Intra-cranial administration of MTL-004, a promising post-resection treatment for glioblastoma

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Introduction

- **Glioblastoma** is the most common malignant primary intracranial tumor.
- **Actual treatments** consist of extensive surgical resection followed by radiation and adjuvant temozolomide chemotherapy.
- **Median survival time with treatments** in adults is around 10 to 14 months. In addition, a survival rate of only 3 to 5% is observed more than 3 years following diagnosis.
- **MTL-004** (5-(aziridine-1-yl)-4-hydroxyaminomethyl-2-nitrobenzamide) is a cytotoxic agent forming covalent inter-strand cross linking bonds between DNA strands. It is rapidly deactivated in contact with plasma/serum proteins, and shows low toxicity and minimal side effects.

- **The study aims** to assess the efficacy of MTL-004 formulated in mannitol-leucine mix (excipient powder), when locally delivered to the tumor resection site in a thermo sensitive polymer (PGLA/PEG) following surgery.

Materials and Methods

- **Animals**
  - Male and female Fischer 344 (F344/DuCrl) immunocompetent rats were purchased from Charles River.
  - Animal housing and all experimental procedures were conducted according to the French and European Regulations and the National Research Council Guide for the Care and Use of Laboratory Animals.
- **Formulation**
  - Temozolomide (TMZ), the standard of care (SoC) was resuspended in a solution of kolliphor, ethanol and glucose 5%.
  - MTL-004 in excipient powder and excipient powder alone were mixed with PGLA/PEG polymer and resuspended in PBS.
- **In vivo efficacy of locally delivered PGLA/PEG/MTL-004 and survival**
  - On day 0 (DS), 2 mm³ tumor fragments were implanted in the cortex of healthy male or female animals.
  - On day 5 (DS), tumors were surgically removed. Both males and females were distributed into 3 groups each, treated as follows:
    - Group 1 (placebo control) animals received a single intracranial dose of excipient powder alone in PGLA/PEG paste.
    - Group 2 (SoC) animals received 5 daily oral doses of TMZ at 50 mg/kg.
    - Group 3 animals received a single intracranial dose of excipient powder containing 1 mg/kg of MTL-004 in PGLA/PEG paste.
- **Magnetic Resonance Imaging (MRI)**
  - Tumor growth of animals was evaluated by MRI at 6 timepoints throughout the study.

Results

- **Female animals**
  - **Health parameters**
    - No significant body weight loss was recorded following surgery.
    - MTL-004 did not induce significant body weight loss following administration to animals, where TMZ treatment induced a significant mean body weight loss of 9.7%.
  - **Anti-tumoral activity and survival**
    - Survival is significantly prolonged in groups treated with MTL-004 compared to both control and TMZ treated animals. T/C = median survival of treated group vs control group.
    - MRI monitoring (below 21 days post tumor resection and treatment initiation) showed smaller tumors in animals treated with MTL-004.

- **Male animals**
  - **Health parameters**
    - Similar results were observed compared to female animals and MTL-004 was better tolerated than TMZ.
  - **Anti-tumoral activity and survival**
    - Survival is significantly prolonged in groups treated with MTL-004 compared to both control and TMZ treated animals. T/C = median survival of treated group vs control group.

Conclusions and Perspectives

- **Consistent trends were observed in both male and female animals.**
- **Treatment with MTL-004 in PGLA/PEG provided good tumor control, was well tolerated and provided a significantly greater probability of survival following tumor resection than oral temozolomide or placebo.**
- **Surgery, followed by local application of MTL-004 in PGLA/PEG polymer is demonstrated to be a well tolerated and promising treatment for glioblastoma suitable for clinical evaluation.**

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