CT240

A first-in-human study of the dual A_{2A}/A_{2B} adenosine receptor antagonist M1069 in patients with advanced solid tumors

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STUDY STATUS

The trial is open and recruiting; patients are being treated at the first dose level

Sites are open to enrollment in Canada and the US

INTRODUCTION

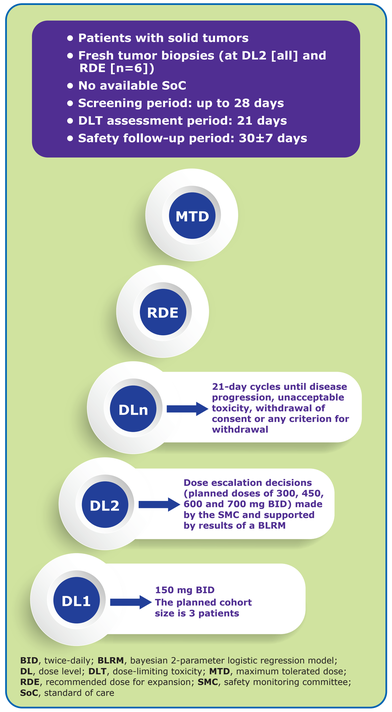
- A_{2A} and A_{2B} adenosine receptors have been shown to mediate immunosuppressive and tumor-promoting signals in the tumor microenvironment[1]
- A_{2A} and A_{2B} adenosine receptor inhibition may be a promising treatment strategy for patients with advanced tumors[1]
- Dual A_{2A}/A_{2B} receptor inhibition has shown an acceptable safety profile as monotherapy as well as early signs of clinical activity in combination with chemotherapy in patients with advanced solid tumors[2,3]
- M1069 is a novel, orally administered, highly selective dual antagonist of the A_{2A} and A_{2B} adenosine receptors that was recently demonstrated to counteract immune-suppressive mechanisms in the presence of high concentrations of adenosine and to enhance the anti-tumor activity of chemotherapies[4]
- The aim of this Phase 1a first-in-human non-controlled, open-label, multicenter, dose escalation clinical study (NCT05198349) is to investigate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and preliminary activity of M1069 in patients with metastatic or locally advanced unresectable solid tumors

TRIAL DESIGN

Phase 1a dose escalation

- The study includes a 28-day screening period, a study intervention period consisting of 21-day cycles, a dose-limiting toxicity (DLT) observation period of 21 days, an end of study intervention visit and a safety follow-up period of 30±7 days
- Patients (approximately 21–30) will receive M1069 twice-daily (BID) monotherapy in 21-day cycles until disease progression, unacceptable toxicity, withdrawal of consent or any criterion for withdrawal from study intervention
- The starting dose is 150 mg BID, with dose escalation decisions (planned doses of 300, 450, 600 and 700 mg BID) made by the Safety Monitoring Committee (SMC) and supported by results of a Bayesian 2-parameter logistic regression model (BLRM)
- The planned cohort size is 3 patients
- Additional expansion cohorts assessing M1069 alone, or in combination with other anticancer agents, and potentially in disease-specific settings, may be added by protocol amendment

Figure 1. Trial design



BID, twice-daily; **BLRM**, bayesian 2-parameter logistic regression model; **DL**, dose level; **DLT**, dose-limiting toxicity; **MTD**, maximum tolerated dose; **RDE**, recommended dose for expansion; **SMC**, safety monitoring committee; **SoC**, standard of care

ELIGIBILITY, OBJECTIVES AND ENDPOINTS

Table 1. Key eligibility criteria

Inclusion criteria	Exclusion criteria
≥18 years of age	Prior treatment with another agent targeting the adenosine signalling pathway (inhibitors of CD39, CD73 and/or A_{2A} or A_{2B} receptors)
ECOG PS ≤1	Prior anticancer treatment within 4 weeks or 5 half-lives
Adequate hematologic, renal and liver function	Persisting toxicity related to prior therapy grade >1 NCI-CTCAE v5.0; however, alopecia, sensory neuropathy, hypothyroidism and diabetes mellitus grade ≤2, despite treatment, are allowed
Histologically or cytologically confirmed, locally advanced or metastatic solid tumors that are refractory to, or have progressed with standard therapy, or for which clinical benefit with standard therapy is not expected	Active bacterial, fungal or viral infection
Paired tumor biopsies (pre- and on-treatment) for DL2 and RDE cohorts	History of (cardio)vascular/cerebrovascular disease/live vaccination
Measurable disease according to RECIST v1.1	

Table 2. Objectives and endpoints

Objectives	Endpoints
Primary	
To determine dose-toxicity relationship and MTD (if reached) of M1069 as a monotherapy	Occurrence of DLTs and AEs/TRAEs
To determine the RDE of M1069 for further exploratory clinical development	In addition to safety, tolerability, PK, PD, on-treatment changes in paired tumor biopsies are considered
Secondary	
To characterize the PK profile of M1069	PK parameter estimates (including AUC, CL/F, Vz/F, $t_{1/2}$, C_{max} and R_{acc})
To evaluate indicators of the clinical activity of M1069	Efficacy parameters (OR, DoR and PFS)
To assess the effect of M1069 on QT interval	Changes from baseline QTc over time
Tertiary/exploratory	
To investigate the PD biomarker changes (pCREB, endogenous biomarkers of CYPs and transporters in plasma) and immunologic effects of M1069	PD and immunologic parameters (including pCREB inhibition, measurements of biomarkers of CYPs and transporters)

AE, adverse event; **BLRM**, Bayesian 2-parameter logistic regression model; **CYP**, cytochrome P450; **DL**, dose level; **DLT**, dose-limiting toxicity; **DoR**, duration of response; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **ECG**, electrocardiogram; **MTD**, maximum tolerated dose; **NCI-CTCAE**, National Cancer Institute Common Terminology Criteria for Adverse Events; **OR**, objective response; **pCREB**, phosphorylated cAMP response element-binding protein; **PFS**, progression-free survival; **PD**, pharmacodynamics; **PK**, pharmacokinetics; **QTc**, QT interval corrected; **RDE**, recommended dose for expansion; **RECIST**, Response Evaluation Criteria in Solid Tumors; **SMC**, Safety Monitoring Committee; **TEAE**, treatment-emergent adverse event; **TME**, tumor microenvironment; **TRAE**, treatment-related adverse event

STATISTICAL ANALYSIS

- This is an exploratory study; no formal statistical hypothesis will be tested and all analyses are considered descriptive
- The dose-toxicity curve will be modelled based on prior assumptions and the available DLT data using a BLRM. The BLRM will support the SMC by recommending a dose for the next cohort based on minimizing the Bayesian risk
- M1069's safety profile will be assessed through recording, reporting and analysis of baseline medical conditions, DLTs, AEs, physical examination findings, vital signs, ECGs and laboratory tests; AEs will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) and the severity of AEs will be graded according to NCI-CTCAE v5.0
- PK parameters will be calculated using noncompartmental analysis
- Efficacy parameters will be determined according to RECIST v1.1; the objective response rate will be calculated with the 2-sided 95% confidence interval using the Clopper-Pearson method

STUDY CONTACT

- The coordinating investigator for this study is Professor Lillian Siu, MD, FRCPC (Lillian.Siu@uhn.ca)
- For further information, please visit https://www.clinicaltrials.gov/ct2/show/NCT05198349

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