

Treating glioblastoma with a cytokine inhibitor, ibudilast in combination with temozolomide extends survival in a patient xenograft model

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Introduction

The standard treatment for newly diagnosed glioblastoma patients consists of concurrent radiotherapy and temozolomide followed by adjuvant temozolomide. The methylation of *MGMT* confers significant survival benefit to this treatment regime. However, despite their better prognosis, resistance to treatment is acquired and the tumour recurs.

The Aims of this study were to:

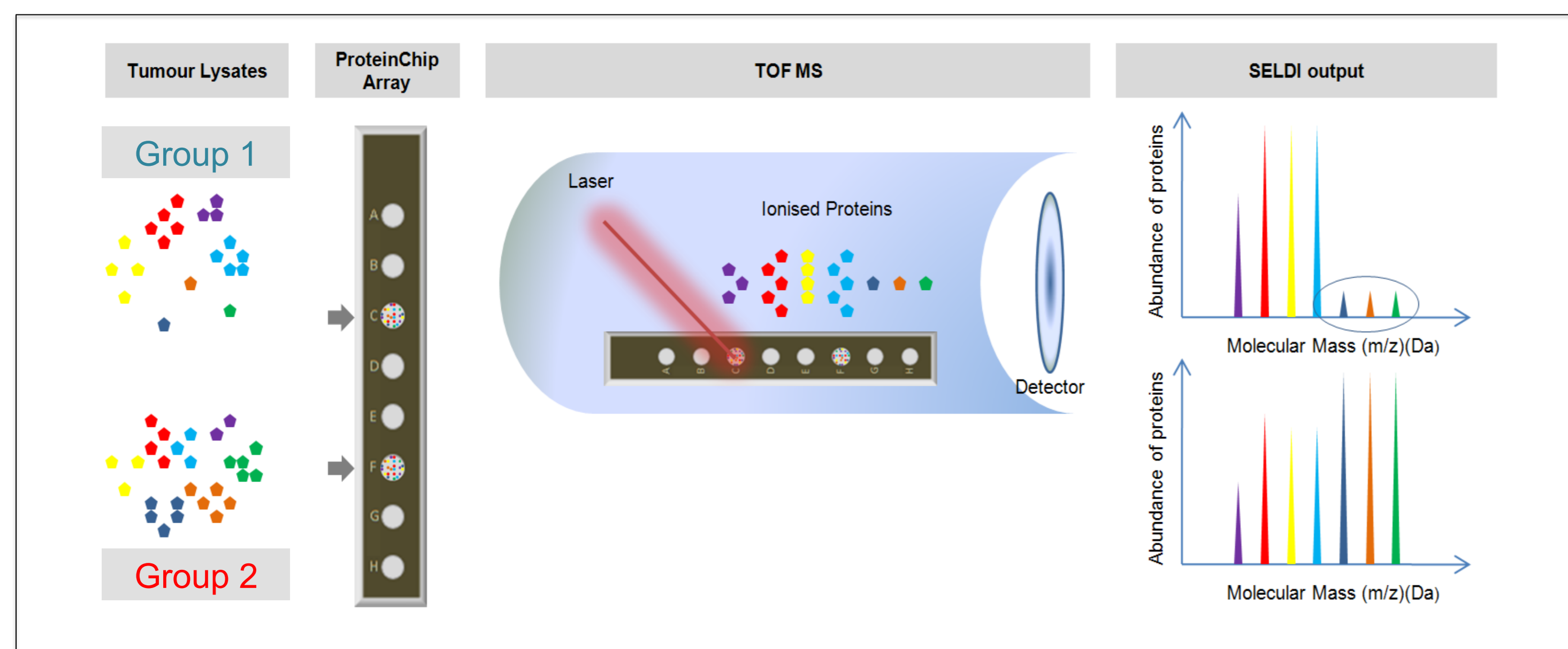
- (1) Compare the proteomic profiles of *MGMT* methylated glioblastoma samples when grouped according to survival (± 1 year)
- (2) Identify novel biomarkers associated with poor survival
- (3) Further explore these biomarkers as potential candidates for treatment.

Mass Spectrometry

Frozen tissue from 30 *MGMT* methylated glioblastomas were identified for proteomic profiling using SELDI-TOF mass spectrometry.

Patients were grouped according to survival:

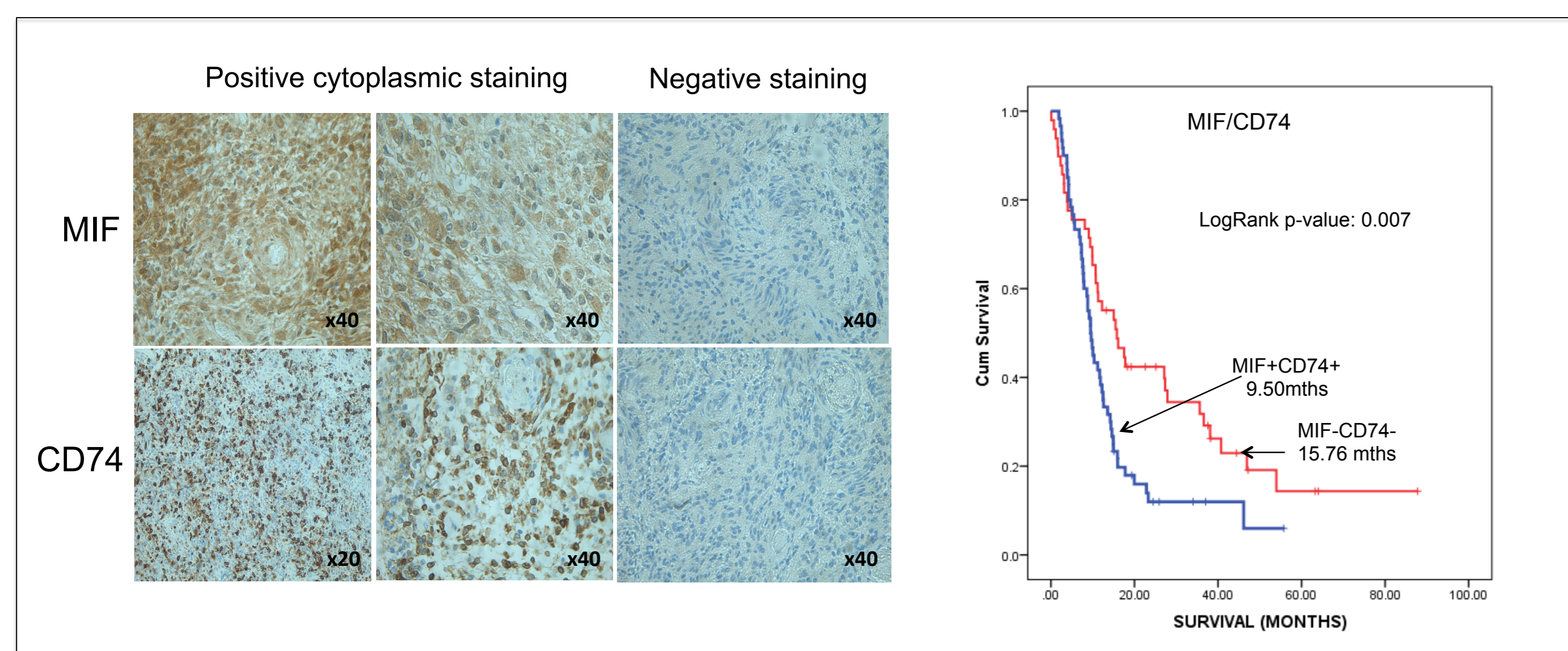
- Group 1: Poor survivors defined by survival of less than 12 months
Group 2: Good survivors defined by survival of more than 12 months



Macrophage Inhibitory Factor (MIF)

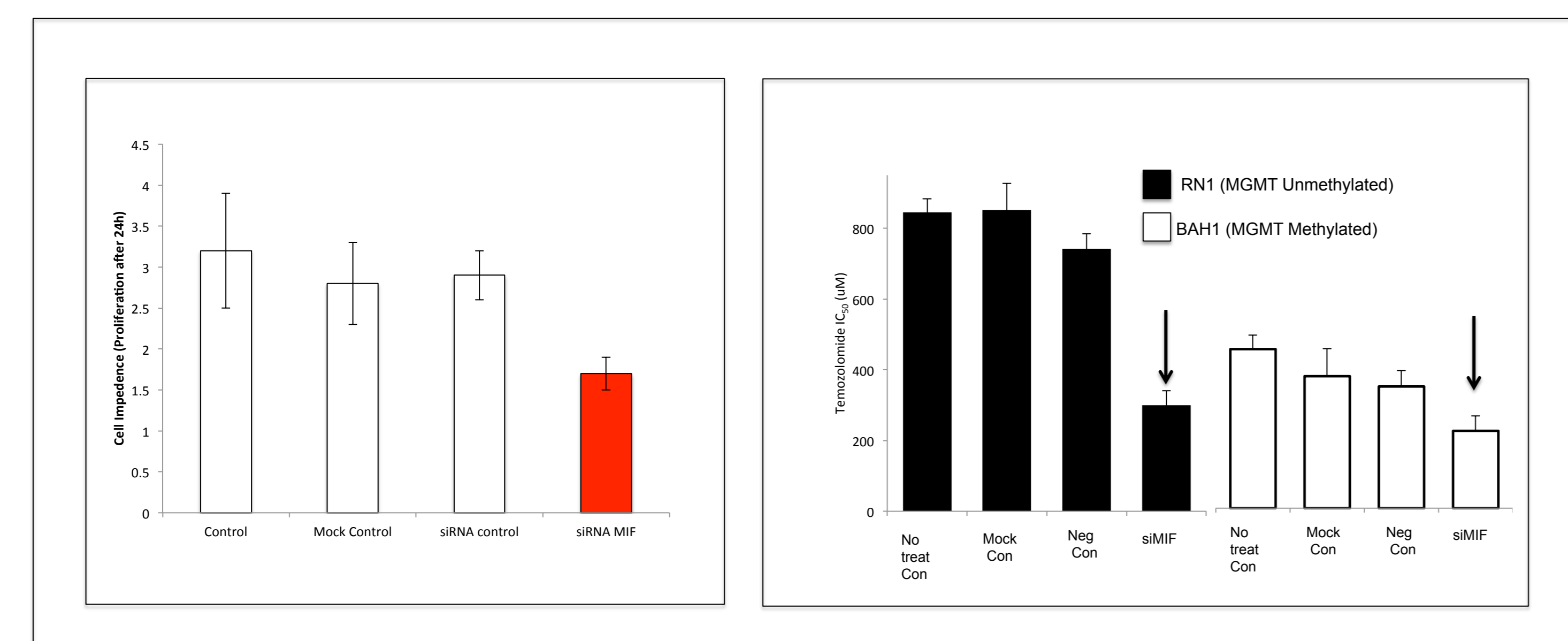
A 12.5 kDa protein specifically expressed in the "poor responders" was identified to be Macrophage Inhibitor Factor (MIF). MIF is an inflammatory-related cytokine secreted by cancer stem cells.

We analyzed expression levels of MIF and its receptor, CD-74 in 168 glioblastoma tissues. Co-expression of MIF and CD-74 were found in 57% of glioblastoma tissues and co-expression was significantly associated with poor overall survival.



siRNA knockdown of MIF reduces tumour cell proliferation and sensitizes cell to TMZ

We blocked MIF expression using a transient knock-down approach. Cell proliferation was impeded. Significant sensitivity to temozolomide was observed when MIF was blocked.

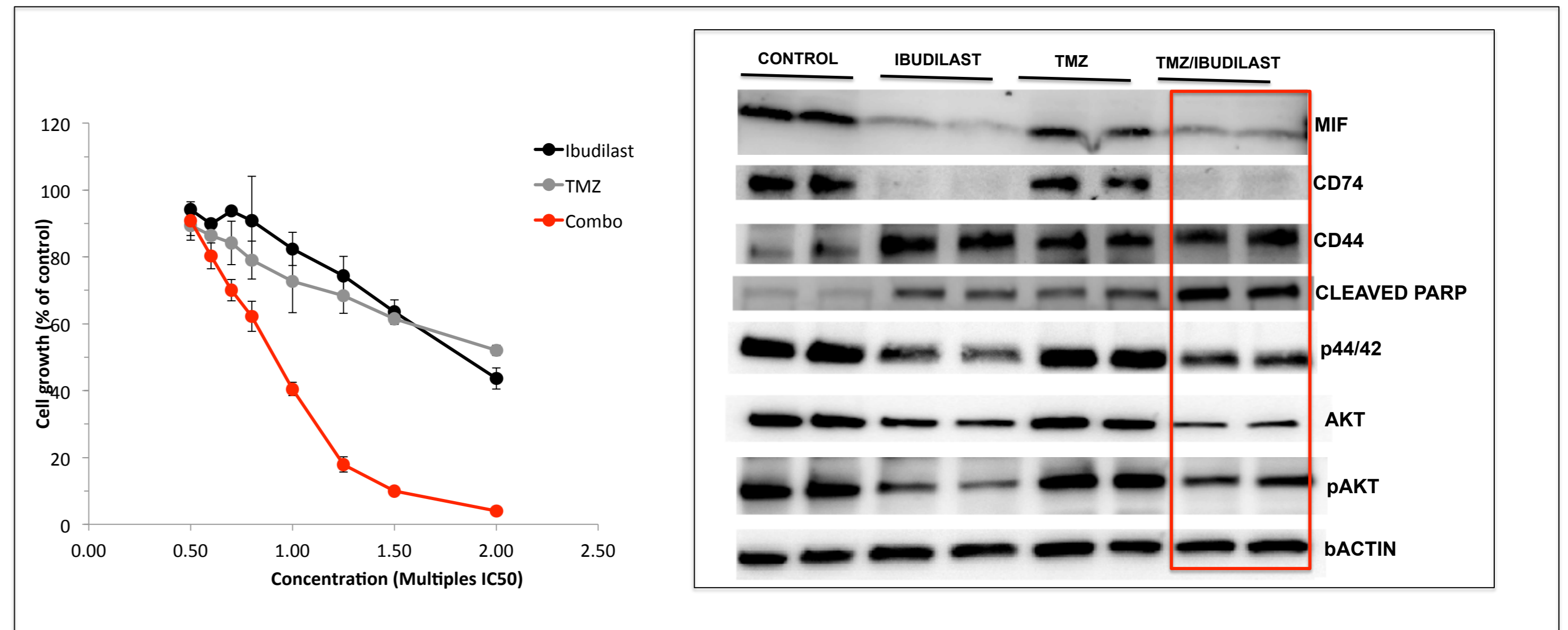


Ibudilast (MN-166)

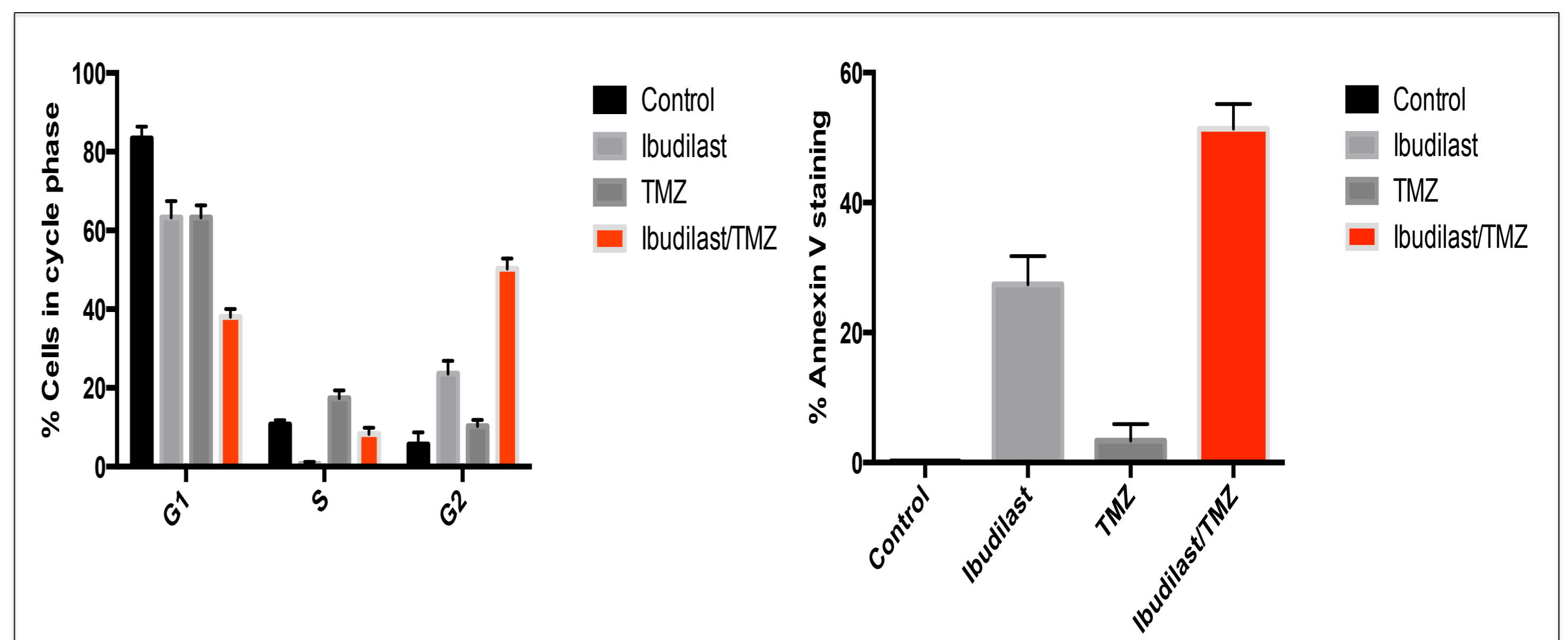
Ibudilast is an orally available, small molecule with anti-inflammatory and neuroprotective effects. It has been available in the Japanese and Korean markets for the treatment of asthma (20 mg/day) and cerebrovascular disorders (30 mg/day) for over 20 years.

Ibudilast is a specific inhibitor of MIF.

We treated a panel of patient-derived cell lines with ibudilast alone and in combination with temozolomide. In each and every cell line tested, we observed significant synergy with ibudilast and temozolomide.

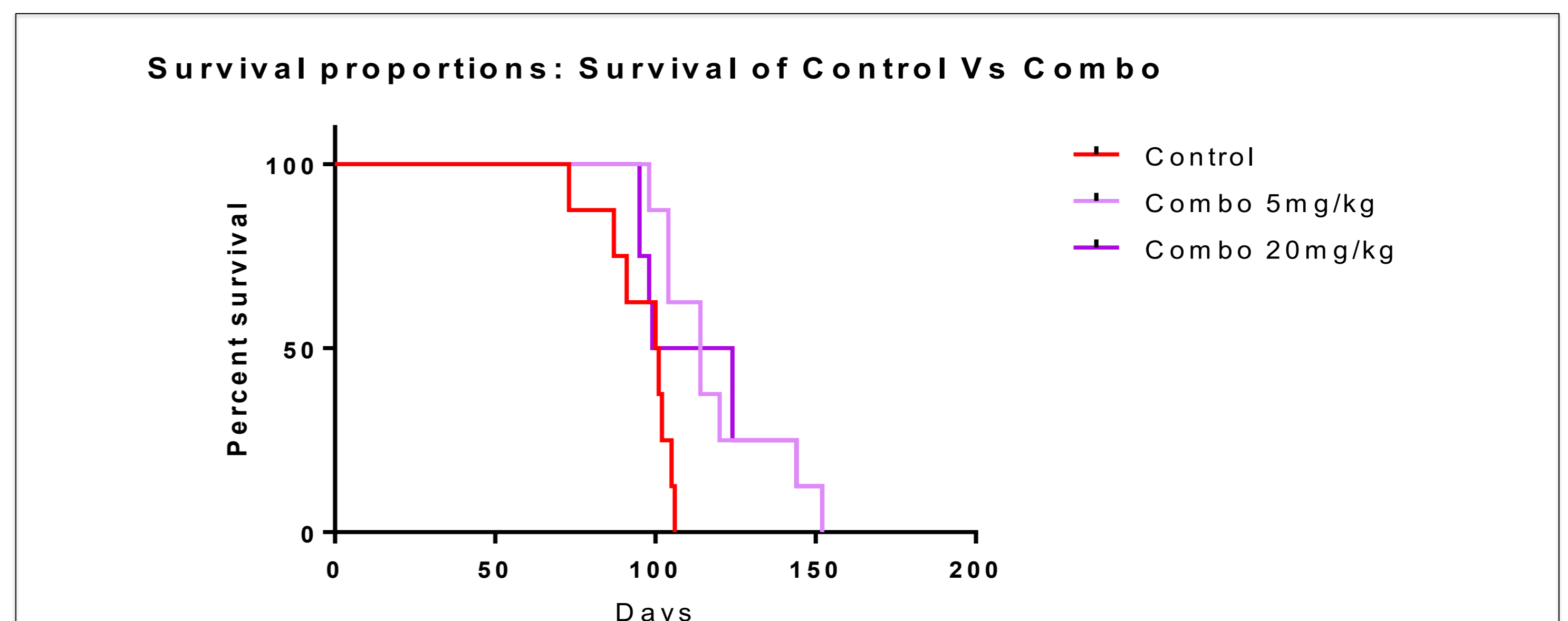


Combination of ibudilast and temozolomide results in G2 arrest and increased apoptosis



In vivo, the combination of ibudilast and temozolomide leads to significantly enhanced survival

We tested the combination of ibudilast and temozolomide in our PDX model: RN1 cells (*MGMT* unmethylated) intracranially implanted into the brains of balb/c nude mice. We administered ibudilast (5mg/kg or 20mg/kg) using oral gavage and temozolomide (10mg/kg) by I.P.



Significantly enhanced survival was observed when mice were treated with combination treatment compared to control mice. Median survival was 114 days (treated with combination) compared to control (100.5 days). Expression levels of MIF and its receptor, CD74 were suppressed.

Conclusions:

The combination of ibudilast and temozolomide leads to improved survival in a patient-derived xenograft model. The combination was well-tolerated.

A phase 1 trial is being planned to assess the efficacy of ibudilast (60mg/kg) combined with temozolomide (5 day schedule) for patients with recurrent glioblastoma.