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

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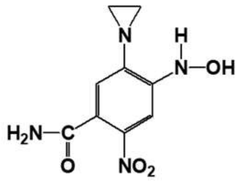
## Introduction

- **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 hydroxylamino-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 (D0), 2 $mm^3$ tumor fragments were implanted in the cortex of healthy male or female animals.
- On day 5 (D5), tumors were surgically removed. Both males and females were distributed into 3 groups each, treated as follow:
  - 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.

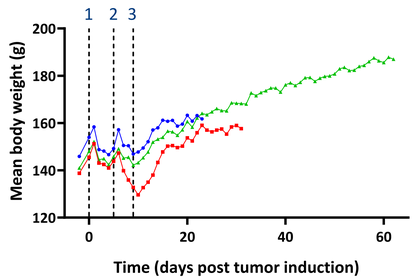
### Magnetic Resonance Imaging (MRI)

- Tumor growth of animals was evaluated by MRI at 6 timepoints throughout the study.

## Results

### Female animals

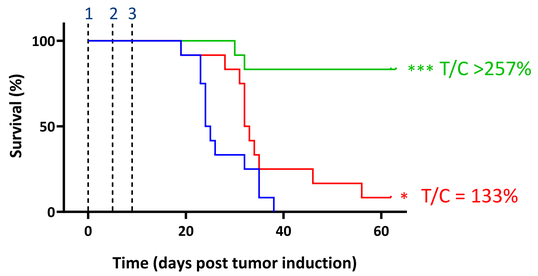
- Health parameters
  - No significant body weight loss was recorded following surgery.
  - **MTL-004 did not induce significant body weight loss** following administration to animals, where TMZ treatment induced a significant mean body weight loss of 9.7%.




Group 1: placebo (excipient powder)
Group 2: 50 mg/kg TMZ
Group 3: 1 mg/kg MTL-004 in excipient powder

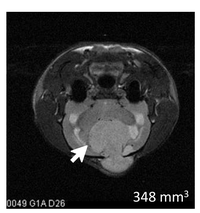
1: Tumor engraftment
2: Tumor resection & Treatment start
3: End of treatment period for SoC

- Anti-tumoral activity and survival
  - **Survival is significantly prolonged in groups treated with MTL-004** compared to both control ant TMZ treated animals. T/C = median survival of treated group vs control group.

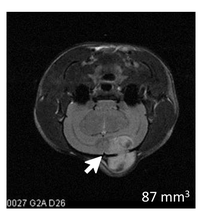



*: p<0.05 ***: p<0.001

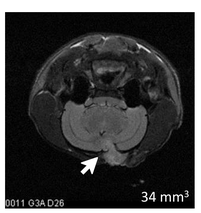
  - MRI monitoring (below 21 days post tumor resection and treatment initiation) showed **smaller tumors in animals treated with MTL-004**.



Group 1



Group 2

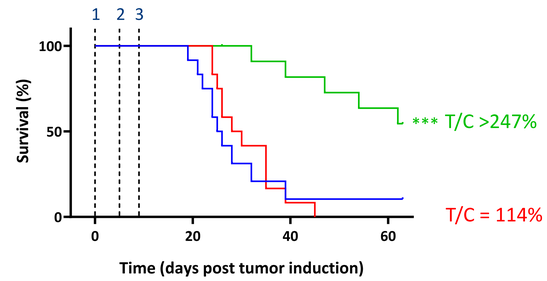


Group 3

### 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 ant TMZ treated animals. T/C = median survival of treated group vs control group.

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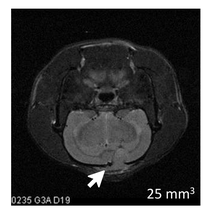
Group 1

Group 2



Group 3

## Conclusions and Perspectives

- Consistent trends were observed both in 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.