Key findings of: Lin T, Ke S, Hu C, Assadi R, Huang J, Gupta S, Rawojc K, Kleinberg L, Mukherjee D, Rincon-Torroella J, Weingart JD, Holdoff M, Grossman S, Ahmed MM, Redmond KJ.
Low Dose Fractionated Radiation Therapy As a Chemo-Potentiator of Temozolomide for Recurrent Anaplastic Astrocytoma and Glioblastoma: A Single-Arm Phase I/II Trial.
Int J Radiat Oncol Biol Phys. 2025 Oct 24:S0360-3016(25)06396-5. doi: 10.1016/j.ijrobp.2025.10.014. PMID: 41138784.

Here is an annotated summary of the key findings of Lin T et al., *Low Dose Fractionated Radiation Therapy As a Chemo-Potentiator of Temozolomide for Recurrent Anaplastic Astrocytoma and Glioblastoma: A Single-Arm Phase I/II Trial* (Int J Radiat Oncol Biol Phys. 2025 Oct 24:S0360-3016(25)06396-5. PMID: 41138784) — formatted with your preferred Vancouver-style bibliography at the end.

Study design & rationale

- Preclinical work demonstrated that low-dose fractionated radiotherapy (LDFRT) may act as a *chemo-potentiator* (i.e., radiosensitise or enhance chemotherapy effects) in solid tumours, including glioma models. PubMed +2
- Based on this, the authors launched a single-arm Phase 1/2 clinical trial in patients with recurrent high-grade gliomas (HGG) – specifically recurrent anaplastic astrocytoma or glioblastoma – previously treated with standard radiotherapy + temozolomide (TMZ). PubMed +1
- Radiotherapy regimen: 0.5 Gy twice daily ("bid") fractions, with concurrent TMZ on days 1–5 of each 28-day cycle for up to 6 cycles, followed by adjuvant TMZ for another 6 cycles. PubMed +1
- Primary endpoints: Phase 1 – acute hematologic toxicity; Phase 2 – 1-year overall survival (OS) with a lower bound of the 80 % confidence interval (CI) >28.6% (based on historical control). PubMed
- Secondary endpoints included incidence of pseudoprogression, and other safety/efficacy metrics. PubMed

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Key preclinical finding

- In glioblastoma and brain metastatic lung cancer cell lines, LDFRT mediated potentiation of temozolomide was more effective than standard 2 Gy fractions. PubMed +1
- This supports the hypothesis that very low dose per fraction (0.5 Gy) may exploit "hyper-radiation sensitivity" (HRS) phenomena to improve chemo-potentiation. cdn.amegroups.cn +1

Clinical results – Safety

- 30 patients were enrolled between 2013 and 2021. PubMed
- The vast majority (≈80 %) had recurrent glioblastoma; ~90% ECOG 0–1. Among those with molecular data, ~61% had methylated MGMT and ~23% were IDH-mutant. PubMed
- Median radiotherapy re-irradiation dose was 30 Gy (range 28.5-30). Median follow-up was 9.5 months (range 0.1-66.3). PubMed
- Treatment was reported as "safe and well-tolerated" in this re-irradiation salvage context. The major acute hematologic toxicity endpoint appears to have been met without unacceptable toxicity. PubMed

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Clinical results – Efficacy

- 1-year overall survival (OS) was 34.5% (95% CI 20.9-57.0), but the lower bound of the 80% CI was 24.8% – hence the pre-specified phase 2 target lower bound (>28.6%) was not achieved. PubMed
- Interestingly, a high incidence of pseudoprogression (PP) was observed: ~77% of patients experienced pseudoprogression (median dose at PP ~10 Gy, range 6-30 Gy). PubMed
- Importantly, pseudoprogression was strongly associated with improved OS: hazard ratio (HR)=0.12, 95% CI 0.03-0.40, P<0.01 compared to those without pseudoprogression. PubMed

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Interpretation & translational considerations

- The authors conclude that the concept of LDFRT + TMZ in recurrent HGG is feasible and safe in the salvage re-irradiation setting. PubMed
- Although the primary survival endpoint (1-year OS >28.6% lower bound) was **not** met, the high pseudoprogression rate suggests the potential presence of radiation-hypersensitivity (or chemo-potentiation) and possible immune modulation. PubMed
- The strong association of pseudoprogression with better outcome could reflect treatment effect (rather than early progression) — meaning that in this context pseudoprogression may be a favourable biomarker.
- The work reinforces the concept of ultra-low dose fractionation (0.5 Gy BID) as a chemosensitiser, providing a platform for further exploration (ideally randomized) in recurrent gliomas.
- From a pediatric neuro-oncology / blood-brain barrier (BBB) perspective (which you are interested in), this trial suggests that very low-dose radiotherapy might modulate both tumour and micro-environmental/vascular/immune compartments — possibly altering BBB dynamics, drug delivery, or tumour micro-environment sensitivity. It would be interesting to evaluate in future whether such LDFRT influences drug penetration (of TMZ or other agents) or changes BBB permeability in recurrent brain tumours.

Limitations

- Single-arm, non-randomised trial → no direct comparator arm (e.g., TMZ salvage alone) so the true incremental benefit cannot be definitively attributed purely to LDFRT.
- Relatively small sample (n = 30) and heterogenous in prior treatments, molecular subgroups, etc.
- Short median follow-up (9.5 months) in a recurrent setting; long-term outcomes (beyond 1 year) not fully mature.
- The trial did not achieve its pre-specified primary OS endpoint (the lower bound threshold).
- Pseudoprogression interpretation may be confounded by imaging/interpretation biases in re-irradiation context; differentiation from true progression remains challenging.
- The mechanism of benefit is still speculative (HRS + chemosensitisation + immune modulation) and needs further correlative studies (molecular/imaging/immune) to verify.

Implications for future research

- A randomised controlled trial comparing TMZ salvage alone vs. TMZ + LDFRT in recurrent glioma would be a logical next step (to isolate the LDFRT effect).
- Correlative biomarker studies (e.g., MGMT status, IDH, immunologic markers, imaging biomarkers of pseudoprogression vs true progression) are needed to identify which patients may benefit most.
- Translational investigations into how LDFRT affects the tumour micro-environment in brain (e.g., BBB permeability changes, vascular/immune changes, microglial activation) would align with your interest in pediatric BBB/drug delivery.
- Given the favourable safety profile, investigation of LDFRT in earlier lines of therapy (or in combination with new agents, e.g., immunotherapy, targeted therapy) may be worthwhile.
- For paediatric high grade gliomas (HGG) or leukaemic CNS involvement, exploring dose-reduced fractionation to enhance drug delivery (with minimal additional toxicity) may hold promise — though careful adaptation is needed given developmental neuro-sensitivity.

Annotated Vancouver-style citation

Lin T, Ke S, Hu C, Assadi R, Huang J, Gupta S, Rawojc K, Kleinberg L, Mukherjee D, Rincon-Torroella J, Weingart JD, Holdoff M, Grossman S, Ahmed MM, Redmond KJ. Low Dose Fractionated Radiation Therapy As a Chemo-Potentiator of Temozolomide for Recurrent Anaplastic Astrocytoma and Glioblastoma: A Single-Arm Phase I/II Trial. *Int J Radiat Oncol Biol Phys.* 2025 Oct 24:S0360-3016(25)06396-5. doi:10.1016/j.ijrobp.2025.10.014. PMID: 41138784.

If you like, I can **pull out detailed subgroup analyses** (e.g., by MGMT methylation, IDH status, anatomical location) and create a **table summarising outcomes**, and also link the preclinical mechanistic data (HRS/chemo-potentiation) for you. Would you like me to do that?

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Yes

Ragionato per 28s ›

Great — I pulled the available trial data and the preclinical summary and made a concise table of subgroup/ cohort characteristics + outcomes (what's reported in the abstract / public sources), and a short note on mechanistic preclinical data with links to the sources. I also call out which subgroup details **are not reported in the abstract** (so would require the full text / supplement to extract). All load-bearing statements below are cited.

Key subgroup / outcome table (reported data)

Item	Value (reported)
Trial design	Single-arm Phase I/II; LDFRT (0.5 Gy BID) + concurrent TMZ (days 1–5 of 28-day cycle) then adjuvant TMZ. PubMed +1
Enrolled (n)	30 patients (enrolled 2013–2021). PubMed
Histology	~80% recurrent glioblastoma (rest anaplastic astrocytoma). PubMed
Performance status	~90% ECOG 0–1. PubMed
MGMT methylation (of those with data)	61%. PubMed
IDH-mutant (of those with data)	23%. PubMed
Re-irradiation median total dose	30 Gy (range 28.5–30). PubMed
Median follow-up	9.5 months (range 0.1–66.3). PubMed
1-year OS (overall cohort)	34.5% (95% CI 20.9–57.0). Pre-specified Phase-2 target: lower bound of 80% CI >28.6% — **not met** (80% CI lower bound = 24.8%). PubMed
Pseudoprogression (PP)	77% experienced PP (median dose at PP ≈10 Gy; range 6–30). PubMed
Association of PP with survival	PP associated with markedly improved OS (HR = 0.12; 95% CI 0.03–0.40; P < 0.01). PubMed
Safety	Regimen reported as safe and well-tolerated; primary hematologic toxicity endpoint met without unacceptable toxicity. PubMed +1

What I could *not* find in the public abstract (would need the full text / supplement)

- **Survival outcomes stratified by MGMT methylation or IDH status** (e.g., 6- or 12-month OS by MGMT/IDH) — abstract reports the cohort proportions but does not give subgroup survival numbers or KM curves.
- **Median progression-free survival (PFS)** and **median OS** (the abstract gives 1-yr OS and follow-up but not medians).
- **Detailed toxicity table** (grade 3–4 events by system), number of treatment-related SAEs, and whether hematologic nadirs required dose-reductions/delays.
- **Detailed imaging criteria used to call pseudoprogression** (RANO vs institutional criteria), and timing of PP events beyond the median dose at PP.
  If you'd like, I can attempt to obtain the full text PDF (it's behind Elsevier/publisher paywall) or you can upload the PDF and I'll extract the exact subgroup KM data and toxicity tables.

Preclinical mechanistic summary (what the paper reports)

- In cell-line work the authors report that LDFRT (very low doses per fraction, e.g., ~0.3–0.5 Gy) **potentiated temozolomide** cytotoxicity more effectively than standard 2 Gy fractions in glioblastoma and brain-metastatic lung cancer cell lines. Cell survival curves were consistent with a low-dose radiation hypersensitivity (HRS) effect (steepest incremental cell kill at ~0.3–0.5 Gy/fx). PubMed +1
- The authors interpret that the clinical high rate of pseudoprogression at low cumulative doses supports an LDFRT-mediated chemo-potentiation (and possibly immune modulation) rather than early true progression. PubMed

Short interpretation (practical takeaways)

- The combination appears **feasible and safe** as a salvage re-irradiation strategy, but the Phase-2 survival goal was not met; therefore efficacy signal is **hypothesis-generating** rather than practice-changing. PubMed
- The **very high pseudoprogression rate** (77%) and its strong association with better survival is intriguing — it suggests that imaging changes after LDFRT+TMZ may reflect treatment effect (and may be a marker of benefit) rather than early progression. This argues for careful imaging/biomarker correlative work in future trials. PubMed
- Mechanistically, the trial ties to the HRS concept (in vitro cell kill peak at low per-fraction doses) and raises questions about microenvironmental/immune/BBB changes that could increase TMZ efficacy or modulate response.

Links / sources

- PubMed abstract (complete trial abstract + key numbers). PubMed
- Journal abstract / Red Journal view. Red Journal
- Earlier conference/PMC summary (preclinical cell survival curves mentioned). PMC

Would you like me to **(A)** try to fetch the full Elsevier PDF (paywall) and extract subgroup KM curves/toxicity tables now (I can attempt to retrieve and will report what I can access), or **(B)** proceed to create a polished figure/table (e.g., a 1-page slide or CSV) summarizing the items above for use in a talk or manuscript? If you prefer (B), tell me which format you want (PowerPoint slide, CSV or Excel table, or a publication-ready figure) and I'll generate it right away.

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