3 mg/m^2 (provided no DLT)
Cohort 4	Dose 1 = 2.7 mg/m^2 Dose 2 = 3.3 mg/m^2 Dose 3 = 3.9 mg/m^2 Continuing dose = 3.9 mg/m^2 (provided no DLT)
Cohort 5	Dose 1 = 3.3 mg/m^2 Dose 2 = 3.9 mg/m^2 Dose 3 = 4.5 mg/m^2 Continuing dose = 4.5 mg/m^2 (provided no DLT)

Safety Assessments

- Physical Examination and Neurocognitive Assessment
  - Hopkins Verbal Learning
  - Grooved pegboard
- Monitoring of Adverse Events
- Monitoring of Concomitant Medications
- Vital Signs
- Clinical Laboratory Tests
- Electrocardiogram
- Telemetry
- Performance Status (Karnofsky Score)

Efficacy Assessments

Tumor Assessment

- All subjects underwent baseline computed tomography (CT) scan (chest and abdominal) or magnetic resonance imaging (MRI) at screening of prospectively defined target lesions (within 28 days prior to the first dose)
  - Additional scans were performed at Day 28 ± 7 days, and every 28 ± 7 days thereafter until the end of the study
- Tumor Response evaluated by RECIST (Response Evaluation Criteria in Solid Tumors)

Tumor Marker Assessments

- Tumor markers for selected tumor types were assessed as indicated by the subject's history (on Day 1 of each cycle)

Dynamic Contrast Enhanced Magnetic Resonance Imaging (DCE-MRI)

- Four subjects underwent an optional DCE-MRI within 72 hours prior to the first dose of MPC-6827 and within 36 hours after end of infusion to evaluate the acute effect of MPC-6827 on tumor blood flow

Patient Demographics (n=66)

Age	Mean	53.1
	Median	52.5
	Range	20-74
Gender	Female	31
	Male	35
CNS Metastasis	Yes	36
	No	30

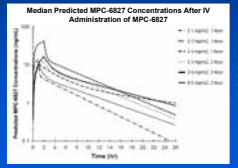
Primary Diagnosis	Number
Melanoma	12
Breast	10
NSCLC	8
Colorectal	8
Ovarian	3
Prostate	3
Pancreas	3
Testicular	2
Other	15

Pharmacokinetics

Median Plasma PK Parameters Day 1: Cohorts 4-9

Cohort	Dose Group (mg/m^2)	Day	Analyte	$t_{1/2}$ (hr)	C_{max} (ng/mL)	AUC_{INF} (hr*ng/mL)	AUC_{0-24} (hr*ng/mL)
4	1.5	1	MPC-6827	3.2	6.5	12.1	10.3
5	2.1	1	MPC-6827	2.8	14.3	32.3	36.9
6	2.7	1	MPC-6827	3.8	10.4	31.2	42.5
7	3.3	1	MPC-6827	6.4	10.7	54.0	66.4
8	3.9	1	MPC-6827	7.7	16.5	81.3	104.7
9	4.5	1	MPC-6827	4.7	29.8	119.2	128.4

Median Predicted MPC-6827 Concentrations After IV Administration of MPC-6827



These median values were fitted into a two compartment, IV infusion, micro-constants, no lag time, first order elimination model to get these predicted plots

Results: Safety

- **Safety Laboratories**
  - No apparent effect on any specific parameter was observed
  - In particular, there was no reduction in neutrophils, platelets or hemoglobin
- **Neurocognitive Testing**
  - Subjects were assessed for neurotoxicity by administration of the MMSE, the Hopkins Verbal Learning test and the Timed Grooved Pegboard test
  - There were no clinically meaningful changes predose to 24 hours postdose at any level, except for 1 subject
    - One subject had a significant reduction in MMSE score from Cycle 1 Day 1 to Cycle 1 Day 8 which was associated with a change in mental status felt to be secondary to CNS hemorrhage into a metastatic melanoma lesion producing edema and a midline shift on CT scan of the head
- **Vital Signs**
  - There was a dose dependent elevation in mean systolic blood pressure over the 1-2 hour infusion and 4-hour follow-up
    - The maximum effect occurred between the end of infusion and 2 hours postinfusion
    - The mean magnitude of the effect was less than 30 mm Hg, however increases were substantially higher in some individuals
  - Effects on mean diastolic blood pressure and heart rate were less apparent

Results: Safety

Mean Change from Baseline to End of Infusion in Heart Rate (b/min), PR Interval (m sec) and QTc Interval (m sec) by Dose Level (Protocol MPC-6827 04-001)

Cohort	1	2	3	4	5	6	7	8	9	10
Dose	0.3 mg/m^2	0.6 mg/m^2	1.0 mg/m^2	1.5 mg/m^2	2.1 mg/m^2	2.7 mg/m^2	3.3 mg/m^2	3.9 mg/m^2	4.5 mg/m^2	3.3 mg/m^2
HR	-2.2	-3.6	-10.1	-4.4	-4.7	-3.7	-10.7	-6.6	-9.6	-8.7
QTc	-13.9	+0.2	+1.1	+3.3	-0.1	-6.5	+3.0	-9.2	+2.4	+3.3
PR	+5.8	-4.1	-7.3	-5.0	-5.7	+4.4	+0.1	+6.8	+5.5	-0.9

Summary: Small but consistent reduction in heart rate without an effect on PR interval. No impact on QTc interval

Results: SAEs and Dose Limiting Toxicity (DLT)

- There were 54 serious adverse events in 33 subjects reported
- SAEs included
  - sinus tachycardia (Cohort 2)
  - atrial fibrillation and elevated liver function tests (Cohort 3)
  - severe allergic reaction experienced on 2 occasions by 1 subject despite pretreatment for hypersensitivity (Cohort 4)
  - cardiac arrhythmia, and convulsions and dyspnea (Cohort 4)
    - Cohort 4 was expanded to 7 subjects. None of these SAEs were observed in the additional subjects, indicating that DLTs had not been identified
  - myocardial infarction (Cohort 8)
    - Cohort 8 was expanded to 6 subjects
  - myocardial infarction and an episode of chest pain (Cohort 9, seven subjects enrolled)
- The MTD was declared at the prior dose level of 3.3 mg/m^2 based on the DLT of myocardial infarction
- There was no evidence of myelosuppression
- Common mild to moderate toxicities included fatigue, headache, flushing, diarrhea, nausea, vomiting and arthralgias

Results: Efficacy

- No objective responses observed by RECIST criteria

Progressive Disease	Stable Disease	Stable Disease	Stable Disease
Completed 1 cycle or less	Completed 2 cycles	Completed 3 to 4 cycles	Completed 5 cycles or more
37	13	3	4

- Best response was stable disease in 20/57 subjects treated at 1.5 mg/m^2 or higher with one subject (rectal carcinoid) stable for 10 months and one subject (cystic adenoid) currently stable for more than 14 months, each treated at 3.3 mg/m^2
- Preliminary evidence from DCE-MRI suggest vascular changes within 24 hours of the first dose of MPC-6827
- In a number of subjects, a biological response was observed in tumors (despite not meeting RECIST) consistent with an active VDA

Conclusions

- MPC-6827 behaves preclinically[2] and clinically as a vascular disrupting agent (VDA)
- The dose limiting toxicity was acute coronary syndrome which was observed in 1/6 subjects at 3.9 mg/m^2 and in 2/6 subjects at 4.5 mg/m^2
- The maximum tolerated dose is 3.3 mg/m^2 where 22 subjects 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 infusion
- The best response was stable disease which has currently lasted for more than 14 months in one individual
- MPC-6827 is proceeding into Phase 2 in a number of primary tumor types with CNS involvement

References:

[1]Kasibhatla S , Baichwal V, Cai SX, et al. 2007. MPC-6827: A Small Molecule Inhibitor of Microtubule Formation that is Not a Substrate for Multi-Drug Resistance Pumps. Cancer Research (in press).

[2]Pleiman CM, Valppu L, Bhoite L, et al. Vascular Disruption Effects of MPC-6827 (Azixa™). 98th Annual Meeting of the American Association for Cancer Research, 2007.

[3]Jessing K, Mauck K, Bradford C, et al. 2005. MPC-6827, a Small Molecule Inhibitor of Microtubule Formation with High Brain Penetration: Absorption, Distribution, Metabolism, Excretion, and Clinical Considerations. 96th Annual Meeting of the American Association for Cancer Research, 2005.