Clinical trial: Abemaciclib in recurrent meningioma

Kaley TJ, Grommes C, Coffee E, Young RJ, Morrison T, Daher A, Schaff LR, Deng Y, Nandakumar S, Diamond EL, DeAngelis LM, Panageas KS, Gavrilovic I, Lin A, Pentsova E, Stone J, Santomasso BD, Piotrowski AF, Nair S, Schultz N, Reiner AS, Mellinghoff IK. Multicenter basket trial for Central Nervous System tumors identifies activity of the CDK4/6 inhibitor abemaciclib in recurrent meningioma. Neuro Oncol. 2025 Aug 16:noaf184. doi: 10.1093/neuonc/noaf184. PMID: 40842355.

Here's a summary of the key findings and implications from the Kaley et al. "Multicenter basket trial for CNS tumors … abemaciclib in recurrent meningioma" (2025) PubMed

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Background & Rationale

- Cyclin-dependent kinases 4 and 6 (CDK4/6) regulate cell cycle progression, and inhibitors of CDK4/6 (such as abemaciclib) are approved for breast cancer. PubMed
- Because dysregulation of the CDK pathway (e.g. via loss of CDKN2A/B) is implicated in aggressive meningiomas, there is biological rationale to test CDK4/6 inhibition in meningioma. SpringerLink+2PubMed+2
- The trial was designed as a *basket trial* across various recurrent central nervous system (CNS) tumor types (glioma, primary CNS lymphoma, meningioma, ependymoma), to test abemaciclib in brain tumors. PubMed+1

Methods

- Patients with recurrent CNS tumors were treated with **abemaciclib 200 mg orally twice daily** (continuous, days 1-28) following the dosing regimen from breast cancer experience. PubMed
- The primary endpoints included radiographic response (by RANO criteria) and progression-free survival (PFS) at 6 months. Secondary endpoints included overall survival (OS) and safety/toxicity. PubMed
- Exploratory analyses included next-generation sequencing of tumor tissue to look for molecular correlates. PubMed

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Results

Overall across cohorts

- The majority of the CNS tumor cohorts **did not** show evidence of meaningful activity of abemaciclib. PubMed
- The exception was the meningioma cohort, which showed signals of activity. PubMed

Meningioma cohort

- 22 patients with recurrent meningioma (grade 2 or 3) were evaluable. PubMed
- **Radiographic outcomes**: of 22 patients, 16 (73 %) had *stable disease* and 6 (27 %) had progressive disease; no partial or complete responses were reported. PubMed
- **Progression-free survival (PFS)**: median PFS was 15 months (95 % CI: 6.5 to not reached). PubMed
- The 6-month PFS rate (PFS-6) was **68.2 %** (95 % CI: 51.3 % to 90.7 %) — exceeding the RANO benchmark for an active agent in meningioma (49 %) PubMed
- **Overall survival (OS)**: median OS was 32.9 months (95 % CI: 10.7 to not reached) in this cohort. PubMed

Safety & tolerability

- The safety profile was acceptable and broadly consistent with known toxicities of abemaciclib. PubMed
- No unexpected safety signals were highlighted in the meningioma cohort in the abstract. PubMed

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Interpretation & Implications

- Among recurrent CNS tumors, abemaciclib appears to show **meaningful activity in recurrent meningioma**, in terms of disease stabilization and prolongation of progression-free and overall survival. PubMed
- The 6-month PFS rate of ~68 % is notably higher than historical benchmarks in meningioma (RANO benchmark ~49 %). PubMed
- The trial supports further investigation of CDK4/6 inhibition in meningioma, possibly in enriched molecular subgroups or combination strategies.
- Limitations include that objective tumor shrinkage was not observed; benefits are primarily from disease stabilization. Also, as a basket trial, the efficacy appears tumor type–specific, and the sample size (especially in subcohorts) is modest.

Additional / Supplementary Findings & Context

While the full manuscript is not freely accessible, the following additional details are available or can be reasonably inferred from related sources, abstracts of companion trials, and clinical trial descriptions:

Trial registration & design details

- The trial corresponds to **ClinicalTrials.gov NCT03220646**, a multicenter study of abemaciclib in recurrent CNS tumors. ICHGCP
- The study began in July 2017 and is estimated to complete by July 2025. ICHGCP
- The trial included multiple CNS tumor types (glioma, primary CNS lymphoma, meningioma, ependymoma). PubMed+1
- The dose and schedule (200 mg twice daily continuously) followed the regimen used in breast cancer settings. PubMed+1
- Exploratory endpoints included next-generation sequencing of tumor biopsies to seek molecular correlates of response. PubMed

Additional insights from related trials / abstracts

Because the full Kaley et al. paper is not available, insights from related or companion trials help contextualize the findings and possible molecular correlates:

- A companion (or parallel) genomically driven trial, **Alliance A071401**, tested abemaciclib in recurrent/progressive **grade 2/3 meningiomas** harboring NF2 or CDK pathway alterations. In its abstract, the trial met its **PFS6 endpoint** (54% PFS6) despite no objective responses. ASC Publications+1
- That suggests that the Kaley et al. trial's favorable results in meningioma may be partly driven by selecting tumors with CDK pathway dysregulation (e.g. loss of CDKN2A/B, or alterations in cyclin-CDK axis). (The basket trial authors specifically expanded the meningioma cohort given a priori evidence of activity.) PubMed
- In other tumor types, the activity of abemaciclib has been mixed. For example, in a phase II trial of abemaciclib in recurrent grade 3 oligodendroglioma, the primary endpoint was *not* met (only 50% PFS-6, below the threshold) despite some partial responses and durable disease stability in a subset of patients. PubMed+1
- Preclinical meningioma models (with related CDK4/6 inhibitors, e.g. palbociclib) have shown that tumors deficient in **p16 (CDKN2A)** and intact Rb are more sensitive to CDK4/6 inhibition; some studies combine CDK inhibitors with radiotherapy to enhance efficacy. PubMed

Likely deeper analyses and caveats (inference)

Given the structure of typical trial reports and what the abstract outlines, we might reasonably expect the following (not confirmed in the public abstract):

1. **Molecular correlates / biomarkers of response**

- The authors likely analyzed tumor sequencing data for CDKN2A/B deletions, CDK4 or cyclin D amplifications, RB1 status, possibly other co-occurring genomic alterations (e.g. PI3K, mTOR, etc.).
- They may have attempted to associate these genomic features with PFS, disease stability, or likelihood of benefit (e.g. whether tumors with CDKN2A/B homozygous deletion did better).

2. **Subgroup or sensitivity analyses**
    - Stratification by meningioma grade (grade 2 vs grade 3).
    - Time since prior therapies, prior radiation, and tumor location (skull base vs non–skull base) might have been assessed for impact on response.
    - Response durability and patterns of progression (e.g. sites of relapse, whether escape by alternative pathways).
3. **Safety and toxicity breakdown**
    - Detailed tables of adverse events (grade 1–4), dose reductions, discontinuations, and comparisons across cohorts.
    - Potential CNS-specific toxicities or events (e.g. neurocognitive effects, hemorrhage, edema) might have been monitored.
4. **Limitations and future directions**
    - Small sample sizes in subcohorts, particularly non-meningioma arms, limiting power.
    - Lack of objective radiographic responses (i.e. no partial or complete responses in meningioma; benefits are stabilization).
    - Need for combination strategies, particularly in tumors where monotherapy shows limited efficacy.
    - Hypothesis that CDK4/6 inhibitors may be most useful in molecularly selected meningiomas (i.e. tumors with dysregulation of the cyclin-CDK axis).
    - Suggestion of future trials combining with e.g. radiotherapy, targeted agents, or checkpoint inhibitors.

Strengths, Limitations & Gaps in Knowledge

Strengths:

- The basket design allowed exploration across multiple CNS tumor types, enabling a head-to-head look at which tumor types might be responsive to CDK4/6 inhibition.

- The meningioma cohort showed a signal of benefit in terms of prolonged PFS and OS compared to historical controls. PubMed
- The observed 6-month PFS of 68.2% in meningioma exceeds the RANO benchmark of 49% for activity in recurrent meningioma, suggesting a meaningful clinical effect. PubMed
- Use of next-generation sequencing as exploratory endpoints is forward-looking and may help define biomarker-driven therapy.

Limitations & Gaps:

- **No radiographic tumor shrinkage**: in the meningioma cohort, all responses were “stable disease” rather than partial or complete response, limiting the strength of claim for cytotoxic effect. PubMed
- **Small numbers**: Only 22 meningioma patients evaluable; other cohorts had even fewer responders or none. This limits statistical power and generalizability. PubMed
- **Selection bias**: Because the meningioma cohort was expanded based on preliminary signals, there is possibility of selection bias (i.e. enriched for patients likely to benefit).
- **Heterogeneity of molecular drivers**: Meningiomas are genetically heterogeneous; it remains unclear which molecular subtypes drive benefit from CDK inhibition.
- **Lack of access to dose modifications / discontinuation data**: Without the full text, we lack insight into how many patients required dose reductions, treatment interruptions, or discontinued because of toxicity.
- **CNS penetration / pharmacokinetics**: The paper likely addresses CNS drug penetration, but without full access I cannot confirm whether drug levels in cerebrospinal fluid or tumor tissue correlated with outcomes.
- **Follow-up duration and late relapses**: The median follow-up and long-term benefit (beyond ~2–3 years) is uncertain.
- **No combination therapy data**: The trial tests abemaciclib monotherapy; it remains unclear whether combining with radiotherapy, other targeted therapy, or immunotherapy might yield better results.

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