Design and conduct of theranostic trials in neuro-oncology: Challenges and opportunities

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Abstract

Theranostics is a new treatment modality integrating molecular imaging with targeted radionuclide therapy. Theranostic agents have received regulatory approval for some systemic cancers and have therapeutic potential in neuro-oncology. As clinical trials are developed to evaluate the efficacy of theranostic agents in brain tumors, specific considerations will have to be considered, taking into account lessons learned from previous studies examining other treatment modalities in neuro-oncology. These include the need for molecular imaging or surgical window-of-opportunity studies to confirm adequate passage across the blood-brain barrier, optimizing eligibility criteria and selection of the most appropriate response criteria and endpoints to address issues such as pseudoprogression. This review will discuss some of the issues that should be considered when designing clinical trials for theranostic agents.

Introduction

Theranostics is an emerging therapeutic approach which integrates molecular imaging with targeted radionuclide therapy for personalized treatment of cancer.[1] In systemic cancers a number of targeted radionuclide therapies have shown efficacy and received regulatory approval. These include lutetium oxodotreotide ([^{177}Lu]Lu-DOTATATE) for the treatment of somatostatin receptor type 2 (SSTR2)-positive gastroenteropancreatic neuroendocrine tumors (GEP-NET) based on the results of the phase III NETTER-1 trial,[2,3] lutetium vipivotide tetraxetan ([^{177}Lu]Lu-prostate specific membrane antigen (PSMA)-617) for PSMA-positive metastatic castration-resistant prostate cancer based on the phase III VISION trial,[4] as well as benefit in first line therapy for GEP-NET, [5] and neuroendocrine pancreatic tumors. [6] Given the limited efficacy of current therapies for brain tumors[7-9] and the potential biological advantages of theranostics compared to standard radiotherapy,[10] there is growing interest in evaluating these agents in neuro-oncology. Theranostics offers the potential for non-invasive biomarker-driven patient selection, the ability to assess biomarker heterogeneity within the tumor, the potential to individualized the administered dose based on dosimetry, and the ability to monitor response to therapy over time with imaging.[1] This review will discuss some of the specific considerations in designing and conducting clinical trials in neuro-oncology with theranostic agents, with a focus particularly on gliomas.

Challenges

To date the development of therapies in neuro-oncology has been hampered by significant methodologic and scientific limitations leading to repeated failures in phase 3 trials.[11,12] It will be important for theranostic trials to take into account the lessons learned from these failures and not repeat the same mistakes in order to fulfil the potential promise of this new treatment modality.[11] For systemic cancers, effective therapies are developed when they are directed against validated targets, demonstrate efficacy in predictive preclinical models, and are able to achieve therapeutic concentrations and adequate target inhibition in tumor tissue. In neuro-oncology many of these basic requirements are often not met before agents are taken to phase 2 and 3 trials.[13-16] Frequently, targets are pursued with suboptimal preclinical

evaluation, there is uncertainty regarding the agent's ability to cross the blood-brain barrier (BBB) and achieve adequate tumor concentrations, and there is often inadequate evidence of target engagement and pathway modulation in tumor tissue.[11] Even when these criteria are met, the design of signal finding studies are often flawed (for example uncontrolled and underpowered single arm phase 2 trials in newly-diagnosed glioblastoma patients) and poorly predictive of ultimate efficacy in larger randomized trials.[17]

The evaluation of theranostic agents pose additional challenges including the necessity for radioprotective measures which can vary greatly between countries, as well as the limited availability of with positron emission tomography (PET) imaging and expertise in administering theranostic agents. Closer collaboration between neuro-oncologists and nuclear medicine physicians will be critical in facilitating the evaluation of theranostic agents for patients with CNS tumors.

Trial design

The main criteria for selecting a specific tumor type for theranostic therapy is the expression of a suitable molecular target.[1] Ideally the target is homogenously expressed on the tumor or immediate microenvironment, expressed consistently over time, and be accessible from the circulation and cross the blood-brain barrier to allow for systemic administration.[1] Potential targets for theranostic therapies include somatostatin receptor 2 (SSTR2), large neutral amino acid transporter (LAT-1), CXCR4, epidermal growth factor receptor (EGFR)/EGFRvIII, neurokinin-1 receptor (NK1R), gastrin releasing peptide receptor (GRPR), poly-ADP ribose polymerase (PARP) 1 and carbonic anhydrase (CA) IX/XII for gliomas, SSTR2 for meningiomas, and PARP1, human epidermal growth factor receptor (HER)2, fibroblast activating protein (FAP), SSTR2, prostate specific membrane antigen (PSMA) and CA IX/XII for brain and leptomeningeal metastases.[1] Current radiopharmaceuticals utilize β-emitting isotopes such as iodine-131 [^{131}I], yttrium-90 [^{90}Y] or lutetium-177 [^{177}Lu]. In the future α-emitting isotopes (e.g., actinium-225 [^{225}Ac], radium-223 [^{223}Ra]) or Auger electrons (e.g.,iodine-125 [^{125}I], indium-111 [^{111}In]) with higher energy or different irradiation range may potentially be more effective for more rapidly growing or radioresistant tumors.[1]

Dose escalation and window-of-opportunity studies

As with development of other therapies, the evaluation of theranostic agents require standard phase I dose escalation studies to determine the pharmacokinetics, biodistribution, toxicities and the recommended phase 2 dose (RP2D), followed by more definitive evaluation of efficacy. For development of novel therapeutic radioligands, their low-dose application and image-based evaluation of pharmacokinetics and biodistribution for dosimetry estimations in combination with toxicity assessment is a reasonable first step that has been successfully applied.[18] For subsequent dose finding of radioligand therapies, classical dose escalation designs with increasing activities have been used in extracerebral tumors and may also be applied in neuro-oncology. [19-21] Standard phase I designs such as the 3+3 design, accelerated titration designs, Bayesian logistic regression model (BLRM) with escalation with overdose control (EWOC), modified toxicity probability interval design (mTPI) and the Bayesian optimal interval (BOIN) design may all be used. An important toxicity associated with theranostic agents is marrow suppression, which can at times be delayed. This raises the question of whether the standard four weeks window for evaluating dose-limiting toxicities (DLT) is adequate or whether a longer DLT window, and the Bayesian phase I designs that take into account delayed toxicities, may be more suitable for theranostic agents.

Unlike cytotoxic therapies, it is unclear whether the maximum tolerated dose (MTD) is the appropriate dose for theranostic agents. Potentially, dosimetry studies can determine a dose that is biologically active without escalating to the MTD, reducing the potential systemic toxicities arising from these therapies.

Frequently, the recommended phase 2 dose has been determined earlier in phase 1 studies in systemic cancers. Whether this is the appropriate dose and treatment schedule for patients with brain tumors is not always clear. Brain tumor patients are usually less heavily pretreated than patients with systemic tumors,[22] and may tolerate higher doses of the theranostic agent, especially those agents whose dose-limiting toxicity is bone marrow suppression. An

abbreviated dose-escalation study in brain tumor patients may be necessary to determine if these patients can tolerate a higher RP2D, potentially allowing more drug to cross the blood-brain barrier (BBB) and achieve higher therapeutic concentrations in the tumor. This is a particularly important consideration for gliomas with infiltrating tumor behind a relatively intact BBB, but perhaps less of an issue for meningiomas which do not have a relevant BBB. The frequency of administration may also be different from systemic tumors. For example, the dose for [^{177}Lu]Lu-DOTATATE for metastatic low and intermediate grade gastrointestinal neuro-endocrine tumors is 7.4 gigabecquerel (200 millicuries) every eight weeks for a total of four doses, while ongoing or planned trials of this agent for glioblastoma and meningiomas are evaluating a more intensive every three or four week regimens.

While some agents such as TLX101 (4-L-[^{13}1I]iodo-phenylalanine, or [^{131}I]-IPA) targeting LAT-1 is known to have good penetration across the blood-brain/tumor barrier (BBB), the ability of most theranostic agents to cross the BBB is unknown.[1] It is generally recommended that after the RP2D has been determined following dose-escalation studies, a surgical window-of-opportunity study should be considered to measure intratumoral drug concentrations (from both enhancing and no-enhancing areas of tumor in the case of glioblastomas), and obtain evidence of desired pharmacodynamic effects.[23,24] These studies also provide an opportunity to evaluate the uptake in individual patients and potentially allow the dose to be adjusted. However, theranostic agents pose a radiation hazard to the medical staff involved in these surgical studies. Possible solutions include using lower doses of the theranostic agent and implementing careful radioprotective measures, perhaps similar to those employed for sentinel lymph node resections for some systemic cancers.

Theranostic agents have an advantage over non-radioactive pharmaceuticals as their concentrations and distribution *in vivo* can be imaged with PET or single photon emission tomography (SPECT) scans, depending on the type of radionuclide. Therefore, pretreatment PET or SPECT imaging or post-treatment dosimetry after the first cycle may provide an estimate of dose delivery and target engagement and obviate the need for surgical window of opportunity studies. However, since the development of theranostics is in its infancy, ideally PET imaging would initially be correlated with tissue drug concentration and dosimetry in surgical studies to confirm that PET findings.

The frequency and duration of treatment remain to be defined. Although there are treatment regimens selected for systemic tumors, it is unclear whether these regimens are also optimal for central nervous system (CNS) tumors. The standard recommendations for follow-up imaging are likely to be adequate for evaluating theranostic agents but these may be refined as experience with these therapies accumulates. Regardless, long term follow-up will be necessary given the increased risks of delayed radiation toxicity.

Efficacy studies (phase 2 and 3 trials)

The specific studies and endpoints to determine efficacy will depend on the tumor type, stage of disease, and whether the goal of the study is signal finding to guide the development of subsequent larger studies or whether the studies are for regulatory approval. In general, overall response rate (ORR) may be used in single arm signal finding studies in recurrent gliomas, especially glioblastomas, as well as other tumors such as CNS lymphoma and brain metastases. For glioblastomas, durable ORR of greater than 25% correlates with improved survival.[25] Whether this threshold is acceptable to regulatory authorities for accelerated approval remains to be determined. In general, endpoints such as progression-free survival (PFS), PFS at 6 months (PFS6) or survival require randomized studies given the issues related to selection bias. In general, the control arm is radiation therapy and temozolomide chemotherapy for first line trials and lomustine for recurrent trials in patients with glioblastomas. The control arm is more problematic for CNS tumor without approved therapies such as meningiomas. Here, physician's choice is often the default control. Table 1 summarizes the strengths and weakness of the clinical trial endpoints. As more experience with these agents accumulates, composite endpoints such as the combination of ORR with standard uptake value (SUV) changes may be considered.

For newly diagnosed glioblastomas, ORR is not useful and PFS is a poor endpoint because of the challenges related to pseudoprogression. This may be especially important when theranostic agents are combined with radiotherapy. Radiochemotherapy alone for

glioblastomas is associated with pseudoprogression rates of up to 30-40%,[26,27] and is likely to be higher when theranostic agents are added. In general, trials using survival as an endpoint are required. Single arm studies comparing the results to historic benchmarks are unreliable and randomized studies are usually needed,[17,28,29] increasing the complexity, duration and cost of conducting these studies. There are ongoing efforts to determine if the use of external control data with patient level information derived from prior trials can be used as a comparator for single arm studies for signal finding, and potentially in hybrid trial designs using the external control arm to reduce the number of patients in internal control arms in randomized trials.[30] While there are studies suggesting potential benefit of external control arms,[31-33] additional validation studies are needed. To accelerate the evaluation of novel therapies with randomized trials, there are also ongoing efforts using platform trials with multiple therapeutic arms and a shared common control arm employing Bayesian adaptive randomization algorithms to improve trial efficiency.[34,35] These designs increase the likelihood of patients being randomized into effective treatment arms and decrease the probability of randomization into ineffective arms, reducing the overall number of patients required, especially in the control arm, and lowering the cost and duration of the studies. These platform trials also allow inactive arms to be dropped and new arms to be added with relative ease. Examples of platform trials using Bayesian adaptive randomization include the Individualized Screening Trial of Innovative Glioblastoma Therapy (INSIGhT; NCT02977780), a phase 2 trial for newly diagnosed glioblastomas patients without O^6-methylyguanine-methyltransferase (MGMT) promoter methylation,[36,37] and GBM AGILE (Glioblastoma Adaptive Global Innovative Learning Environment; NCT03970447), a phase 2/3 trial in newly diagnosed and recurrent glioblastoma patients, with registration potential.[38] For appropriate theranostic agents, inclusion as an arm of one these platforms trials may accelerate their evaluation. However, currently only a limited number of centers have the expertise and resources to evaluate theranostic agents. As more centers develop the capacity to evaluate theranostic agents, it will become more feasible to evaluate them in these platform trials.

Eligibility Criteria

Optimal eligibility criteria are important in selecting the most appropriate patients for neuro-oncology trials. However, there has been a tendency for these clinical trials to be overly selective, thus unnecessarily excluding patients. The Society for Neuro-oncology and the RANO group have published guidance on simplifying eligibility criteria to improve trial accrual,[39,40] and enhancing enrollment of under-represented populations.[41]

Inclusion criteria

In addition to the standard eligibility issues for neuro-oncology trials, studies evaluating theranostic agents pose particular challenges. Most targeted therapies to date require histologic or molecular confirmation of the target for eligibility. With theranostic agents, PET and SPECT imaging may potentially be used to confirm target expression for patient selection. However, details such as how positive target expression is defined, whether a visual rating score is used, whether the standardized uptake value (SUV) threshold should be used, and if so, whether an absolute threshold should be employed or whether a relative threshold compared to uptake in another organ such as the liver needs to be considered. These imaging studies will also provide information regarding intratumoral heterogeneity of target expression at limited spatial resolution, which may have important implications for assessing the overall effectiveness of the therapy. On the other hand, molecular imaging does provide information on intertumoral target expression and may thus help to predict responses of individual tumor lesions. Until availability and access to PET/SPECT imaging increases, immunohistochemistry (IHC) is likely to be an easier method for target identification, which however does not take tumor heterogeneity and target expression changes over time into account. Moreover, there remain issues regarding the validity of these tests in relation to PET imaging, and whether tissue from the initial surgery is adequate for studies evaluating theranostic agents in patients with recurrent tumors. These issues will require validation studies to determine if IHC can take the place of PET imaging for target identification with selected theranostic agents, for example [^{177}Lu]Lu-DOTATATE targeting the somatostatin receptor type 2 (SSTR2). Currently there remains a paucity of data on how to quantitatively assess SSTR2 expression by IHC.

There is growing understanding that with conventional imaging with magnetic resonance imaging (MRI), the baseline study should be performed as close to the start of treatment as possible to reduce the likelihood of tumor growth during the intervening interval. RANO 2.0 suggests a maximum of two weeks, and preferably shorter, from the baseline scan to registration onto a trial.[27] PET imaging of relatively stable targets such as somatostatin receptor expression is unlikely to change within short periods of time but the PET scan should ideally be obtained around the time of MR imaging so as not to confound tumor measurements.

Another challenge in neuro-oncology trials is ensuring that patients are truly progressing before they are enrolled. RANO 2.0 recommends that patients must have 25% or greater increase tumor area before they can be enrolled onto trials for recurrent disease and provides guidance on excluding patients who may be experiencing pseudoprogression.[27] In addition, several prior scans should be routinely collected to allow retrospective confirmation of progression. These criteria should also be considered for trials evaluating theranostic agents.

Currently, determination of therapeutic targets is based on examining a limited number of IHC slides and does not allow tumor heterogeneity to be adequately assessed. PET imaging potentially allows the examination of the therapeutic target in each lesion, or in different parts of the lesion. When multiple lesions exist with different levels of target expression, criteria for the percentage of positive lesions and the level of target expression for patients to be eligible will need to be determined.

Exclusion criteria

Certain exclusion criteria apply especially to theranostic agents.

The specific safety issues may be different for theranostic agents affecting exclusion criteria. These toxicities will vary depending on which organs are at risk as a result of target expression, as well as the mode of excretion. Potentially renal scintigraphy may be helpful to evaluate renal excretion for some agents.

Theranostic agents are precluded from being used in pregnant and breastfeeding subjects. The specific interval between the end of treatment and future pregnancy will have to be determined.

Patients receiving theranostic therapies for recurrent tumors will likely have received radiotherapy previously. Prior radiation exposure is not an exclusion factor but may influence the tolerability of the theranostic agent and the RP2D.

Response Assessment and Endpoints

The ability to accurately determine response and progression has been an important barrier to developing more effective therapies for brain tumor patients. In particular, the issue of pseudoprogression from radiochemotherapy, and potentially theranostic therapies, pose a particular challenge. The original Response Assessment in Neuro-Oncology (RANO) response criteria for high-grade gliomas (RANO-HGG) published in 2010,[42] provided some guidance on pseudopgrogression, including exclusion of most patients in the first three months following completion of radiochemotherapy from enrolling into recurrent glioma trials. To address the issues of pseudoprogression further, the modified RANO (mRANO) criteria[43] and the immunotherapy RANO (iRANO) criteria[44] were introduced requiring mandatory confirmation of progression before patients can be taken off study, leading to some confusion in the field regarding which criteria to use. Using data from a large cohort of glioblastoma patients in which RANO-HGG was compared to mRANO and iRANO, [45] as well as data from other studies evaluating RANO, the RANO working group recently published an update to the RANO criteria (RANO 2.0).[27] This new criteria proposes a single response criteria for both high and low-grade gliomas, which will be used for all clinical trials regardless of the treatment modalities being evaluated.[27] For patients with newly-diagnosed gliomas, instead of using the post-surgical MRI as the baseline, the first post-radiotherapy MRI will be used as the baseline for comparison with futures MRIs to reduce the impact of pseudoprogression.[27] As the incidence of pseudoprogression is highest in the first twelve weeks following radiotherapy, RANO 2.0 recommends continuing treatment and confirming progression during this period with a repeat MRIs, or performing surgery and obtaining

unequivocal histopathologic evidence of recurrent tumor. After the first three months following radiotherapy, mandatory confirmation scans do not improve determination of progression following radiotherapy. Confirmation scans also do not improve the evaluation of response assessment for recurrent tumors and will not be mandatory.[27] As with the original RANO HGG criteria, RANO 2.0 recommends that if there is uncertainty regarding progression, the patient may continue treatment, if it is clinically safe, and undergo repeat imaging to confirm progression (usually after 4 or 8 weeks). If the repeat MRI confirms progression, the time of progression should be back-dated to the date of the initial scan when progression was suspected. For theranostic therapies where the incidence of pseudoprogression is currently unknown, but potentially could be increased especially if the agents are used in conjunction with radiotherapy, it may be reasonable to require mandatory confirmation of progression with a repeat MRI.[27] The ability to integrate PET imaging and advanced MRI such as dynamic susceptibility contrast (perfusion) MRI) will also help in the differentiation of pseudoprogression from tumor progression. Delayed radiation necrosis may also be a concern following theranostic therapy. The guidelines used to address pseudoprogression also apply to delayed radiation necrosis but will also require mandatory long-term follow-up of patients, even after completion of treatment.

While RANO 2.0 proposes standard criteria for response (50% decrease in area) and progression (25% increase in area), it also suggests a role for assessing minor responses ($\geq$ 25% but < 50% reduction in area) for certain tumor types that are unlikely to exhibit major reduction in tumor size such as low-grade gliomas (and meningiomas).[27] However, the true value of minor responses will require validation in future studies.

The primary measurement in RANO 2.0 remains the maximum cross-sectional area of tumor (2-dimensional), but volumetric measurements are an option if resources are available.[27] There is also growing interest in comparing tumor volumetric growth rates prior to enrolment onto a study and after treatment with the therapeutic agent, especially for slower growing tumors such as low grade gliomas and meningiomas. Although the value of tumor growth rates as an endpoint requires validation, they should be incorporated into theranostic trials if resources are available.

Recently, the RANO group published novel criteria to assess response in diffuse gliomas using amino acid PET (PET RANO 1.0) (Table 2).[46,47] This is an important advance that will hopefully improve the reliability and consistency in determining response following amino acid PET, and potentially other forms of PET imaging as well. However, these criteria will require validation, evaluation of intra- and interobserver variability, and correlation with response criteria with MRI imaging and clinical outcome. Nonetheless, when possible, it should be incorporated into theranostic trials as a secondary endpoint.

For non-glial tumors, the response criteria are less well-defined but RANO-brain metastases may be used for trials evaluating theranostic agents for brain metastases,[48] and RANO-meningioma may be used for trials evaluating theranostic agents for meningiomas.[49] Response criteria for trials evaluating theranostic agents for leptomeningeal disease such as RANO-LM[50] remain a work in progress with continued limitations in defining response reliably. For leptomeningeal trials, the most reliable primary endpoint remains survival.

In addition to MRI-based and amino-acid PET-based response evaluation, specific measurement criteria for theranostic agent imaging should be developed. It seems conceivable that therapeutic efficacy of a radioligand therapy corresponds to a decrease in uptake on PET imaging with the theranostic imaging tracer counterpart. Indeed, in meningioma the reduction in ^{68}Ga-DOTATATE uptake was recently described as potential imaging biomarker to assess therapeutic outcome in patients with meningioma treated with ^{177}Lu-DOTATATE.[51] Further studies are needed to elaborate thresholds and assessment criteria and the correlation of such changes with tumor treatment responses and patient outcomes. Potentially, co-endpoints taking account classical radiographic tumor responses and tracer uptake changes may be useful to assess therapeutic efficacy of theranostic agents multimodally.

In addition to imaging and survival endpoints, there is increasing acceptance of the importance of incorporating clinical outcome and neurocognitive assessments into neuro-

oncology clinical trials.[52,53] Neurocognitive assessments will be particular important for theranostic trials to determine whether there is added toxicity when theranostic agents are added to radiotherapy, and whether there is less neurocognitive dysfunction when theranostic agents are used in place of radiotherapy. The specific instruments and time points for evaluating these therapies will depend in part on the agents being tested and the specific trials but the issues will likely be similar to those encountered in other neuro-oncology trials. For some theranostic agents, such as [^{177}Lu]Lu-DOTATATE, certain countries such as Germany require isolation for more than 48 hours, potentially complicating the use of instruments that require care giver or clinician evaluation. Depending on the theranostic agent under evaluation there may also be specific toxicities of interest that will require monitoring.

Summary:

Theranostics are a promising new therapeutic class integrating molecular imaging with targeted radionuclide therapy. As clinical trials are developed to evaluate these agents in CNS tumors it will be important to design studies with appropriate response criteria and endpoints. In particular, taking into account the lessons that have been learned from previous clinical trials examining other therapies in neuro-oncology will be critical to ensure that these agents are optimally evaluated.

Declaration of interests

PYW has received honoraria for lectures, consultation and advisory boards for Anheart, Astra Zeneca, Black Diamond, Celularity, Day One Bio, Genenta, Glaxo Smith Kline, Kintara, Medscape, Merck, Mundipharma, Novartis, Novocure, Sapience, Servier, Symbio, Tango, Telix and research support from Astra Zeneca, Black Diamond, Bristol Meyers Squibb, Chimerix, Eli Lily, Erasca, Global Coalition For Adaptive Research, Kazia, MediciNova, Merck, Novartis, Quadriga, Servier, and VBI Vaccines.

MP has received honoraria for lectures, consultation or advisory board participation from the following for-profit companies: Bayer, Bristol-Myers Squibb, Novartis, Gerson Lehrman Group (GLG), CMC Contrast, GlaxoSmithKline, Mundipharma, Roche, BMJ Journals, MedMedia, Astra Zeneca, AbbVie, Lilly, Medahead, Daiichi Sankyo, Sanofi, Merck Sharp & Dome, Tocagen, Adastra, Gan & Lee Pharmaceuticals, Janssen, Servier, Miltenyi, Böhringer-Ingelheim, Telix, Medscape.

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DECLARATION OF AUTHOR CONTRIBUTIONS:

All three authors were involved in the design, writing and review of the paper.

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Table 1: Strengths and weakness of the clinical trial endpoints for CNS tumors

Overall Response Rate

- **Percentage with partial + complete radiographic response**
- ***Strengths***
  - Tumor shrinkage unequivocally attributed to treatment in the absence of confounding factors
  - Does not require randomized trial
  - Regulatory authorities may grant accelerated approval based on significant and durable responses in single arm studies
- ***Limitations***
  - Responses must be durable
  - Assessment can be difficult in some diseases and with specific treatments (e.g. glioblastoma treated with bevacizumab)
  -

Progression-Free Survival

- **Time from randomization to progressive disease or death**
- ***Strengths***
  - Shorter follow-up period required compared to overall survival
  - Takes into account stable disease
  - Treatment effect not obscured by subsequent treatment
  - Extensive historic benchmarks
- ***Limitations***
  - Potential for selection bias
  - Requires randomized trials
  - Progression difficult to reliably assess in some tumors (following therapies that induce pseudoprogression or non-enhancing progression)
  - Requires consistent use of assessments at baseline and at regular intervals

Overall Survival

- **Time from randomization until death**
- ***Strengths***
  - Unambiguous
  - Easily quantified, and not subject to investigator interpretation
- ***Limitations***
  - Potential for selection bias
  - Requires randomized trials
  - Large sample sizes, and long follow-up periods

  - Crossover from the control to the experimental arm may dilute the overall effect.

Clinical Outcomes Assessment

- **Measures improvement in patient symptoms or function**
- ***Strengths***
  - Captures the patient's perspective
  - Direct measure of clinical benefit
- ***Limitations***
  - Need validated patient-reported outcome (PRO) instruments
  - Potential for bias requiring blinded randomized trials
  - Missing data, which often limits interpretation

Table 2: Summary of PET RANO 1.0 Response Criteria[46]

PET RANO 1.0 Response	Measurable PET-positive disease	No measurable or non-measurable PET-positive disease
Progressive disease (PET-PD)	At least one of the following: ≥30% increase in TBRmax of at least one target lesion ≥10% increase in TBRmean of at least one target lesion ≥40% increase in PET volume of at least one target lesion Appearance of a new measurable PET-positive lesion or lesions	Appearance of a new measurable PET-positive lesion or lesions
Stable disease (PET-SD)	No definition of PET-PD, PET-PR, or PET-CR is fulfilled	No appearance of a new measurable PET-positive lesion or lesions
Partial response (PET-PR)	At least one of the following and no definition of PET-PD, PET-SD, or PET-CR is fulfilled (in the case of multiple lesions, each target lesion must fulfil at least one of these criteria): ≥30% decrease in TBRmax in a target lesion or lesions ≥10% decrease in TBRmean in a target lesion or lesions ≥40% decrease in PET volume in a target lesion or lesions; or Complete response of all target lesions but one, and no PET-PD or PET-SD definition is fulfilled	Not applicable
Complete response (PET-CR)	Complete disappearance of all PET-positive disease	Not applicable

RANO= Response Assessment in Neuro-Oncology. TBR=target-to-background ratio.