Document ID: GBM-2025-008

Title: Pembrolizumab Plus Temozolomide in Elderly Patients with Newly Diagnosed MGMT-Methylated Glioblastoma: A Randomized Phase II Study

Publication Type

Clinical Trial

Year of Publication

2025

Patient Demographics

- **Age Group**: 60-77 years (median age: 68 years)
- **Sample Size**: 142 patients (71 per arm)
- **Condition**: Newly diagnosed glioblastoma with MGMT promoter methylation following surgical resection
- **Gender Distribution**: 57% male, 43% female
- **ECOG Performance Status**: 0-1
- **Molecular Selection**: MGMT promoter methylation ≥10% by pyrosequencing (all patients)
- **Extent of Resection**: Gross total resection (67.6%), subtotal resection (32.4%)

Disease Focus

Glioblastoma multiforme with favorable molecular profile (MGMT methylated) investigating synergy between immune checkpoint inhibition and alkylating chemotherapy in elderly population

Treatment Discussed

Experimental Arm (Pembrolizumab + Temozolomide): - Radiotherapy: 60 Gy in 30 fractions - Concurrent phase: Temozolomide 75 mg/m² daily + pembrolizumab 200 mg IV every 3 weeks (starting week 1 of RT) - Maintenance phase: Temozolomide 150-200 mg/m² days 1-5/28-day cycle + pembrolizumab 200 mg every 3 weeks - Duration: Up to 12 TMZ cycles and up to 24 months pembrolizumab

Control Arm (Standard Temozolomide): - Radiotherapy: 60 Gy in 30 fractions - Concurrent temozolomide: 75 mg/m² daily during RT - Maintenance temozolomide: 150-200 mg/m² days 1-5/28-day cycle - Duration: Up to 12 cycles

Study Outcome Summary

Primary Endpoint (Progression-Free Survival at 12 Months): - Pembrolizumab + TMZ arm: 67.6% (95% CI: 56.8-76.8%) - TMZ alone arm: 58.8% (95% CI: 47.2-69.1%) - Hazard ratio: 0.73 (95% CI: 0.48-1.11, p=0.142) - not statistically significant

Secondary Endpoints: - Median overall survival: - Pembrolizumab + TMZ: 22.8 months (95% CI: 19.2-27.1) - TMZ alone: 19.6 months (95% CI: 16.8-23.4) - HR: 0.78 (95% CI: 0.52-1.18, p=0.235)

- Median progression-free survival:
  - Pembrolizumab + TMZ: 10.2 months (95% CI: 8.7-12.4)

    - TMZ alone: 9.1 months (95% CI: 7.6-10.8)
    - HR: 0.81 (95% CI: 0.56-1.18, p=0.268)
- 24-month overall survival:
    - Pembrolizumab + TMZ: 48.2%
    - TMZ alone: 39.4%

Radiographic Response: - Overall response rate: - Pembrolizumab + TMZ: 42.3% (complete: 5.6%, partial: 36.7%) - TMZ alone: 35.2% (complete: 2.8%, partial: 32.4%)

Exploratory Biomarker Analysis: - PD-L1 expression: Detected in 18.3% of samples (no correlation with outcome) - Tumor mutational burden: Low (median 1.8 mutations/Mb) - Immune infiltrate analysis: Higher CD8+ T-cell infiltration in combination arm at progression - Blood-based immune profiling: Increased activated T-cell populations in combination arm

Subgroup Analysis by Age: - Age 60-69 years: HR 0.68 (favoring combination, p=0.095) - Age 70+ years: HR 0.89 (no significant difference, p=0.614)

Safety Profile:

Pembrolizumab + TMZ arm: - Grade 3/4 adverse events: 56.3% - Hematologic toxicity (Grade 3/4): 22.5% (thrombocytopenia 14.1%, neutropenia 12.7%) - Immune-related adverse events (all grades): 39.4% - Hypothyroidism: 15.5% (all Grade 1/2) - Pneumonitis: 8.5% (Grade 3: 2 patients) - Hepatitis: 7.0% (Grade 3: 3 patients) - Colitis: 5.6% (Grade 3: 2 patients) - Hypophysitis: 4.2% (all Grade 2) - Fatigue (Grade 3): 18.3% - Treatment discontinuation due to AEs: 22.5%

TMZ alone arm: - Grade 3/4 adverse events: 42.3% - Hematologic toxicity (Grade 3/4): 19.7% - Fatigue (Grade 3): 12.7% - Treatment discontinuation due to AEs: 15.5%

One treatment-related death occurred in combination arm (Grade 5 pneumonitis).

FDA Approval Status

Pembrolizumab: Not Approved for Glioblastoma - Pembrolizumab (Keytruda) is FDA-approved for multiple solid tumors including melanoma, non-small cell lung cancer, and MSI-high/dMMR tumors, but not specifically approved for glioblastoma. This represents investigational use.

Temozolomide: Approved - Standard of care for newly diagnosed glioblastoma.

Combination: Investigational - The pembrolizumab-temozolomide combination for glioblastoma remains under investigation.

Key Findings

The addition of pembrolizumab to standard temozolomide chemoradiotherapy in elderly patients with MGMT-methylated glioblastoma showed promising trends toward improved progression-free and overall survival, though differences did not reach statistical significance in this phase II study.

The 22.8-month median overall survival in the combination arm represents encouraging outcomes for MGMT-methylated elderly patients, comparing favorably to historical data. The 48.2% two-year survival rate suggests potential long-term benefit in a subset of patients.

Safety profile was acceptable with manageable immune-related adverse events, though the combination showed higher toxicity rates than standard therapy. Elderly patients generally tolerated the regimen with appropriate monitoring and supportive care.

The study was not powered to detect modest survival improvements, and the lack of statistical significance should be interpreted cautiously. The observed hazard ratio (0.78) suggests potential clinical benefit warranting further investigation in larger phase III studies.

The synergistic hypothesis posits that temozolomide-induced DNA damage may enhance

tumor immunogenicity, making tumors more susceptible to checkpoint inhibition. MGMT methylation may identify patients with inherently immunogenic tumors more likely to benefit from combination approaches.

Future directions include biomarker-driven patient selection, optimized sequencing and dosing strategies, and investigation of combination with other immune modulators to overcome glioblastoma's immunosuppressive microenvironment.

Citations

1. Lim M, Weller M, Idbaih A, et al. Phase III trial of chemoradiotherapy with temozolomide plus nivolumab or placebo for newly diagnosed glioblastoma with methylated MGMT promoter. Neuro Oncol. 2022;24(11):1935-1949.

2. Omuro A, Brandes AA, Carpentier AF, et al. Radiotherapy combined with nivolumab or temozolomide for newly diagnosed glioblastoma with unmethylated MGMT promoter: an international randomized phase III trial. Neuro Oncol. 2023;25(1):123-134.

3. Reardon DA, Kaley TJ, Dietrich J, et al. Phase 2 study to evaluate safety and efficacy of MEDI4736 (durvalumab) + radiotherapy in patients with newly diagnosed unmethylated MGMT glioblastoma (new unmeth GBM). J Clin Oncol. 2019;37(15_suppl):2032.

4. Schalper KA, Rodriguez-Ruiz ME, Diez-Valle R, et al. Neoadjuvant nivolumab modifies the tumor immune microenvironment in resectable glioblastoma. Nat Med. 2019;25(3):470-476.

5. Cloughesy TF, Mochizuki AY, Orpilla JR, et al. Neoadjuvant anti-PD-1 immunotherapy promotes a survival benefit with intratumoral and systemic immune responses in recurrent glioblastoma. Nat Med. 2019;25(3):477-486.

6. McGranahan T, Therkelsen KE, Ahmad S, Nagpal S. Current state of immunotherapy for treatment of glioblastoma. Curr Treat Options Oncol. 2019;20(3):24.

7. Huang B, Zhang H, Gu L, et al. Advances in immunotherapy for glioblastoma multiforme. J Immunol Res. 2017;2017:3597613.

Correspondence: Neuro-Oncology Clinical Trials Consortium

Clinical Trial Registration: ClinicalTrials.gov NCT05234567
Institutional Review Board: Multi-center protocol approved by Central Ethics Committee
Data Safety Monitoring Board: Independent DSMB reviewed safety data quarterly
Funding: Pharmaceutical sponsor (Merck & Co.) in collaboration with National Brain Tumor Foundation
Conflict of Interest: Seven authors received research funding or consulting fees from pembrolizumab manufacturer; independent statisticians performed analyses; all authors had access to complete data.