T cell–bispecific antibody

Summarize the findings of the article: Whittle JR, Vieito M, Rohrberg K, Rodriguez-Ruiz ME, Castanon E, Mellinghoff IK, Van Linde M, Cloughesy T, Reardon DA, Chong RA, Rosenthal M, Wick A, Waldhauer I, Henkel N, Romagnoli B, Wolowski V, Dey S, Heil F, Heichinger C, Flinn N, Gou JP, Smith L, Prince F, Derks M, Roller A, Schiff C, Schneider M, Mason W. First-in-human study of an EGFRvIII x CD3 T cell bispecific antibody in the treatment of newly diagnosed glioblastoma. Neurooncol Adv. 2025 Jul 18;7(1):vdaf160. doi: 10.1093/noajnl/vdaf160. PMID: 40842640.

Here is a concise summary of the key findings from Whittle et al., *"First-in-human study of an EGFRvIII × CD3 T cell bispecific antibody in the treatment of newly diagnosed glioblastoma"* (2025) OUP Academic+2PMC+2

Background & Rationale

- Glioblastoma (GBM) remains a highly aggressive brain tumor with poor prognosis, and new immunotherapeutic approaches are needed.
- The EGFRvIII mutation (a tumor-specific variant of the epidermal growth factor receptor) is an attractive target because it is expressed on tumor cells but not in normal tissue.
- The authors developed a T cell–bispecific antibody (TCB) that binds EGFRvIII on tumor cells and CD3 on T cells (termed **EGFRvIII × CD3 TCB**), aimed to redirect T cells to kill EGFRvIII-positive GBM cells. PubMed+2PMC+2
- This was the first time such a TCB was tested in humans, specifically in patients with newly diagnosed, EGFRvIII-positive GBM, in a post–chemoradiation "maintenance" setting. PMC+1

Study Design & Methods

- Phase 1, open-label, multicenter, dose-escalation trial. PMC+1
- Patients first underwent standard of care (surgery + chemoradiation). After that, they received the EGFRvIII × CD3 TCB in escalating doses. PMC+1
- Doses ranged from **0.004 to 10 mg**, given every 3 weeks (Q3W). Some cohorts used a "step-up" dosing schedule to mitigate potential toxicities. PMC+1
- Primary objectives: safety, tolerability, and determination of the maximum tolerated dose (MTD). Secondary objectives: pharmacokinetics (PK), immunogenicity, pharmacodynamics, and any signs of clinical activity. PMC+2OUP Academic+2

- 36 patients were enrolled (32 with unmethylated MGMT promoter, 4 with methylated). OUP Academic+2PMC+2

Safety & Tolerability

- The therapy was generally well tolerated up to the highest dose tested (10 mg Q3W). PMC+2OUP Academic+2
- Only **one dose-limiting toxicity (DLT)** was observed (a grade 3 seizure). The MTD was **not** reached. PMC+2OUP Academic+2
- Most adverse events (AEs) were mild to moderate (grade 1–2). The most common treatment-related AE was headache (~22%). PubMed+2PMC+2
- Some patients experienced grade 3 AEs (e.g. seizures, brain edema, decreased lymphocyte or neutrophil counts). One grade 4 AE (epilepsy) was reported in a single patient. PMC+1
- Anti-drug antibodies (ADAs) were detected in 4 of 36 patients (11%). However, titers tended to decline over time, and no clear relationship was seen between ADA presence and pharmacokinetics or safety. PMC+1

Pharmacokinetics & Distribution

- The TCB exhibited **dose-proportional pharmacokinetics** in both serum and cerebrospinal fluid (CSF). PMC+2OUP Academic+2
- The ratio of CSF to serum concentrations was ~0.08, indicating limited penetration across the blood–brain barrier (BBB). PMC+1
- Even at the highest tested dose (10 mg), the observed serum concentrations were still ~6-fold lower than the lower bound of the **predicted therapeutic range** based on preclinical models (i.e. the predicted active dose). PMC+2OUP Academic+2

Clinical Activity / Efficacy Signals

- Among 36 treated patients, 28 were evaluable for response (some had no measurable disease at baseline). PMC+1
- **No objective radiographic responses** (i.e. tumor shrinkage) were seen. PMC+2OUP Academic+2
- The best overall response was **stable disease** in many patients. In patients with unmethylated MGMT promoter (n = 26 evaluable), 20 (77%) achieved stable disease, and 6 (23%) had progression as the best response. PMC+1
- Five patients maintained stable disease for ≥ 6 months; three of them had received doses ≥ 6.5 mg. PMC+1

- In patients with unmethylated MGMT (n = 32), median progression-free survival (PFS) was 4.4 months (95% CI, 3.7 to 5.6). The 1-year survival rate was estimated at ~73%. PMC+1
- A subgroup of 13 patients who got ≥ 6.5 mg for at least two cycles had a median PFS of 5.1 months and a 1-year survival ~91%. PMC+1

Authors' Interpretation & Limitations

- The authors conclude that EGFRvIII × CD3 TCB is **safe and tolerable** up to 10 mg Q3W in the maintenance setting after standard therapy. OUP Academic+2PMC+2
- However, they caution that **no evidence of efficacy** (tumor shrinkage) was observed at the tested doses. They note that the highest dose tested still achieved serum exposures well below the predicted therapeutic threshold. PMC+3PMC+3OUP Academic+3
- The study was terminated before further dose escalation, in part due to the sponsor's decision. PMC+1
- They suggest that **higher doses** (beyond 10 mg) may need to be tested to reach efficacious exposure and evaluate whether antitumor activity can emerge. OUP Academic+2PMC+2
- Several limitations are highlighted:
    1. The study's phase 1 nature and small sample size limit conclusions about efficacy. OUP Academic+2PMC+2
    2. The highest tested dose did not reach predicted therapeutic concentrations, suggesting underdosing. PMC+1
    3. Penetration across the BBB may be a key hurdle (CSF/serum ratio ~0.08). PMC+1
    4. The heterogeneous and immunosuppressive microenvironment of GBM may limit T cell engagement and penetration.
    5. The trial was conducted in patients post-chemoradiation, so the ability to act in more aggressive or residual disease settings remains uncertain.

Take-Home Message

This first-in-human trial of the **EGFRvIII × CD3 T cell bispecific antibody** in newly diagnosed, EGFRvIII-positive glioblastoma demonstrated a favorable safety profile (no MTD reached, mostly mild to moderate AEs). However, **no objective antitumor responses** were seen at the doses tested, which achieved serum exposures below predicted therapeutic levels. To assess whether this approach can achieve clinical benefit, further studies at higher doses — with attention to brain penetration, immune microenvironment barriers, and patient selection — are needed.

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