

Phase II Clinical Trial of ZYC300 in Recurrent Glioblastoma Multiforme (GBM) Patients

Scientific Abstract

Cytochrome P450 1B1 (CYP1B1) has been shown to be over-expressed in a wide range of hematologic malignancies and solid tumors (1). Both normal human astrocytes and neurons have been reported to express CYP1B1 (2), but this expression is confined to the cell nucleus. Among central nervous system (CNS) malignancies, expression of CYP1B1 has been demonstrated on human medulloblastoma cells (3) and on malignant gliomas (4). CYP1B1 is immunologically recognized (5) and cytotoxic T-cells can be generated against it within cancer patients (1).

ZYC300 (MGI Pharma®) consists of a plasmid CYP1B1 DNA encapsulated in biodegradable microparticles that is administered intramuscular (i.m.). No significant adverse events have been observed in human subjects. In one study of six subjects with advanced malignancies that developed immunity to CYP1B1, three developed disease stabilization. Of note, these were heavily pretreated patients with solid and hematologic tumors. Of the patients that did not develop immunity to CYP1B1, the cancer progressed and did not respond to salvage chemotherapy. In the patients that developed immunity to CYP1B1 that required salvage therapy for progressive disease, there was marked response to their next treatment regimen, most of which lasted longer than one year (6). The association of immunity to response to next salvage therapy suggests that the chemotherapy resistant population was eliminated with the immunotherapy and induced subsequent chemotherapy sensitivity. Current standard of care for patients with GBM has been temozolomide (Schering-Plough) in combination with, and following radiation therapy. Conventional thought has been that chemotherapy would ablate the immunotherapy efficacy, however, upon administering the vaccine during recovery of the white blood cell nadir, there is potent immune enhancement likely secondary to the suppression of Tregs. Preliminary data from a peptide vaccine for GBM patients delivered sequentially with temozolomide in a Phase II clinical trial demonstrates even greater immunological responses and marked clinical activity compared to peptide alone (7), likely secondary to the inhibition of trafficking of Tregs into the tumor microenvironment (8).

This is a phase II, open-label, randomized study of ZYC300 in combination with standard and dose intensive temozolomide (TMZ) in patients with recurrent GBM. This protocol will be conducted with randomization by M.D. Anderson Cancer Center (MDACC) to assure balance. The adaptive sample size is based on the primary endpoint, TTP, in each of the experimental arms and will be monitored using the method of Thall (9). The trial will be stopped early if, given the current data, there is less than 1% chance that the median TTP will improve by more than 0.6 months in patients treated with the new regimen. If one treatment arm is superior, then the remaining patients will be accrued on that arm. If there is no difference, but there appears to be superiority compared to historical data, patients will continue to be accrued to both treatment arms. Up to 80 recurrent patients with GBM could be enrolled in this study. Patients are qualified for the trial within 2 weeks after re-resection and are eligible to receive ZYC300 vaccinations with temozolomide. All patients will undergo magnetic resonance imaging (MRI) of the brain every 8 weeks +/- 7 days and monthly blood draws for immunological monitoring.

The subjects will continue to receive monthly vaccinations until recurrence is documented by MRI.

At suspected recurrence, if clinically indicated, biopsy or surgery specimens will be obtained to determine if progression is related to treatment effect (i.e. radiation necrosis) or tumor progression. Furthermore, the CYP1B1 expression within the tumor and the type and activation state of the tumor infiltrating immune cells will be determined if the patient is resected. If there is uncertainty regarding progression the subject can be re-imaged in 30 days or alternative imaging can be employed such as SPECT MRI or PET. If there is continued progression, then the PFS will be set at the time when progression was first suspected. The patient will be taken off study when progression has been established and followed for survival.

(See body of protocol for a complete list of references).