Tissue-Based Trials

Windows of Opportunity in Neuro-Oncology Drug Development

Charuta G. Furey, MD[a,b], Rian Chang[b], An-Chi Tien, PhD[c], Artak Tovmasyan, PhD[c], Shwetal Mehta, PhD[b], Nader Sanai, MD[a,b,*]

KEYWORDS

• Phase 0 • Exploratory investigational new drug (IND) • Pharmacokinetics • Pharmacodynamics • Brain tumor • Window-of-opportunity • Blood–brain barrier • Drug development

KEY POINTS

- In tissue-based trials, small patient cohorts receive pharmacologically active drug exposures, generating human pharmacokinetic (PK) and pharmacodynamic (PD) data.
- Hybrid phase 0 and window-of-opportunity trials in patients with brain tumors typically use presurgical exposures at pharmacologically active doses.
- In trigger-based hybrid designs, individual patients who meet predefined PK/PD thresholds proceed to a therapeutic expansion arm, combining scientific rigor with therapeutic intent.
- In window-of-opportunity trial designs, ongoing therapeutic dosing is interrupted by a planned surgical procedure, followed by continuation of therapeutic dosing.
- Tissue-based trials data can guide go/no-go decisions, dose and schedule optimization, and patient selection, but they do not establish efficacy.

INTRODUCTION

Developing a new cancer therapy from laboratory discovery to regulatory approval usually takes more than a decade, with capitalized preapproval development costs estimated at $2.6 billion per approved drug.[1] Attrition remains high despite this

[a] Department of Neurosurgical Oncology, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, 350 West Thomas Road, Phoenix, AZ 85013, USA; [b] Ivy Brain Tumor Center, Barrow Neurological Institute, Phoenix, AZ 85013, USA; [c] Department of Translational Neuroscience, Ivy Brain Tumor Center, Barrow Neurological Institute, Phoenix, AZ 85013, USA
* Corresponding author. Department of Neurosurgical Oncology, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, 350 West Thomas Road, Phoenix, AZ 85013.
E-mail address: nader.sanai@ivybraintumorcenter.org

Hematol Oncol Clin N Am 40 (2026) 955–966
https://doi.org/10.1016/j.hoc.2026.08.007 **hemonc.theclinics.com**
0889-8588/26/© 2026 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Abbreviations	
BBB	blood–brain barrier
CNS	central nervous system
CSF	cerebrospinal fluid
FDA	Food and Drug Administration
IND	investigational new drug
PD	pharmacodynamic
PK	pharmacokinetic
RP2D	recommended phase 2 dose

investment: approximately 90% of oncology candidates that enter clinical testing ultimately fail, many only after years of development and substantial commitments of time, capital, and critically, patient participation.[2] The record in neuro-oncology is especially sobering. Thirty years after the current standard of care for glioblastoma was established, no intervention has substantially improved long-term survival, despite hundreds of clinical trials and considerable public and private investment.[3–5]

Central nervous system (CNS) drug development repeatedly encounters 3 well-established risks: inadequate drug penetration into tumor tissue across the blood–brain barrier (BBB), insufficient modulation of the intended molecular target, and rapid adaptive resistance driven by cellular plasticity and profound intratumoral heterogeneity.[6,7] All 3 are compounded by the same information gap: the absence of human, tumor-specific pharmacokinetic (PK) and pharmacodynamic (PD) data when pivotal development decisions are made.[8,9] Even sophisticated preclinical animal models remain inconsistent predictors of intracranial drug exposure and biological effect in humans. When an investigational agent enters a large efficacy trial without direct evidence that it reaches human tumor tissue and engages its target, late-stage failure becomes predictable.

Tissue-based clinical trials were developed to close this gap. In many cases, they use brief, pharmacologically active but nontherapeutic exposures in small numbers of patients to obtain in-human mechanism-of-action, PK, and PD data early in clinical development, between preclinical studies and conventional phase 1, 2, and 3 testing. Neuro-oncology is particularly suited to this approach because a planned craniotomy provides direct access to drug-exposed tumor tissue. Here, the phase 0 paradigm has expanded into a family of tissue-based, PK/PD-driven designs that are changing how agents are prioritized for further development.[8,9] This chapter sets out their rationale and regulatory framework, distinguishes the major tissue-based designs, and addresses trial preparation, conduct, and interpretation. It also draws on illustrative clinical experience to consider how PK/PD findings should guide subsequent development, with particular attention to CNS tumors.

RATIONALE FOR PHASE 0 TRIALS

Traditional investigational new drug (IND) development follows a linear sequence: preclinical toxicology, first-in-human phase 1 dose escalation, phase 2 signal-seeking, and phase 3 confirmation. Because many agents fail only after entering clinical testing, it is critical to reach the first-in-patient stage efficiently and extract as much information as possible at that stage. Tissue-based trials can shorten this timeline substantially, advancing first-in-human data acquisition by an estimated 2.5 years relative to conventional development.[10]

The scientific goals of tissue-based trials can be grouped into 4 broad categories, all reflected in the US Food and Drug Administration (FDA) guidance discussed below: (1)

confirming in humans a drug's mechanism of action observed in preclinical models; (2) defining the PK and PD parameters needed to design subsequent trial phases; (3) evaluating novel imaging probes and biodistribution; and (4) comparing the PK/PD profiles of multiple analogs within a single chemical class to select the most promising candidate for full development. Each rests on the same premise: a small, brief human study can answer questions that animal models cannot before the major costs of development are incurred.

CNS tumors present 2 disease-specific obstacles. First, preclinical models do not fully recapitulate human glioma biology. Orthotopic xenografts and genetically engineered models reproduce neither the complexity of the human BBB nor the regional heterogeneity of human gliomas.[7] Second, BBB disruption varies within a single tumor: contrast-enhancing regions may allow drug entry, whereas the nonenhancing, infiltrative tumor that drives recurrence remains behind a largely intact barrier.[6] Plasma PK, cerebrospinal fluid (CSF) sampling, and even contrast-enhanced imaging are therefore unreliable surrogates for the measurement of greatest interest: unbound drug concentration within infiltrative tumor tissue. Likewise, predictions based on biophysical properties an *in silico* experiments remain inadequately predictive. Direct analysis of surgically acquired, drug-exposed tissue offers the most definitive assessment of whether an agent achieves pharmacologically relevant intratumoral exposure and modulates its intended target. Tissue-based PK/PD trials therefore represent a move away from the traditional linear phase 1–2–3 paradigm toward a scientifically informed, iterative, reverse-translational model of drug development.[8,9]

REGULATORY FRAMEWORK: THE EXPLORATORY INVESTIGATIONAL NEW DRUG

In January 2006, the FDA issued its Guidance for Industry, Investigators, and Reviewers on Exploratory IND Studies, establishing the regulatory basis for what are now generally called phase 0 trials.[11] The exploratory IND mechanism allows limited human exposure to an investigational agent without therapeutic or diagnostic intent and can be supported by a reduced preclinical data package relative to a conventional IND. Acceptable approaches under the guidance include microdose PK studies, imaging-based biodistribution studies, and PD biomarker studies used to confirm target engagement in humans.[11]

The exploratory IND framework permits several dosing approaches. Classical microdose studies use exposures that are not expected to produce pharmacologic effects. Under current guidance, a microdose is generally capped at 1/100th of the pharmacologically active dose and at 100 μg for a single or divided exposure, with further constraints based on the no-observed-adverse-effect level (NOAEL); repeated-microdose approaches allow as many as 5 administrations under specified dose and washout conditions.[11] Pharmacologically active exploratory studies may use higher exposures to produce measurable PD effects and therefore require a more substantial, though still abbreviated, preclinical foundation.[11]

Classical microdosing is generally unsuitable for tissue-based trials in patients with brain tumors. Systemic exposure low enough to meet microdose criteria may produce intratumoral concentrations below analytically or biologically informative thresholds, especially behind an intact BBB. Neuro-oncology trials therefore commonly use a subtherapeutic-duration strategy: one or more presurgical exposures at pharmacologically active doses, sometimes as high as a previously established maximally tolerated dose or recommended phase 2 dose (RP2D), administered for a limited period before planned resection. In this context, *subtherapeutic* describes the duration and nontherapeutic intent of exposure, not necessarily a low administered dose. This

strategy maximizes the opportunity to detect CNS penetration and target modulation while keeping the phase 0 component nontherapeutic. We call this a *pure* phase 0 clinical trial.

In the United States, the FDA considers PD readouts and other early markers of drug activity potentially informative for subsequent development and recommends early consultation with the relevant review division as part of the broader development plan.[11] European Medicines Agency guidelines are less specific for tissue-based phase 0 oncology studies, particularly regarding appropriate endpoints and the supporting data needed to inform subsequent development. International clinical development programs should account for these regulatory differences early in their design.

A TAXONOMY OF TISSUE-BASED TRIAL DESIGNS

Pure phase 0 trials are part of a broader family of tissue-based, PK/PD-driven designs. All are designed to generate pharmacologic data from tissue, but their objectives, dosing intensity, and therapeutic intent differ. Three principal designs have been described.[8]

A pure phase 0 trial uses a limited preoperative exposure to determine whether an investigational agent reaches the tumor, engages its intended target, and produces the expected biological effect. It carries no expectation of clinical benefit.

Postoperative treatment with the study agent is generally not part of the design. Its main advantage is speed: human tissue PK/PD data can be obtained quickly, under either an exploratory IND supported by an abbreviated preclinical package or, when appropriate, a conventional IND. The absence of anticipated clinical benefit, however, can make patient accrual difficult.[12,13]

Window-of-opportunity trials use the interval before surgery to administer therapeutic dosing, usually informed by the RP2D. They also generate PK/PD data, but their aims are both biological and clinical, and patients may proceed to postoperative treatment regardless of the tissue findings. The design can incorporate clinical endpoints and offers the possibility of benefit, though at the cost of greater clinical risk. These trials are generally conducted under a conventional IND, and as the name implies, are opportunistic, often tacked onto a conventional adjuvant therapy trial.

Hybrid phase 0 (trigger) designs pair a limited presurgical exposure with a therapeutic extension phase. Each patient's own tissue PK/PD results determine whether that patient proceeds to postoperative treatment with the study agent. These designs are discussed in detail below.

Several practical features are common to all tissue-based trials. Unlike phase 1 studies of nononcologic agents conducted in healthy volunteers, tissue-based trials enroll the target patient population, most often patients undergoing a clinically indicated resection for a disease with limited effective treatment options, such as recurrent glioblastoma. A single-agent study typically enrolls 4 to 20 subjects, so many tissue-based trials can accrue more rapidly and with fewer participants than conventional phase 1/2 programs. Their demanding perioperative logistics make these trials most practical at a single, high-volume center with dedicated infrastructure.

TRIGGER-BASED HYBRID DESIGNS: PHASE 0/1 AND PHASE 0/2

Stand-alone pure phase 0 studies are nontherapeutic, which creates both ethical and practical concerns. The most important design advance of the past decade has been to link the phase 0 component to therapeutic expansion through a prespecified PK/PD "trigger", forming the hybrid phase 0 study design. In a combined phase 0/2 trial, for example, the phase 0 data determine for each patient whether the agent reaches a

predefined threshold of tumor exposure (eg, an unbound intratumoral concentration above a biologically active level) and modulates its target. Patients who meet the trigger enter a therapeutic expansion arm, structured either as an exploratory cohort or as a formal, statistically-designed phase 2 component. There, they receive the agent at therapeutic doses until progression. Because the cohort is small, the expansion is generally not powered to establish definitive efficacy; instead, it is intended to detect a therapeutic signal in a highly selected, biomarker-enriched population. In phase 0/1 designs, patients advancing beyond the phase 0 component may instead undergo dose escalation.

By turning a purely observational study into a patient-selection tool, the trigger enriches the expansion cohort for patients in whom the drug demonstrably reaches and modulates its target. This is particularly valuable in CNS tumors, where BBB heterogeneity and intratumoral heterogeneity can confound interpretation of unselected phase 2 results.[6,7] The design also gives patients who meet the biological trigger a prespecified path to therapeutic dosing, partly addressing a central ethical concern about nontherapeutic research in vulnerable populations. The tradeoff is operational: treatment assignment depends on rapid, analytically validated tissue assays, with Clinical Laboratory Improvement Amendments (CLIA)/College of American Pathologists (CAP)-compliant testing where required, because each patient's go/no-go decision must be available within days of resection. Meeting that timetable is difficult. PD endpoints are often incompletely standardized, appropriate control tissue may be limited, and discontinuing treatment in patients without a predefined PD response may forfeit opportunities to identify biomarkers of response or resistance.

PREPARING THE TRIAL

Patient Selection

Only a subset of patients with brain tumors can participate in tissue-based studies. Eligibility is usually restricted to patients scheduled to undergo a clinically indicated biopsy or resection at a center with the necessary infrastructure. Glioblastoma, for example, primarily affects older adults, and frailty, comorbidity, corticosteroid dependence, and concomitant medications narrow the pool further.[14] Dexamethasone warrants particular attention in immunotherapy studies because it may profoundly blunt immune PD readouts.[15] Diagnostic uncertainty creates a separate problem in newly diagnosed disease: some lesions presumed on imaging to be glioblastoma prove to have another diagnosis on histology. Recurrent disease offers greater diagnostic certainty but a smaller, often more heavily pretreated population, as well as potential for more intratumoral heterogeneity. Under current guidelines, surgery often follows radiologic diagnosis within 2 weeks, leaving little time for counseling, consent, and trial logistics.[16] Contemporary retrospective data suggest that modest delays in resection are not independently associated with worse outcomes in appropriately selected, clinically stable patients, allowing some latitude for scheduling tissue-based trials.[17,18] Unpublished data from our program at the Ivy Brain Tumor Center suggests that enrollment in tissue-based trials delay surgery by less than a week, compared to conventional treatment avenues.

Analyses should generally separate biologically distinct populations. Isocitrate dehydrogenase (IDH)-mutant and IDH-wildtype gliomas differ substantially in molecular drivers, microenvironment, natural history, and potentially BBB integrity and drug disposition, while newly diagnosed and recurrent tumors differ because of disease evolution and prior therapy.[6,14] Eligibility criteria should exclude clinically significant laboratory abnormalities and define washout or dose-stabilization periods for

concomitant medications. Particular attention is needed for P-glycoprotein and cytochrome P450 inducers and inhibitors; agents that affect coagulation or wound healing, including bevacizumab; and anesthetic, corticosteroid, and antiseizure regimens that could alter surgical safety, PD effects, or systemic PK.

Endpoints

Endpoints must be prespecified and quantitatively justified. Preclinical work must rigorously establish both the biological rationale and the benchmarks that will define success. PK and PD are complementary parts of a single assessment, not independent measures. When brain penetration is uncertain, PK must be measured alongside PD so that biological effects can be interpreted in light of the exposure achieved. When PK is already well characterized, the emphasis shifts to PD, although exposure data remain relevant for defining exposure–effect relationships.

Small-molecule studies require validated bioanalytical assays, and PK analysis should emphasize unbound drug concentration, consistent with the free-drug hypothesis.[19] Tissue PK should be measured across multiple tumor regions, with primary emphasis on non–contrast-enhancing tumor, which is increasingly regarded as the most informative compartment because it harbors the infiltrative disease that survives resection.[20] For targeted and cytotoxic agents, PD assessment should span proximal target inhibition, downstream pathway modulation, and functional cellular consequences such as altered proliferation or apoptosis. Assessment across these levels provides a more robust measure of biological activity than target inhibition alone. For immunotherapies, PD endpoints should capture changes in the tumor microenvironment, including T-cell infiltration, activation and exhaustion states, cytokine profiles, and spatial immune organization. Key endpoints should be defined prospectively by measurable thresholds. Interpretation should account for corticosteroid exposure, prior treatment, and perioperative tissue injury, each of which can independently alter immune readouts. When feasible, unbiased exploratory analyses (eg, omics-based) should be included to identify unexpected drug effects and candidate resistance mechanisms.

Sample Size and Controls

Tissue-based endpoints are usually continuous biomarker measures, so required sample sizes are often small. PK objectives may be met with cohorts of 3 to 6 patients, although variability in BBB integrity, tumor vascularization, and comedications may warrant modest expansion. PD-driven endpoints generally need larger cohorts because biological variability is greater and changes in target engagement or downstream signaling must be distinguished from that background noise. If a PD readout is a primary or secondary endpoint rather than exploratory, sample size should reflect the expected effect size relative to controls. The analysis must also account for dropouts and nonevaluable samples, including radiologic misdiagnoses.

Choosing a comparator requires care. Contemporaneous within-patient samples obtained before and after treatment are the methodological ideal. When that is not feasible, paired specimens from a subset of patients can be combined with well-annotated historical tissue. Archival tissue may then serve as the baseline comparator, but intervening tumor evolution and prior therapies can confound interpretation. Even paired tissue should not automatically be treated as a biologically inert control: biopsy or prior resection may induce inflammatory, wound-healing, vascular, and immune programs that alter subsequent PD readouts. Where feasible, matched untreated controls, longitudinal reference cohorts, or randomization to presurgical treatment versus no treatment can help separate drug-specific effects from background biological and

procedural change. External controls are reliable only when tightly matched across disease subtype, treatment context, tumor compartment, tissue handling, and assay methodology.[21] Randomizing concurrent patients to no presurgical treatment overcomes these problems and improves rigor, but the added sample-size requirement must be balanced against the speed and efficiency that motivate the phase 0 approach.

Ethical Considerations

Pure phase 0 trials warrant particular ethical scrutiny because participants accept investigational drug exposure, additional testing, and scheduling burdens without direct benefit. Valid consent depends on a clear explanation of the nontherapeutic intent. Any protocol-driven departure from standard neurosurgical practice must be explicitly justified and accompanied by risk mitigation. Limiting dose or duration is intended to reduce toxicity, but a nontherapeutic agent can still cause harm; brief exposure windows and short washout periods mitigate, but do not abolish, that risk. Trigger-based hybrid designs address the concern in part by providing a therapeutic component for patients who meet predefined PK/PD criteria. The ethical case for these trials depends on strict eligibility, brief exposures, and close monitoring to minimize participant risk, weighed against biological data that may speed development and reduce future exposure to ineffective therapies. Trial evaluation should also assess participant experience and acceptability, including understanding, burden, and barriers to participation.[22]

CONDUCTING THE TRIAL

Coordinating Drug Administration and Surgery

All tissue-based trials studies depend on precise coordination of dosing and resection. The key controlled variable is the interval from the last dose to tissue excision. Scheduling should also account for time to maximum concentration and attainment of steady state. For many oral agents, accumulation from the first dose to steady state approaches twofold, so the number of presurgical dosing days materially affects measured tissue concentrations even when the dose-to-resection interval is unchanged. The preoperative dosing period should therefore be justified in relation to the elimination half-life. Time-escalation arms, which hold the dose constant while varying the dose-to-resection interval, can efficiently characterize exposure–effect relationships and identify the most informative sampling window. Presurgical dosing should be timed so that tissue acquisition occurs near steady state, but it may not capture progressive CNS accumulation; this limits extrapolation to chronic dosing. Neuroanesthetic management can also introduce PK variability, so anesthetic regimens should be documented and reviewed.

Imaging and Intraoperative Sampling

Preoperative imaging determines the sampling map. Acquisition should be standardized and consistent with the brain tumor imaging protocol, and the images should be imported into neuronavigation as a sampling atlas.[23] Perfusion MRI, MR spectroscopy, and amino acid PET refine that atlas by revealing heterogeneity in vascularity, BBB integrity, and biologic activity.[24] The sampling plan should be protocolized and rehearsed with operating room personnel so that spatial heterogeneity can be captured without increasing surgical risk. Consensus recommendations call for tissue from every MRI-visible compartment (ie, the core, contrast-enhancing tumor, and surrounding nonenhancing tumor) to limit undersampling, a concern reinforced by

microdialysis data showing slower drug distribution and lower peak concentrations in nonenhancing regions.[25,26] Research sampling must remain confined to tissue already indicated for removal for diagnosis or cytoreduction, keeping the research aims within standard surgical intent. Because brain shift reduces neuronavigation accuracy, specimens should be obtained early in the resection, with navigated ultrasound or intraoperative MRI available to reregister when needed. Each specimen's location should be recorded electronically in the navigation system, creating a permanent link between the sample and its imaging coordinates for downstream PK/PD interpretation in the context of the tumor's three-dimensional biology.[27]

Tissue Handling and Analytical Validation

Control of preanalytical variables is essential for interpretable results. Standard operating procedures should follow National Cancer Institute biospecimen guidance and specify prelabeled cryogenic containers; assigned team roles, including a specimen runner; minimized and documented cold ischemia time, optimally under 20 minutes; partitioning into assay-ready aliquots; and snap-freezing in liquid nitrogen, with fallback methods defined in advance.[28] In keeping with Biospecimen Reporting for Improved Study Quality recommendations, teams should systematically record time stamps for dose, incision, excision, and stabilization, along with compartment labels and handling conditions.[29] Drug measured in resected tissue may include intravascular drug rather than reflect true interstitial penetration, particularly when the surgical field is contaminated with blood. Protocols should therefore prespecify mitigation and analytical handling, such as standardized rinse practices and paired plasma timing. Because phase 0 drug concentrations may fall in the picogram-to-femtogram range, ultrasensitive analytical platforms, typically liquid chromatography–tandem mass spectrometry, must be validated before trial launch.

ILLUSTRATIVE CLINICAL EXPERIENCE

The first oncology phase 0 study conducted under the exploratory IND guidance tested ABT-888 (veliparib), a poly (ADP-ribose) polymerase (PARP) inhibitor, in 13 patients with advanced malignancies at the National Cancer Institute.[30] Within 5 months of activation, investigators had defined the drug's PK profile and documented PARP inhibition in tumor biopsies and peripheral blood mononuclear cells. These findings provided the foundation for subsequent combination trials of veliparib with temozolomide in pediatric recurrent CNS tumors and with topotecan in adults with refractory solid tumors.[31,32] Rather than rely on microdosing, investigators used pharmacologically meaningful doses for a subtherapeutic duration, preserving the study's nontherapeutic intent.

A tissue-based trial of the CDK4/6 inhibitor ribociclib in recurrent glioblastoma used a hybrid trigger design.[33] Patients received nontherapeutic presurgical dosing, followed by planned resection 2, 8, or 24 hours after the final dose. Intensive plasma sampling was paired with intraoperative collection of blood, CSF, and tumor tissue from contrast-enhancing and nonenhancing regions identified by preoperative MRI and neuronavigation. CNS pharmacokinetics were assessed from unbound drug concentrations. Patients whose tissue met prespecified PK and PD thresholds then entered a therapeutic expansion cohort. The protocol integrated dose-to-resection intervals, compartmental sampling, and trigger-based patient selection into a routine surgical workflow. Neoadjuvant immunotherapy trials show a limitation of tissue-based readouts: presurgical PD-1 blockade measurably altered the glioblastoma immune microenvironment, but the resulting immunologic modulation did not

necessarily translate into clinical benefit.[34,35] Immune-mediated strategies in tissue-based trials are often confounded by the long interval from treatment exposure to maximal immune response, as well as the questionable need for an immune modulator to be brain-penetrant.

INTERPRETING RESULTS AND GO/NO-GO DECISION-MAKING

Tissue-based trials are meant to answer a development question: should this therapeutic strategy move forward? Reports should make that decision process explicit by linking biomarker findings to the development plan. Meeting predefined PK thresholds (ie, adequate unbound drug exposure in tumor tissue, including nonenhancing regions) together with clear target engagement and pathway modulation provides strong biological support for continued development with a refined dose, schedule, and biomarker strategy. Heterogeneous, subthreshold, or compartment-restricted exposure accompanied by partial or nonvalidated PD effects instead calls for optimization of the drug, dose, delivery, timing, or patient selection before expansion. Minimal tumor exposure is a no-go signal, as is adequate exposure without biological activity. In either case, development should not proceed without substantial redesign of the formulation, delivery, mechanism, or patient-selection strategy; the findings may also indicate that the tumor lacks oncogenic dependence on the target. Go/no-go decisions should reflect the full evidence of tissue PK, PD, safety signals, and mechanistic data, not simply a single biomarker endpoint.[36]

The conclusions must remain commensurate with the design. Tissue-based trials assess biological activity and target engagement, not efficacy. Greater T-cell infiltration after neoadjuvant immunotherapy may not correlate with clinical benefit; likewise, reduced signaling-pathway activity after a targeted agent may indicate target engagement without a meaningful clinical effect, as observed with PI3K pathway inhibition in recurrent glioblastoma.[34,35,37] Primary biomarkers and hypotheses should be prespecified, and post hoc analyses identified as such. Investigators must also control bias in patient selection and specimen processing, guard against overfitting high-dimensional datasets, and emphasize effect sizes and confidence intervals rather than *P* values, which may be unstable in small samples. Because tissue-based trials cannot establish efficacy, they should pave the way to a randomized study, or at least a large-scale, statistically-designed Phase 2.

LIMITATIONS AND CONCERNS

Tissue-based trials have several important limitations. A stand-alone phase 0 trial is nontherapeutic and yields no efficacy information. Even in a hybrid phase 0 design, the nonrandomized expansion has the same interpretive limitations as any single-arm phase 2 study. Extrapolation poses a central methodological problem: PK/PD data obtained after a brief, subtherapeutic exposure may not fully predict drug behavior during chronic therapeutic dosing, particularly for agents with time-dependent accumulation. Analytical validation is also demanding because drug concentrations are at ultra-trace levels. Operational weaknesses can erase the expected time savings; if the tissue-based trials program is not coordinated with subsequent development, it may add delay rather than shorten the timeline. Broader use of these designs would also disrupt established industry development programs, although proponents regard such disruption as necessary to address 90% attrition rates and prohibitive development costs.[2,10] The ethical burden remains substantial. Nontherapeutic exposure in a vulnerable population requires continued vigilance, transparent consent, and, whenever feasible, a trigger-based therapeutic component.

FUTURE DIRECTIONS

Standardizing nomenclature, endpoints, sampling, tissue handling, and reporting across institutions would improve reproducibility and allow comparisons across tissue-based trials. Multiarm platforms can test several analogs from the same drug class in parallel and identify the superior CNS-penetrant candidate before full development. Spatially resolved and single-cell profiling can give PD endpoints mechanistic resolution that bulk assays cannot provide, while quantitative imaging of BBB integrity may refine patient selection. Longitudinal observation can add information unavailable from a single operation. Liquid biopsy, molecular imaging, and, in selected patients, serial tissue sampling may show how long target engagement persists and when adaptive resistance emerges during therapy. Broader use will require early regulatory input, jointly developed academic–industry protocols, and funding that covers the added work of perioperative trials. These changes would allow more neuro-oncology development decisions to be based on human tumor biology rather than empiric testing.

SUMMARY

Tissue-based trials, whether stand-alone or linked to therapeutic components by PK/PD triggers, address a basic weakness of traditional IND development in neuro-oncology: programs can take a decade, cost billions of dollars, and still face attrition approaching 90%. In small cohorts already scheduled for clinically indicated resection, a brief, pharmacologically active but nontherapeutic exposure allows investigators to determine directly in human tumor tissue whether a drug penetrates the tumor, engages its target, and produces the intended biological effect. This is particularly useful in neuro-oncology, where the BBB and intratumoral heterogeneity have repeatedly confounded conventional development. Used early, pure phase 0, window-of-opportunity, and hybrid phase 0 studies can stop compounds that fail to reach or affect the tumor and focus later trials on agents supported by human tissue data. That filter can limit patient exposure to ineffective agents and direct resources to compounds with demonstrated biological plausibility, but it depends on rigorous trial design, standardized tissue practices, validated assays, and interpretation within the limits of the design.

CLINICS CARE POINTS

- Before enrollment, confirm that tumor resection is clinically indicated independent of the tissue-based trials. Research sampling must never extend the surgical footprint beyond standard intent.
- Counsel patients clearly when the phase 0 component is nontherapeutic. In trigger-based designs, explain the specific pharmacokinetic (PK)/pharmacodynamic (PD) criteria that govern access to the therapeutic expansion arm.
- Presurgical dosing may require a modest delay to surgery. Delays of up to 1 to 2 weeks from diagnostic MRI do not appear to compromise outcomes in newly diagnosed central nervous system tumors, but patients requiring urgent surgery because of rapid progression or symptoms are not appropriate candidates.
- Review concomitant medications carefully. CYP450 and P-glycoprotein inducers or inhibitors, anticoagulants, bevacizumab, corticosteroids, and enzyme-inducing antiseizure drugs can confound PK/PD readouts or increase surgical risk.
- Interpret tissue-based trials findings as evidence of biological activity, not efficacy. Target engagement without clinical benefit is well documented, and a well-designed phase 2 trial or randomized study remains the necessary next step after a *go* decision.

DISCLOSURES

The authors report no commercial or financial conflicts of interest relevant to this work. Preparation of this chapter received no funding.

REFERENCES

1. DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: new estimates of R&D costs. J Health Econ 2016;47:20–33.
2. Kola I, Landis J. Can the pharmaceutical industry reduce attrition rates? Nat Rev Drug Discov 2004;3(8):711–5.
3. Bagley SJ, Kothari S, Rahman R, et al. Glioblastoma clinical trials: current landscape and opportunities for improvement. Clin Cancer Res 2022;28(4):594–602.
4. Khasraw M, Pristo E, Stupp R. 20 years of the stupp protocol: confronting stagnation in glioblastoma therapy. Lancet Oncol 2026;27(3):277–80.
5. Kim Y, Armstrong TS, Gilbert MR, et al. A critical analysis of neuro-oncology clinical trials. Neuro Oncol 2023;25(9):1658–71.
6. Arvanitis CD, Ferraro GB, Jain RK. The blood-brain barrier and blood-tumour barrier in brain tumours and metastases. Nat Rev Cancer 2020;20(1):26–41.
7. Berens ME, Sood A, Barnholtz-Sloan JS, et al. Multiscale, multimodal analysis of tumor heterogeneity in IDH1 mutant vs wild-type diffuse gliomas. PLoS One 2019;14(12):e0219724.
8. Hotchkiss KM, Karschnia P, Schreck KC, et al. A brave new framework for glioma drug development. Lancet Oncol 2024;25(10):e512–9.
9. Singh K, Hotchkiss KM, Parney IF, et al. Correcting the drug development paradigm for glioblastoma requires serial tissue sampling. Nat Med 2023;29(10):2402–5.
10. Burt T, Young G, Lee W, et al. Phase 0/microdosing approaches: time for mainstream application in drug development? Nat Rev Drug Discov 2020;19(11):801–18.
11. Guidance for industry, investigators, and reviewers: exploratory IND studies. US Food and Drug Administration; 2006.
12. Sanai N. Phase 0 clinical trial strategies for the neurosurgical oncologist. Neurosurgery 2019;85(6):E967–74.
13. Sanai N, Li J, Boerner J, et al. Phase 0 trial of AZD1775 in first-recurrence glioblastoma patients. Clin Cancer Res 2018;24(16):3820–8.
14. van den Bent MJ, Geurts M, French PJ, et al. Primary brain tumours in adults. Lancet (London, England) 2023;402(10412):1564–79.
15. Swildens KX, Sillevis Smitt PAE, van den Bent MJ, et al. The effect of dexamethasone on the microenvironment and efficacy of checkpoint inhibitors in glioblastoma: a systematic review. Neuro-oncology advances 2022;4(1):vdac087.
16. Wen PY, Weller M, Lee EQ, et al. Glioblastoma in adults: a Society for Neuro-Oncology (SNO) and European Society of Neuro-Oncology (EANO) consensus review on current management and future directions. Neuro Oncol 2025;27(11):2751–88.
17. Müller DMJ, De Swart ME, Ardon H, et al. Timing of glioblastoma surgery and patient outcomes: a multicenter cohort study. Neuro-oncology advances 2021;3(1):vdab053.
18. Young JS, Al-Adli NN, Muster R, et al. Does waiting for surgery matter? How time from diagnostic MRI to resection affects outcomes in newly diagnosed glioblastoma. J Neurosurg 2024;140(1):80–93.
19. Webborn PJH, Beaumont K, Martin IJ, et al. Free drug concepts: a lingering problem in drug discovery. J Med Chem 2025;68(7):6850–6.

20. Grossman SA, Barone A, Strowd RE, et al. Evaluating "brain permeability": a critical issue for the development of therapeutic agents for primary and metastatic brain tumors. Neuro Oncol 2026;28(7):1599–611.
21. Polley MC, Schwartz D, Karrison T, et al. Leveraging external control data in the design and analysis of neuro-oncology trials: pearls and perils. Neuro Oncol 2024;26(5):796–810.
22. Drummond KJ, Spiteri M, Cain SA, et al. Perioperative IDH inhibition in treatment-naive IDH-mutant glioma: a pilot trial. Nat Med 2025;31(10):3451–63.
23. Kaufmann TJ, Smits M, Boxerman J, et al. Consensus recommendations for a standardized brain tumor imaging protocol for clinical trials in brain metastases. Neuro Oncol 2020;22(6):757–72.
24. Albert NL, Galldiks N, Ellingson BM, et al. PET-based response assessment criteria for diffuse gliomas (PET RANO 1.0): a report of the RANO group. Lancet Oncol 2024;25(1):e29–41.
25. Blakeley JO, Olson J, Grossman SA, et al. Effect of blood brain barrier permeability in recurrent high grade gliomas on the intratumoral pharmacokinetics of methotrexate: a microdialysis study. J Neuro-oncol 2009;91(1):51–8.
26. Karschnia P, Smits M, Reifenberger G, et al. A framework for standardised tissue sampling and processing during resection of diffuse intracranial glioma: joint recommendations from four RANO groups. Lancet Oncol 2023;24(11):e438–50.
27. Mathur R, Wang Q, Schupp PG, et al. Glioblastoma evolution and heterogeneity from a 3D whole-tumor perspective. Cell 2024;187(2):446–63.e16.
28. NCI best practices for biospecimen resources. National Cancer Institute; 2016.
29. Moore HM, Kelly AB, Jewell SD, et al. Biospecimen reporting for improved study quality (BRISQ). Cancer cytopathology 2011;119(2):92–101.
30. Kummar S, Kinders R, Gutierrez ME, et al. Phase 0 clinical trial of the poly (ADP-ribose) polymerase inhibitor ABT-888 in patients with advanced malignancies. J Clin Oncol 2009;27(16):2705–11.
31. Kummar S, Chen A, Ji J, et al. Phase I study of PARP inhibitor ABT-888 in combination with topotecan in adults with refractory solid tumors and lymphomas. Cancer Res 2011;71(17):5626–34.
32. Su JM, Thompson P, Adesina A, et al. A phase I trial of veliparib (ABT-888) and temozolomide in children with recurrent CNS tumors: a pediatric brain tumor consortium report. Neuro Oncol 2014;16(12):1661–8.
33. Tien AC, Li J, Bao X, et al. A phase 0 trial of ribociclib in recurrent glioblastoma patients incorporating a tumor Pharmacodynamic- and pharmacokinetic-guided expansion cohort. Clin Cancer Res 2019;25(19):5777–86.
34. McFaline-Figueroa JR, Sun L, Youssef GC, et al. Neoadjuvant anti-PD1 immunotherapy for surgically accessible recurrent glioblastoma: clinical and molecular outcomes of a stage 2 single-arm expansion cohort. Nat Commun 2024;15(1):10757.
35. 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):470–6.
36. Lesser GJ. Way to Go/No-Go. Neuro Oncol 2020;22(5):596–7.
37. Wen PY, Touat M, Alexander BM, et al. Buparlisib in patients with recurrent glioblastoma harboring phosphatidylinositol 3-Kinase pathway activation: an open-label, multicenter, multi-arm, phase II trial. J Clin Oncol 2019;37(9):741–50.