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Abstract

Durable objective response rate (ORR) remains a meaningful endpoint in recurrent cancer; however, the target ORR for single-arm recurrent glioblastoma trials has not been based on historic information or tied to patient outcomes. The current study reviewed 68 treatment arms comprising 4793 patients in past trials in recurrent glioblastoma in order to judiciously define target ORRs for use in recurrent glioblastoma trials. ORR was estimated at 6.1% [95% CI 4.23; 8.76%] for cytotoxic chemothera + pies (ORR = 7.59% for lomustine, 7.57% for temozolomide, 0.64% for irinotecan, and 5.32% for other agents), 3.37% for biologic agents, 7.97% for (select) immunotherapies, and 26.8% for anti-angiogenic agents. ORRs were significantly correlated with median overall survival (mOS) across chemotherapy (*R2 = 0.4078, P < .0001*), biologics (*R2 = 0.4003, P = .0003*), and immunotherapy trials (*R2 = 0.8994, P < .0001*), but not anti-angiogenic agents (*R2 = 0, P = .8937*). Pooling data from chemotherapy, biologics, and immunotherapy trials, a meta-analysis indicated a strong correlation between ORR and mOS (*R2 = 0.3900, P < .0001*; *mOS [weeks] = 1.4xORR + 24.8*). Assuming an ineffective cytotoxic (control) therapy has ORR = 7.6%, the average

ORR for lomustine and temozolomide trials, a sample size of ≥40 patients with target ORR>25% is needed to demonstrate statistical significance compared to control with a high level of confidence (*P* < .*01*) and adequate power (*>80%*). Given this historic data and potential biases in patient selection, we recommend that well-controlled, single-arm phase II studies in recurrent glioblastoma should have a target ORR >25% (which translates to a median OS of approximately 15 months) and a sample size of ≥40 patients, in order to convincingly demonstrate antitumor activity. Crucially, this response needs to have sufficient durability, which was not addressed in the current study.

Keywords

glioblastoma | objective response rate | overall survival | recurrent GBM

Objective response rate (ORR), defined as the proportion of patients with a specific reduction in tumor size sustained over a predefined minimum amount of time, that is durable is regarded as a valid endpoint for drug approval. According to US FDA guidance, durable ORR can be used as a primary clinical endpoint for traditional approval, a surrogate endpoint for traditional approval, as well as a surrogate endpoint in support of accelerated approval.[1] In non-central nervous system (CNS) cancers, the FDA has granted accelerated or even full approval for numerous agents using ORR as a primary endpoint including Abraxane® (paclitaxel protein bound particles) for metastatic breast cancer and non-small cell lung cancer (NSCLC),[2] Erivedge® (vismodegib) for basal cell carcinoma,[3] Xgeva® (denosumab) for giant cell bone tumors,[4] Sutent® (sunitinib malate) for renal cell carcinoma,[5] and FOLFOX, or Eloxatin® (oxaliplatin) plus 5-fluorouracil plus leucovorin for metastatic colorectal carcinoma.[6] In CNS cancers, everolimus was approved for subependymal giant cell astrocytoma on the basis of a small, single-arm phase 2 trial where a combination of ORR and improvement in symptoms, most notably seizure control were the basis for this approval.[7] Importantly, many of these approvals were based on single-arm clinical trials, suggesting this may be a possible path forward for drug development in recurrent glioblastoma (rGBM) if we can succinctly define a meaningful target ORR that will have a strong likelihood of a significant survival benefit. The current manuscript outlines historic evidence supporting the hypothesis that ORR is a meaningful clinical endpoint for most therapeutics as it is strongly related to median overall survival (mOS). In this manuscript, we also outline the target ORR for a given trial size that provides sufficient statistical confidence that the ORR is higher than that of historically non-active therapies often used as a control in rGBM (ie, lomustine).

RANO-Defined ORR

The standard and modified response assessment in neuro-oncology criteria (Response Assessment in Neuro Oncology (RANO)[8] and mRANO[9]), as well as the Macdonald and Levin criteria that preceeded these criteria, define a "response" as having either a "partial response" (PR) or a "complete response" (CR). The ORR is defined as the proportion of all recurrent GBM patients in a clinical trial with measurable disease at baseline (pretreatment) that exhibit a confirmed (durable) PR or CR. All RANO as well as the Macdonald criteria define PR as having ≥50% decrease in the sum of products of perpendicular diameters of all measurable enhancing lesions compared with baseline, and this must be sustained for at least 4 weeks. The first scan exhibiting ≥50% decrease in the sum of products of perpendicular diameters is often considered a "preliminary PR" event, contingent on whether the second scan (made at least 4 weeks later) exhibits a sustained ≥50% decrease in the sum of products with respect to the baseline time point. If the second scan exhibits disease progression (PD) with respect to the "preliminary PR" scan, then the response is not sustained and this is noted as no response. If the second, confirmatory scan exhibits Stable Disease (SD), PR, or CR with respect to the pretreatment baseline, it is considered a *durable PR*. Importantly, steroid dose is required to be the same or lower compared with the baseline scan and clinical assessments (eg, KPS, ECOG) should also be stable or improved.

Similarly, all RANO criteria as well as the Macdonald criteria consider a CR defined as the disappearance of all enhancing measurable and non-measurable disease, and with RANO this has to be sustained for at least 4 weeks. The first scan exhibiting the disappearance of all enhancing measurable and non-measurable disease is often considered the point of "preliminary CR", again contingent on whether the second scan (minimum 4 weeks later) confirms the durability of this response. If the second scan continues to exhibit the disappearance of enhancing disease and no emergence of non-measurable disease it is considered a *durable CR*, dependent on whether the patients are completely off corticosteroids (excluding physiologic replacement doses) and whether the neurological status has stabilized or improved. It is important to note that although confirmation of response is required at a minimum of 4 weeks per RANO recommendations, a more prolonged duration of response (eg, 6 months) provides stronger evidence of treatment efficacy and may be valuable when considering regulatory approval.

RECIST-Defined ORR Benchmarks in Common Solid Tumors

Generally speaking, many solid tumors are vastly more responsive to select therapies compared with GBM. Breast cancers demonstrate Response Evaluation Criteria in Solid Tumors (RECIST)-defined ORRs of between 70 and 80%, as demonstrated by a meta-analysis of 4756 individual patient data from 10 randomized trials in early breast cancer by the Early Breast Cancer Trialists' Collaborative Group[10] and a systematic review and meta-analysis of 2109 patients from 9 randomized controlled trials by Poggio et al[10] in triple-negative breast cancer. RECIST-defined ORR in lung cancer is highly dependent on the particular subtype (eg, small cell vs non-small cell, EGFR mutated vs wild type, etc.) and can range from 10 to 70%, with small cell averaging around 60% ORR in first-line and 30–40% during second-line therapy as reported between 1997 and 2017[11] and roughly 20–40% in NSCLC in phase II and III trials as reviewed article by Shanafelt et al.[12] This appears similar to metastatic castration-resistant prostate cancer, which illustrates response rates of 43.5% in rucaparib,[13] 33–44% in PARP inhibitors,[14] and between 12 and 37% in combination immunotherapies.[14]

Advanced pancreatic cancer (PDA) is similar to GBM in terms of dismal outcomes and lack of treatment options, leading to similarly low ORRs. Similar to GBM, PDA lacks markers for early detection and there are no screening programs and chemotherapy provides only a modest benefit due to the molecular and microenvironmental conditions leading to multiple levels of therapeutic resistance including immune suppression.[15,16] As summarized by Lee and Park,[17] advanced pancreatic cancer was treated with 5-fluorouracil through the mid-1990s, with ORRs of near zero in phase III trials,[18,19] until 1997 when gemcitabine was evaluated in a randomized trial compared with 5-fluorouracil and exhibited an ORR of 5.4%, sustained a minimum of 4 weeks, compared with 0% for 5-fluoruracil. With additional evidence of clinical benefit including a reduction in symptom severity, weight loss, and an increase in survival, gemcitabine was approved as a first-line therapy for advanced pancreatic cancer. Since 1997, trials in advanced pancreatic cancer including gemcitabine combined with a variety of other cytotoxic agents to try and build on the success of gemcitabine monotherapy, including 5-fluorouracil, cisplatin, docetaxel, and irinotecan. Interestingly, this is the same approach that appeared in trials for a time in neuro-oncology, where survival benefits in first-line temozolomide (TMZ) treatment led to a series of relatively unsuccessful trials combining TMZ with other agents. In 2007 the combination of gemcitabine and erlotinib showed a small, yet significant, increase in mOS of 6.3 vs 5.9 months (P = .039) compared to gemcitabine monotherapy in a phase III trial involving 569 patients and this combination was approved for use in first-line advanced pancreatic cancer.[20] Importantly, ORR was only 8.6% in the combination compared to 8.0% in gemcitabine monotherapy. In the last decade, more combination trials demonstrated superiority to gemcitabine monotherapy including increased ORR and mOS. Among these trials was a phase III 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan combination (FOLFIRINOX) trial[21] in 2011 that showed a response rate of 31.6% compared with gemcitabine monotherapy (9.4%) as well as a near doubling in mOS (11.1 months vs 6.8 months), at the expense of significantly higher toxicity. Additionally, a phase III gemcitabine plus nab-paclitaxel trial[22] in 2013 showed a response rate of 23% compared with 7% in the monotherapy arm as well as an improved survival of around 2 months.

When putting historic ORRs for Isocitrate Dehydrogenase (IDH) wild-type recurrent GBM into context with these other solid tumors, it is worth noting that many common solid tumor types have dramatically different ORR and mOS depending on the genetic or phenotypical subtype of cancer, which may or may not have a particularly strong response to targeted therapies (eg, ER+ breast cancer, ALK-positive lung cancer, etc.) or immunotherapies (eg, melanoma, lung cancer subtypes, etc.). Similarly, target response rates and expectations in GBM may need to be adjusted as we identify therapeutically relevant tumor subtypes, although no such subtypes have been identified yet, despite considerable efforts.

Historic Benchmarks for ORR in Recurrent GBM

To establish benchmarks for target ORR in recurrent GBM as well as the association between ORR and mOS, we first searched for representative, recent, later-stage clinical trials (phase II–III when available) in recurrent GBM represented by 4 major therapeutic classifications: cytotoxic chemotherapies, biologic agents (excluding anti-angiogenic agents), anti-angiogenic agents, and immunotherapies. Major studies were included for estimates of ORR if they utilized RANO, Macdonald, Levin, or even the early WHO criteria to define response, but were excluded from examining the correlation between ORR and mOS if they (1) included resective surgery, convection-enhanced delivery (CED), or intratumoral injections as part of the trial, which may bias the results toward longer mOS due to potential cytoreduction of the tumor burden; (2) IDH mutant gliomas included in the trial at a significant proportion (>5–10%), which may similarly lead to a bias in the results toward longer ORR and mOS; (3) if the trial didn't include the same patients for ORR and mOS evaluations (eg, a subset of patients were evaluated for response based on having a measurable disease, but a larger cohort of patients were evaluated for mOS); and (4) if studies did not explicitly include both ORR and mOS in the published results of the trial. All responses in the included studies were presumed to have a minimum of 4 weeks duration of response as determined by a subsequent confirmatory scan. A search for representative trials resulted in a total of 68 unique treatment arms and 4793 recurrent GBM patients. Meta-analysis was performed in R[23] using the *metafor* package[24] applied to published data, including the *metaprop()* function for estimating ORR and *rma()* function for estimating the correlation between ORR and mOS. Random effect models were used to account for heterogeneity among the studies in the meta-analysis[25–27]. We note that a random effects model treats the studies in our meta-analysis as a random sample from an imagined universe of individual

Representative Phase ≥ II Trials for Recurrent GBM Patients Evaluating Cytotoxic (Chemotherapy) Agents

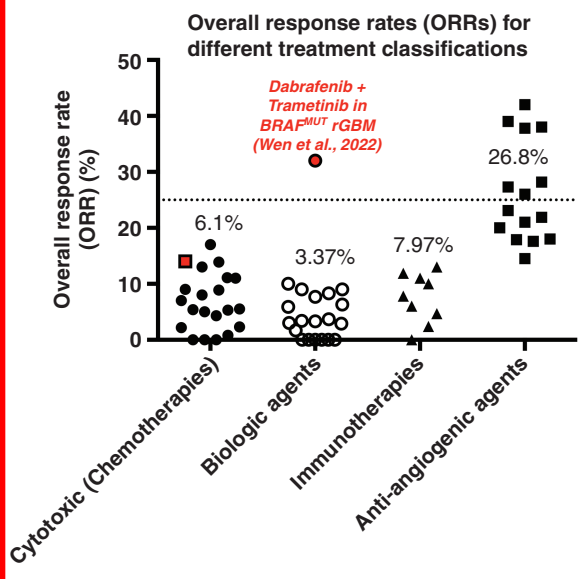
Agent	# Patients	Response criteria	# Recurrences	Primary trial endpoint	ORR (%)	mOS [weeks]	Citation
12 Phase II NABTC Trials (TMZ, BCNU, CPT-11, etc.)	437	Macdonald	≤3	PFS6 or ORR	7	30	Lamborn et al[30]
Carboplatin + thymidine	45	Macdonald	≤2	ORR	2.2	23	Robins et al[36]
BCNU +TMZ	36	Macdonald	≤1	PFS6	5.5	34	Prados et al[35]
Carboplatin + erlotinib	43	Macdonald	≤2	PFS	2.3	30	de Groot et al[38]
CCNU	92	Levin	≤2	PFS	4.3	28.6	Wick et al[39]
CCNU	65	RANO	1	PFS	8.9	42.5	Batchelor et al[40]
CCNU	137	RANO	1	OS	13.9	37.4	Wick et al[41]
CCNU (BELOB)	46	RANO	1	OS9	5	34.8	Taal et al[42]
Hydroxyurea	120	Macdonald	1	PFS	0.8	19	Dresemann et al[34]
CPT-11	40	Macdonald	≤2	ORR	0	22.2	Santisteban et al[43]
CPT-11	48	Macdonald	≤1	ORR	17	43	Friedman et al[44]
CPT-11	40	Macdonald	≤1	ORR	0	17.4	Chamberlain et al[45]
PCV	63	Macdonald	≤1	ORR	11	33	Kappelle et al[33]
Procarbazine	113	Macdonald	≤1	PFS6	5.3	25.6	Yung et al[32]
TMZ	112	Macdonald	≤1	PFS6	5.4	27.8	Yung et al[32]
TMZ	128	Macdonald	1	PFS6	8	23.5	Brada et al[46]
TMZ*	33	Macdonald	1	PFS6	9	40	Brandes et al[47]
TMZ*	54	Macdonald	1	PFS6	13	51.3	Norden et al[48]
TMZ*	27	RECIST	1	PFS6	11.1	40.4	Perry et al[49]
TMZ + disulfiram + Cu	23	RANO	1	ORR	0	30.9	Huang et al[37]
NovoTTF-100A	120	Macdonald	No limit	OS	14	28.7	Stupp et al[31]

TMZ = Temozolomide.
TMZ* = Temozolomide with alternative dose scheduling.
CPT-11 = Irinotecan.
BCNU = Carmustine.
CCNU = Lomustine.
Cu = Copper.
RANO = Response assessment in neuro-oncology criteria.
PCV = Procarbazine hydrochloride, lomustine, and vincristine sulfate.
PFS = Progression-free survival.
PFS6 = Proportion of patients with PFS at or beyond 6 months from start of treatment (or randomization).
OS = Overall survival.
OS9 = Proportion of patients alive after 9 months from the start of treatment (or randomization).

studies that might have been performed, which accounts for both between-study and within-study variations. As a result, confidence intervals tend to be wider than that from a fixed-effects meta-analysis. Additionally, simulations to estimate the target ORR for a given sample size (Figure 3) was calculated using PASS[28,29] using a one-sided one-proportion test with >80% statistical power.

Cytotoxic Chemotherapies

A total of 21 study arms from representative trials (Table 1) totaling 1822 recurrent GBM patients were used to estimate the ORR for cytotoxic chemotherapies (Table 1; Figure 1). These treatments were grouped by whether they involved lomustine (CCNU), temozolomide (TMZ), irinotecan (CPT-11), or another type of chemotherapy. Based on these historic data, ORR for CCNU was 7.59% [95% CI 2.87; 18.59%], TMZ was 7.57% [4.75; 11.86%] (including studies with alternative dose scheduling and combinations including TMZ), CPT-11 was 0.64% [0.00; 1.00%], and all other chemotherapies was approximately 5.32% [2.59; 10.62%] (Figure 1; Supplementary Figure S1). These "other chemotherapies" included a summary of data from 437 GBM patients enrolled in 12 different chemotherapy phase II trials within the North American Brain Tumor Consortium between 1998 and 2002 (ORR = 7%),[30] the NovoTTF-100A study with 120 patients (ORR = 14%),[31] as well as single agent procarbazine (ORR = 5.3%),[32] PCV (ORR = 11%),[33] hydroxyurea (ORR = 0.8%),[34] and combination chemotherapies including BCNU and TMZ (ORR = 5.5%),[35] carboplatin and thymidine (ORR = 2.2%),[36] and the combination of TMZ, disulfiram, and copper



Objective response rates (ORRs) for various types of treatments including cytotoxic chemotherapies, biologic-based agents, immunotherapies (select trials), and anti-angiogenic agents. Filled circle under biologic-based agents shows the ORR for a recent trial of dabrafenib and trametinib in BRAF-mutated rGBM. Filled square under "chemotherapies" designates the ORR for NovoTTF-11A.

(ORR = 0%).[37] ORR across all cytotoxic chemotherapies was approximately 6.1% [4.23; 8.76%] (Figure 1).

Biologic-Based (Non-Angiogenic) Therapies

A total of 20 treatment arms from 18 representative studies (Table 2) totaling 1249 recurrent GBM patients were used to estimate ORR for biologic-based (non-angiogenic) therapies. While the targets and penetration of these agents vary widely, these data suggest that many of these agents have little efficacy in terms of radiographic response, with one exception. While studies evaluating rilotumumab,[50] erlotinib plus sirolimus,[51] fenretinib,[52] temsirolimus,[53] perifosine,[54] and buparlisib[55] failed to demonstrate a single patient with a radiographic response, one recent and notable study by Wen et al[56] demonstrated an ORR of 32% in BRAF mutant rGBM patients when treated with dabrafenib and trametinib. Of note, dabrafenib and trametinib recently received accelerated FDA approval in BRAF V600E mutant solid tumors including rGBM. The ORR across all treatment arms evaluated excluding BRAF mutant rGBM was 3.37% [1.81; 6.18%] (Figure 1; Supplemental Figure S2A). However, because of the broad range of targets, penetration, and evaluation criteria, it is challenging to generalize about efficacy across this broad category of therapeutics.

Immunotherapies

Accurately estimating ORRs for recurrent GBM treated with immunotherapies was similarly challenging, as there are a variety of different therapeutic targets, delivery methods, and many studies that enrich for particular subpopulations of patients (eg, PD-L1 positive, etc.). Many immunotherapy trials involve either a significant surgery (eg, to obtain enough tissue for a vaccine) or surgical procedure (eg, CED, intratumoral injections), or trials reported ORR in only a subset of patients with measurable disease and mOS for the entire treatment cohort.[65] Additionally, some studies utilized RECIST criteria (eg, Reardon et al[66] and Izumoto et al[67]), so these studies were not included in the final estimates of ORR *or* the relationship between ORR and mOS. In the end, a total of 11 treatment arms from 10 trials totaling $N = 436$ recurrent GBM patients were included in estimates of ORR (Supplementary Table S1). Among these important studies are those involving single agent nivolumab[65,68] (ORR = 7.8–11%), pembrolizumab[69] (ORR = 0%), the combination of nivolumab and ipilimumab[68] (ORR = 10%), as well as oncolytic viral therapies[70–72] (ORR = 4.7–13%). The ORR across all these immunotherapy studies was 7.97% [5.32; 11.77%] (Figure 1; Supplementary Figure S2B).

The ORR across *all non-anti-angiogenic agent studies*, including cytotoxic therapies, biologics, and immunotherapies was 5.03% [3.76; 6.69].

Anti-Angiogenic Agents

Contrast enhancement on post-contrast T1-weighted MR images serves as a reasonable surrogate for tumor burden in GBM.[73] However, contrast enhancement relies on extravasation of intravascular contrast into the extravascular space as a consequence of increased vascular permeability in regions of neovasculature. Anti-angiogenic agents, which mostly reflect anti-VEGF agents and drugs that target tumor vasculature, by nature may alter vascular characteristics including permeability and have demonstrated a significant reduction in the extent and intensity of contrast enhancement,[74–76] resulting in artificially high ORRs in rGBM for this class of therapeutics when compared with other types of treatment. A total of 16 treatment arms from 10 trials including $N = 1286$ rGBM patients were included (Supplementary Table S2). The ORR for all studies involving bevacizumab,[42,65,75,77,78] single agent or in combination, was around 28.19% [23.02; 34.01%] while the ORR for all study arms examined was 26.8% [21.59; 32.66%], (Figure 1; Supplementary Figure S2C). Importantly, the trials included in this list were those known to have significant effects on contrast-enhanced MRI. However, pazopanib, sorafenib, regorafenib, and other agents that do *not* demonstrate such strong changes in vascular permeability may require additional consideration.

Association Between ORR and mOS in rGBM

Next, the potential association between ORR and mOS was explored for each of the treatment groups separately. When examining relevant cytotoxic chemotherapy trials (Table 1), a strong linear correlation was observed between ORR and mOS (Figure 2A; $R^2 = 0.4078$, $P < .0001$). Similarly,

Representative Recent Phase ≥ II Clinical Trials for Recurrent GBM Patients Evaluating Non-angiogenic, Biologic-Based Therapeutics

Agent	# Patients	Response Criteria	# Recurrences	Primary trial endpoint	ORR (%)	mOS [Weeks]	Citation
Rilotumumab	61	Macdonald	≤3	ORR	0	23.5	Wen et al[50]
Cilengitide	81	Macdonald	≤1	PFS6	9	43	Reardon et al[57]
Enzastaurin	174	Levin	≤2	PFS	2.9	28.7	Wick et al[39]
Erlotinib	54	Macdonald	≤1	PFS6	3.7	33.5	van den Bent et al[58]
Erlotinib	48	WHO	≤1	ORR	6.3	42.1	Yung et al[59]
Erlotinib + sirolimus	32	Macdonald	1	PFS6	0	33.8	Reardon et al[51]
Fenretinib	23	Not stated	≤2	PFS6	0	30	Puduvalli et al[52]
Imatinib	51	Macdonald	≤2	ORR or PFS6	5.9	23	Raymond et al[60]
Imatinib + hydroxyurea	33	Macdonald	No limit	PFS6	9	48.9	Reardon et al[61]
Imatinib + hydroxyurea	231	Macdonald	1	ORR	3.4	26	Reardon et al[62]
Imatinib + hydroxyurea	120	Macdonald	1	PFS	1.7	21	Dresemann et al[34]
Temsirolimus	65	Macdonald	≤2	PFS6	0	19	Galanis et al[53]
Vorinostat	66	Macdonald	≤2	ORR	3.0	24.8	Galanis et al[43]
Perifosine	16	RANO	No limit	PFS6	0	14.7	Kaley et al[54]
Buparlisib	65	RANO	≤2	PFS6	0	42.6	Wen et al[55]
Marizomib	30	RANO	≤2	ORR	3.3	39.5	Bota et al[63]
Selinexor	68 (24 50 mg 2xWK) (14, 60 mg 2xWK) (30, 80 mg 1xWK)	RANO	≤3	PFS6	8.3 (50 mg) 7.7 (60 mg) 10 (80 mg)	45.6 33.5 43.5	Lassman et al[64]
† Dabrafenib + trametinib (in BRAF mutant rGBM)*	31	RANO	1	ORR	32	59.5	Wen et al[56]

†Believed to be a "positive" study, with ORR = 32% and mOS of more than a year.
*Note this involved an enriched patient population.
PFS = Progression-free survival.
PFS6 = Proportion of patients with PFS at or beyond 6 months from start of treatment (or randomization).
OS = Overall survival.

examination of biologic-based therapeutics, excluding the study by Wen et al[56] showed a strong linear correlation (Figure 2B; $R^2 = 0.4003$, $P = .0003$). When the study by Wen et al[56] was included, which represents a recent study contributing to accelerated FDA approval of dabrafenib and trematinib, this association was stronger ($R^2 = 0.5024$, $P < .0001$, results not shown).

Evaluation of the association between ORR and mOS was more challenging for immunotherapy trials investigated, as studies needed to be excluded if they (1) only reported ORR for a subset of patients, but reported mOS for the larger cohort;[65] (2) used the RECIST criteria instead of the WHO, Macdonald, RANO, or mRANO criteria,[66,67] which have more similar definitions of response; (3) included a relatively large proportion of IDH mutant tumors, potentially skewing mOS estimates;[69] and (4) involved surgical resection of the tumor or CED of study drug.[72,79] This resulted in a total of 5 treatment arms from 4 trials in only $N = 138$ patients. However, a linear correlation was also observed in this limited dataset of immunotherapy trials (Figure 2C; $R^2 = 0.8994$, $P < .0001$). (Notably, this association was based on a very limited number of trials and small sample sizes, so these results should be interpreted with caution).

Lastly, the association between ORR and mOS was explored in anti-angiogenic therapies (Figure 2D). No significant association was observed between ORR and mOS for this class of agents, either as single agents or in combination (Figure 2D; $R^2 = 0$, $P = .8937$).

Pooling together the patients included in the chemotherapy, biologics-based therapies, and select immunotherapy trials, excluding the study by Wen et al[56] resulted in 46 treatment arms from a combined $N = 3243$ rGBM patients available to generalize the association between ORR and mOS. A strong, positive, linear correlation was observed between ORR and mOS (Figure 2E; $R^2 = 0.3900$, $P < .0001$), with a slope of 1.4 ± 0.3 and an intercept of 24.8 ± 1.9 weeks. This results in the linear equation $mOS[weeks] = 1.4xORR + 24.8$ allowing us to extrapolate and estimate the resulting mOS for given ORR thresholds. For example, an ORR>25% would result in an approximate mOS of 15 months (60 weeks), around double the mOS expected from an ORR = 5% (31.8 weeks, average of all non-anti-angiogenic trials), while an ORR of >40% would result in an approximate mOS of 20 months (80.8 weeks). When the study by Wen et al[56] is superimposed on this data, representing a study that resulted

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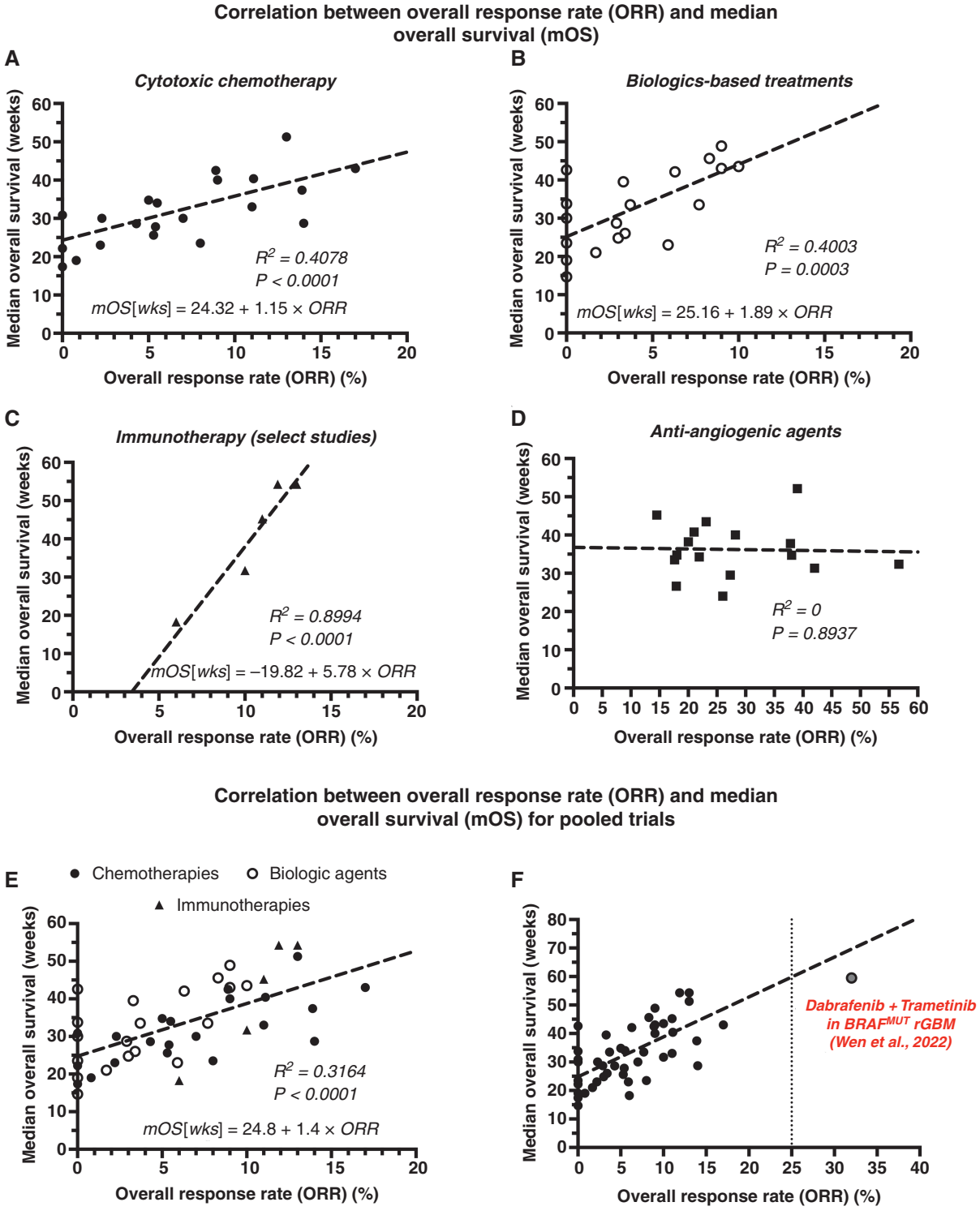


Correlation between ORR and median overall survival (mOS) for (A) cytotoxic chemotherapies, (B) biologics-based (non-antiangiogenic) agents, (C) immunotherapies (select studies), and (D) anti-angiogenic agents. Note that a strong correlation was observed in all therapeutic categories besides anti-angiogenic agents. (E) Correlation between ORR and mOS for pooled studies in chemotherapies, biologics-based agents, and immunotherapies (46 treatment arms in 3243 rGBM patients). ORR vs mOS in pooled patients split by individual treatment types. showing strong linear correlation ($R^2 = 0.3900$, $P < .0001$; *mOS [weeks] = 1.4xORR + 24.8*). (F) ORR vs mOS pooled together along with ORR and mOS in recent study in a recent trial of dabrafenib and trametinib in BRAF-mutated rGBM (filled circle).

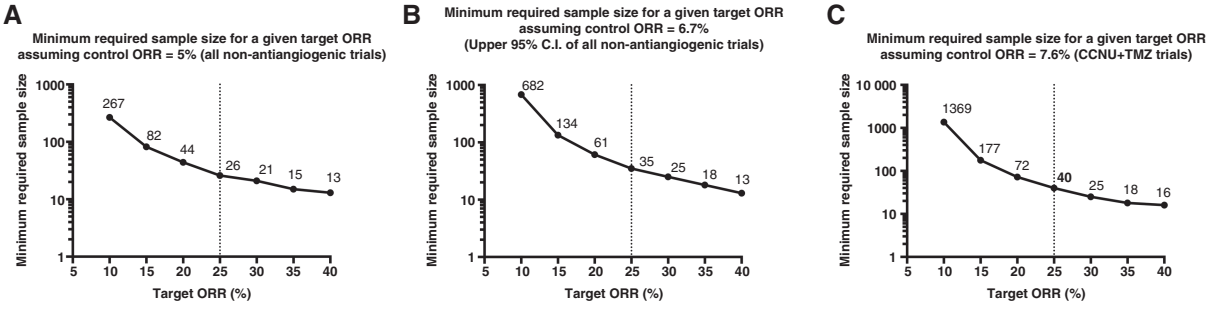
in accelerated approval at least in part due to the high ORR, we can clearly see that the high ORR appears to be consistent with, but slightly lower than, the projected estimate of mOS (Figure 2F). Together, this data supports the use of the general association between ORR and mOS to predict the desired survival benefit for given the target ORR.

Estimating Target ORR for a Given Study Sample Size

While an ORR of 25% appears to be an appropriately high bar to essentially double the mOS when compared with relatively ineffective therapies, the choice of the target ORR for a given trial should be considered within the context of statistical power for a given study sample size, while also maintaining a minimum number of patients to ensure there is no skew from potential bias in accrual. If we assume that ineffective therapies have an ORR of 5%, or the average ORR from cytotoxic, biologics, and select immunotherapy trials, then ≥26 patients are required for a target ORR of >25% (≥7 of 26) in order to demonstrate statistical significance with a high level of confidence ($P < .01$) and adequate statistical power ($1\text{-}\beta$>80%) (Figure 3A) assuming a one-sided interval for one proportion using the Clopper-Pearson method for estimating the confidence intervals.[80] Alternatively, one might consider a more cautious assumption for the control arm ORR based on the upper bound of the 95% confidence interval for the distribution of ORR across all non-anti-angiogenic trials, or an ORR = 6.7%. Using this assumed ORR for the control group, ≥35 patients are required for a target ORR of >25% (≥9 of 35) in order to demonstrate statistical significance ($P < .01$) with power >80% (Figure 3B). An even more conservative, and potentially more realistic, estimate for ORR for the control arm would be to use an ORR based on the average ORR observed in lomustine and temozolomide studies, or ORR = 7.6%, as lomustine is often used as the control arm in rGBM trials[39–42] including contemporary trials such as GBM AGILE.[81] Using an assumed control ORR of 7.6%, ≥40 patients are required for a target ORR of >25% (>10 of 40) in order to demonstrate statistical significance ($P < .01$) with power >80% (Figure 3C). It is important to note that more than 40 patients may be required to ensure adequate confidence in the results, particularly if pretreatment tumor growth is not confirmed before entering the trial[82,83] and if tumors are relatively small,[84] as these factors can skew the number of observed responses and significantly impact outcomes.[85] In contrast, the use of a standardized brain tumor imaging protocol[86] and standardized approaches to central radiographic reads[87] may help reduce noise in our estimate of ORR. Thus, we recommend rGBM studies contain a minimum sample size of 40 and strive for a target ORR >25% (>10 of 40), while adhering to standardized image acquisition, radiographic read paradigm, and response assessment guidance.

Conclusions and Limitations

Durable ORR remains an important endpoint in a number of cancers, including recurrent GBM. After reviewing contemporary studies, the median ORR was estimated to be around 6.1% for cytotoxic chemotherapies (7.6% for lomustine and temozolomide), 3.37% for biologic agents, 7.97% for select immunotherapy trials, and 26.8% for anti-angiogenic agents. While ORRs were significantly correlated with median overall survival (mOS) across chemotherapy, biologics, and immunotherapy trials, we did not find a strong correlation between ORR and mOS in anti-angiogenic agents that are known to reduce blood-brain barrier permeability and alter the degree of contrast enhancement. Combined data from chemotherapy, biologics, and immunotherapy trials showed a strong correlation between ORR and mOS, and the trendline describing this relationship suggests an ORR>25% results in an mOS of more than 15 months. Finally, it should be noted that we do not have comparative data in prospective randomized studies on recurrent glioblastoma, confirming changes in ORR translate in OS benefit. While the use of ORR as a primary endpoint in single-arm studies is not as controversial as the use of time-to-event endpoints including



Minimum required sample size for (A) a control ORR = 5% (average of all non-antiangiogenic trials); (B) a control ORR = 6.7% (upper 95% confidence interval for all non-antiangiogenic trials); and (C) a control ORR = 7.6% (average from CCNU and TMZ monotherapy trials) assuming a level of significance $P < .01$ and power >80%. Results suggest a minimum of 40 patients are required for a target ORR of 25% using an assumed control ORR of 7.6%.

PFS and OS, prospective corroboration of the observed trends in a randomized trial would strengthen the claims made in the current manuscript.

It is important to point out a few limitations and confounds to the current study. First, we attempted to report and include ORRs from a wide variety of studies that utilized RANO, Macdonald, and Levin, which all have *similar,* but not equivalent, definitions of response and requirements for durability of response (DOR). Additionally, the association between ORR and mOS for immunotherapy trials should be interpreted with caution because it was based on a very limited number of trials and small sample sizes, as many studies were excluded for a variety of reasons including a mismatch between the patients included in ORR and mOS estimates. Additionally, we did not have access to patient-level data for our analyses, so questions surrounding the impact of known prognostic variables (eg, MGMT status, etc.) were not specifically addressed in the current study, which may have led to some variability in ORRs across the same drug or drug category. Consequently, only study-level, published data was included in the current meta-analysis. Therefore, it is important to point out that publication bias, data availability bias, and reviewer selection biases are of potential concern when interpreting our results.[88–92] Indeed, our estimation of publication bias and data heterogeneity support this concern (see Supplementary Data). Another potential limitation is uncertainty around the proportion of patients who truly exhibited progressive disease at the time of trial entry, as patients with unrecognized pseudoprogression could contaminate our estimates of true therapeutic response. Lastly, and perhaps most critically, radiographic responses need to have sufficient *durability*, which was not directly addressed in the current study. While most of the studies included required confirmation of response >4 weeks after response was first observed in order to be considered a response, durable responses much longer than this are almost certainly required to truly make a real impact on survival this disease. While the >4 week confirmation scan sets the *minimum durability* that appears meaningful in recurrent glioblastoma, except for in the setting of potent anti-VEGF therapies, it is likely the both a high ORR and *DOR* will be required for prolonged survival.

In summary, we recommend a minimum target ORR for phase II studies in recurrent GBM of more than 25%, for a sample size of at least 40 patients, in order to reach a target mOS of around 15 months and ensure the ORR is higher than 7.6%, the average ORR for historic lomustine and temozolomide trials. Radiographic responses should be determined according to RANO criteria, including the use of a confirmation scan a minimum of 4 weeks after the initial response. Importantly, the framework we have laid out for rGBM can also be used for other tumor types, including IDH mutant tumors and diffuse midline gliomas.

Supplementary material

Supplementary material is available *Neuro-Oncology* online.

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Conflict of Interest

BME is a Paid Consultant and Advisor for Siemens; Medicenna; MedQIA; Imaging Endpoints; Agios Pharmaceuticals; Neosoma; Janssen; Kazia; VBL; Oncoceutics; Boston Biomedical Inc; ImmunoGenesis; and Ellipses Pharma. BME has received grant funding from Siemens, Agios, and Janssen. T.F.C. is cofounder, major stock holder, consultant and board member of Katmai Pharmaceuticals, member of the board for the 501c3 Global Coalition for Adaptive Research, holds stock option of Notable Labs, holds stock in Chimerix and receives milestone payments and possible future royalties, member of the scientific advisory board for Break Through Cancer, member of the scientific advisory board for Cure Brain Cancer Foundation, has provided paid consulting services to GCAR; Gan & Lee; BrainStorm; Katmai; Sapience; Inovio; Vigeo Therapeutics; DNATrix; Tyme; SDP; Novartis; Roche; Kintara; Bayer; Merck; Boehinger Ingelheim; VBL; Amgen; Kiyatec; Odonate Therapeutics QED; Medefield; Pascal Biosciences; Bayer; Tocagen; Karyopharm; GW Pharma; Abbvie; VBI; Deciphera; VBL; Agios; Genocea; Celgene; Puma; Lilly; BMS; Cortice; Wellcome Trust; Novocure; Novogen; Boston Biomedical; Sunovion; Human Longevity; Insys; ProNai; Pfizer; Notable labs; Medqia Trizel; Medscape and has contracts with UCLA for the Brain Tumor Program with Oncovir; Merck; Oncoceutics; Novartis; Amgen; Abbvie; DNAtrix; Beigene; BMS; AstraZeneca; Kazia; Agios; Boston Biomedical; Deciphera; Tocagen; Orbus; AstraZenica; Karyopharm. M.J.v.d.B. has received honoraria from Carthera; Genenta; Nerviano; Cellgene; Astra Zeneca and Boehringer. H.C. has received in the last year honoraria or consulting fees from Best Doctors/Teladoc; Orbus Therapeutics; Adastra Pharmaceuticals; Bristol Meyers Squibb and research funding (instutional contracts) from Orbus; Merck; DNATrix; Abbvie; Beigene; Forma Therapeutics; GCAR; Array BioPharma; Karyopharm Therapeutics; Nuvation Bio; Bayer; Bristol Meyer Squib. W.W. reports to be inventor and patent-holder on "Peptides for use in treating or diagnosing IDH1R132H positive cancers" (EP2800580B1) and "Cancer therapy with an oncolytic virus combined with a checkpoint inhibitor" (US11027013B2). He consulted for Apogenix; Astra Zeneca; Bayer; Enterome; Medac; MSD; and Roche/Genentech with honoraria paid to the Medical Faculty at the University of Heidelberg. MW has received research grants from Apogenix and Quercis, and honoraria for lectures or advisory board participation or consulting from Bayer; Medac; Merck (EMD); Nerviano Medical Sciences; Novartis; Orbus; Philogen and y-Mabs. MAV has patent royalty rights from Infuseon Therapeutics. He has received honoraria from Olympus and Chimerix. His institution has received grant funding from Infuseon Therapeutics; Oncosynergy; and Denovo Pharma for clinical trials for which he is the site primary investigator. EG has received honoraria for advisory board participation from Kiyatec, Inc. (personal compensation) and Karyopharm Therapetuics, Inc. for Data Safety and Monitoring Board participation (compensation to employer). Her institution has received grant funding from Servier Pharmaceuticals

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Author Contribution

Drs. Ellingson, Wen and Cloughesy conceived the review. All authors took part in discussions, analysis, editing and final approval of the manuscript.

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