Immunohistochemistry evaluation on pre-treatment tumor tissue predicts treatment response to MN-166 (ibudilast) and Temozolomide combination therapy in glioblastoma patients.

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Introduction

- MN-166-GBM-1201 is a Phase I/II open-label clinical trial to evaluate MN-166 (ibudilast) and Temozolomide (TMZ) combination treatment in newly diagnosed and recurrent glioblastoma (GBM) patients (NCT03782415).
- 62 GBM patients (36 newly diagnosed and 26 recurrent) were enrolled in the study.
- All patients received MN-166 and TMZ combination treatment until disease progression or withdrawal from the study for other reasons.
- Glioblastoma creates an immunosuppressive microenvironment
- MN-166 has been shown to disrupt the MIF-CD74 signaling axis which is critical for myeloid deriver suppressor cell generation.

Methods

- Immunohistochmeistry evaluation was conducted with the subjects whose pre-treatment tumor tissue samples were available from the resected tumors at the initial surgery or biopsy. Tumor tissue was stained for CD3, CD74, MIF, pERK, Ki67, and CD11b.
- C57BL/6 mice were intra-cranially injected with SB28 tumor cells at 4 weeks of life. Mice were treated with either isotype control, vehicle control, MN-166, anti-PD1 antibodies, anti-PDL1 or a combination therapy.

RESULTS

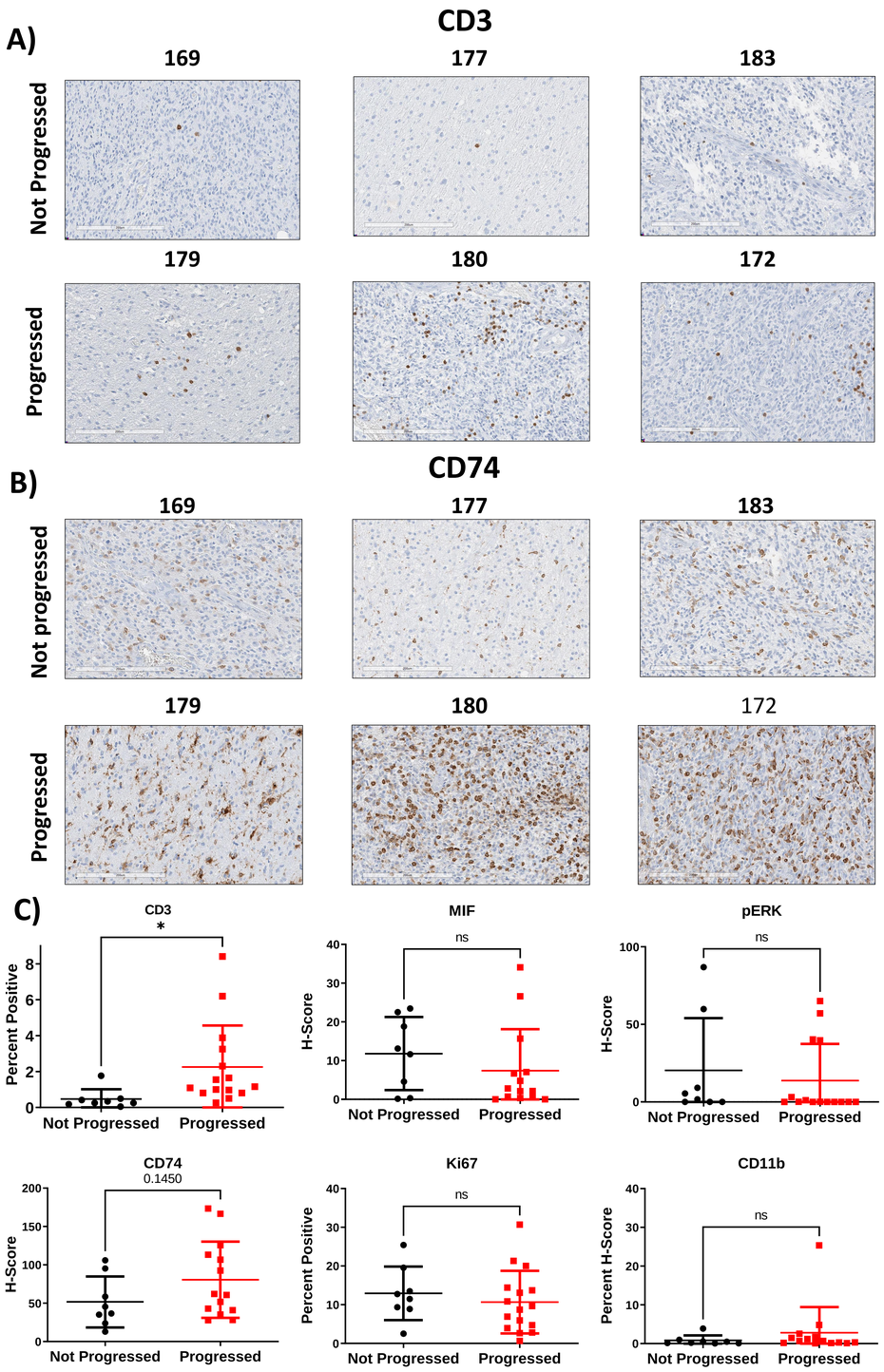

Figure 1. Patients with no progression at 5 months of MN-166 therapy had decreased CD3 tumor infiltration

A) CD3 immunohistochemistry and B) CD74 immunohistochemistry from a selected group of patients with tissue available. C) Comparison of immune markers between patients that progressed within 5 months (n=16) and those that did not progress (n=8). T-test, * <0.05, ** <0.01, *** <0.001

Key Finding

- **Response to Ibudilast in patients with GBM is correlated with CD3 expression**
- **Pre-clinical evidence indicates a combination with anti-PD1/PDL1 is synergistic in GBM**

Additional Data

Bayik et al. Cancer Discovery 2020

Alban et al. Frontier Immunology 2020

Alban et al. JCI Insight 2018

Alban et al. JCI Insight 2023

RESULTS

Total Enrolled (N=62)	Newly Diagnosed (N=36)	Recurrent (N=26)
Age at Screening Mean ± SD	58.9 ± 11.6	59.6 ± 9.7
Gender (% female)	39%	39%
Race n (%)		
Caucasian	34 (94)	26 (100)
Black or African American	1 (3)	0 (0)
Asian	1 (3)	0 (0)

Table 1. Patient clinical characteristics

Subject Type (N=62)	PFS6 n (%)
Newly Diagnosed (n=36)	16 (44%)
Recurrent (n=26)	8 (31%)

Table 2. Six-month progression free survival of patients that received at least 5 cycles of MN-166

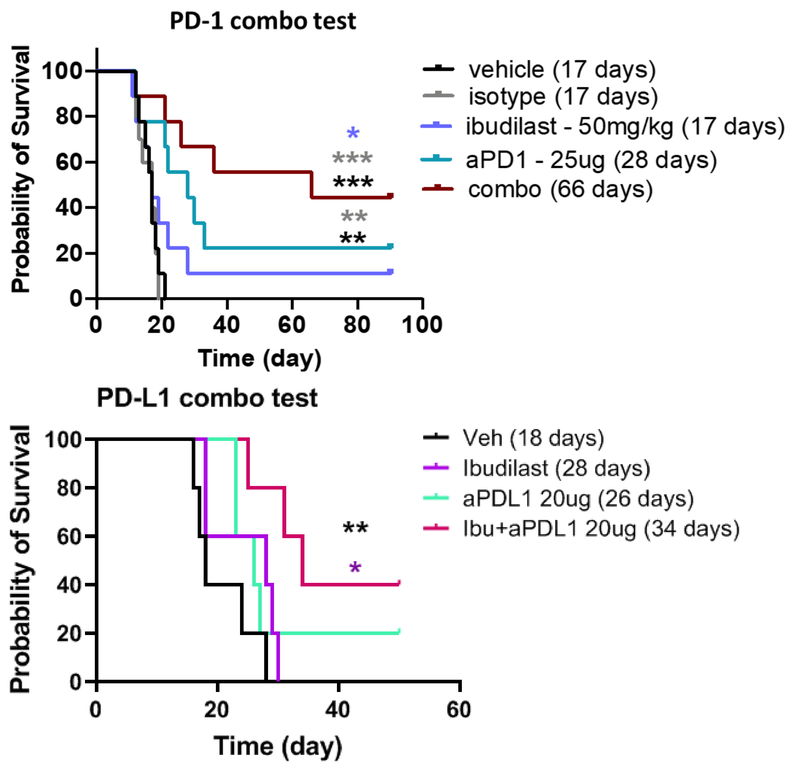

Figure 2. MN-166 and anti-PD1 or anti-PD-L1 combination therapy was efficacious in pre-clinical models

A) Anti-PD-1 and B) Anti-PD-L1 in combination with MN-166 (Ibudilast) in preclinical model of GBM.15,000 SB28 cells were intracranially injected at 4weeks of age. Log-rank test, * <0.05, ** <0.01, *** <0.001

CONCLUSIONS

- CD3 expression was a good predictor for tumor progression for five months in recurrent glioblastoma patients treated with MN-166 and TMZ.
- T cell infiltration within GBM tumors has been an active area of research with the success of immune checkpoint blockade (ICB) therapies in other cancers.
- Moreover, Ibudilast has been shown to impact immune suppressive myeloid cells, which are linked to the immune suppressive tumor microenvironment and a resistance mechanism to ICB.

Future Directions

- Together, this suggests that the efficacy of Ibudilast in GBM could be further enhanced with combination treatment with ICBs.
- Investigate impact of combination therapy on immune cell compartments in pre-clinical models

Acknowledgements

Thank you to the patients and families that participated in this clinical trial.

These studies were supported by the following MediciNova, R35NS127083, PO1CA245705, R01NS109742