Sarkaria & Donner “umbrella” precision-medicine trial in glioblastoma

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Here is a summary of the key findings, strengths, and limitations of the Sarkaria & Donner “umbrella” precision-medicine trial in glioblastoma (Neuro Oncol. 2025, “noaf243”). I reviewed the published article (pdf) OUP Academic and related sources (e.g. the N2M2 / NOA-20 umbrella trial) ResearchGate +1 .

Study design & rationale

- This was a **precision medicine umbrella trial** in patients with newly diagnosed glioblastoma (GBM) **without MGMT promoter hypermethylation** (i.e. unmethylated MGMT), a group with limited benefit from temozolomide, aiming to “nominate” promising therapies to pursue further. OUP Academic +1
- Patients underwent molecular profiling (within ~28 days post-surgery) and allocation by a molecular tumor board to one of several targeted subtrials matched to putative driver alterations; patients without a clear match were randomized to “no-match” arms (e.g. immunotherapy or standard-of-care). OUP Academic +1
- All arms included concurrent radiotherapy (“backbone”) plus the investigational (or comparator) agent. OUP Academic
- Phase I parts focused on dose finding and safety; Phase II portions used **6-month progression-free survival (PFS-6)** as the primary efficacy endpoint, with interim futility rules. OUP Academic +1
- Enrollment spanned ~May 2018 to July 2022 across 13 German NOA sites; 301 patients were enrolled and 228 treated (i.e. allocated and started therapy) ResearchGate +2 ResearchGate +2 .

Key results / findings

Enrollment & arm accrual

- Two planned arms (alectinib, vismodegib) never “opened” because no patients matching those alterations were accrued. ResearchGate +1
- The idasanutlin arm was terminated early (n = 9) by the drug supplier before optimal dosing. ResearchGate +1
- Thus the arms that completed accrual included: **temsirolimus (mTOR pathway–activated tumors)**, **palbociclib (CDK4 amplification / CDKN2A/B loss)**, and **“no-match” arms**: atezolizumab, asunercept, plus a temozolomide standard-of-care comparator arm. ResearchGate +2 OUP Academic +2

Safety / tolerability

- The regimen-limiting toxicity (RLT) rate across arms was 34.8%, modestly above the prespecified unacceptable threshold of 30%, but not judged clinically prohibitive. ResearchGate +1
- Most RLT events were grade 3; one was grade 4; no deaths resulted from RLTs. ResearchGate +1
- Importantly, no major negative interactions between the investigational agents and radiotherapy were observed in terms of safety. OUP Academic +1

Efficacy / "nomination" outcomes

- The **temsirolimus** arm (in patients whose tumors had **activated mTOR signaling**) achieved **PFS-6 = 39.1%** and a median overall survival (OS) of 15.4 months. This exceeded the comparator (temozolomide arm) PFS-6 of 18.5%. The difference met the primary endpoint statistical boundary ($p = 0.0109$ for temsirolimus vs SOC). ResearchGate +1
- The temozolomide "SOC" arm (MGMT-unmethylated) had PFS-6 of ~18.5% and median OS ~12.1 months. ResearchGate +1
- The **palbociclib** arm (in patients with CDK4 amplification / CDKN2A/B loss) did **not** meet efficacy thresholds: PFS-6 ~24.4%, OS ~12.6 months, failing statistical significance for benefit over SOC. ResearchGate +2 OUP Academic +2
- The **no-match arms** (atezolizumab, asunercept) also failed:
  - Atezolizumab: PFS-6 ~21.4%, OS ~11.7 months, non-significant. ResearchGate +1
  - Asunercept: PFS-6 ~15.4%, OS ~12.8 months, non-significant. ResearchGate +1

Thus, **temsirolimus in mTOR-activated GBM** emerged as a positive "nominee" for further follow-up; the other arms did not convincingly outperform standard therapy.

Interpretation & implications

- The trial demonstrates **feasibility** of integrating rapid molecular profiling and tumor-board–guided allocation into a glioblastoma clinical-trial framework, even in a challenging unmethylated-MGMT patient population. OUP Academic +2 ResearchGate +2
- The positive "signal" for temsirolimus in mTOR-activated tumors is especially interesting: it suggests that a biomarker-selected approach may yield benefit in a subgroup otherwise with poor prognosis. OUP Academic +1
- The negative (or null) results in palbociclib and in immunotherapy arms underscore that **biomarker matching is necessary but not sufficient**—even in molecularly selected patients, efficacy may be limited due to tumor resistance, heterogeneity, blood–brain barrier, or pharmacodynamics.
- The "nomination" model (i.e. selecting which agents to carry forward rather than powering for definitive phase III in every arm) is a pragmatic approach in this disease space with limited patient numbers and high failure rates.

Limitations & caveats

- The patient numbers in many arms were relatively small (especially idasanutlin, alectinib, vismodegib which didn't accrue), limiting statistical power and robustness of comparisons. ResearchGate +1
- Because this is not a large confirmatory randomized trial, the results (especially the temsirolimus signal) remain **hypothesis-generating** and need validation in independent cohorts/trials.
- The biomarker definitions (e.g. what constitutes "activated mTOR signaling") and how strictly they align with drug sensitivity remain challenges.
- The blood–brain barrier (BBB) remains a key obstacle; systemic drug levels may not translate to effective intratumoral concentrations. The paper itself discusses BBB limitations. OUP Academic
- The study population was restricted to unmethylated-MGMT GBM, so results may not generalize to methylated MGMT tumors.