HIGH SCHOOL EDITION
Journal of Student Research
Volume 12 Issue 3 (2023)

An Analysis of Interventional Clinical Trials and Trends in Potential Glioblastoma Therapeutics

Ananya Uddanti

Little Rock Central High School

ABSTRACT

Glioblastoma Multiforme (GBM), an aggressive malignant tumor of the central nervous system, carries a poor prognosis. This research aimed to analyze the current and future trends of interventional GBM clinical trials. Analyzed trials met the following eligibility criteria: registration between January 1st, 2012, and July 19, 2022, of interventional study type, in trial phases II-IV, and were either completed, recruiting, or active. Of 1,728 GBM-related trials, 336 were eligible. A majority of trials were of open-label masking (89.58%, n=301), academia-sponsored (44.94%, n=151), and systemic interventions (87.20%, n=293). Despite an increasing trend in the number of trials initiated, other findings provided a basis for concern: negligible focus on localized interventions, minimal funding by industry, and widespread use of open-label masking. Lack of funding by industry and minimal trials examining localized therapies hinders the availability of interventions and the improvement of treatment techniques, respectively. Likewise, open-label masking is not the standard, nor is the use supported in clinical trial studies, as it does not eliminate placebo responses. These conclusions are the basis of concerns and areas of improvement in the GBM clinical trial landscape.

Introduction

Glioblastoma Multiforme (GBM) is an aggressive malignant primary tumor of the central nervous system (CNS) with a median survival of 12-15 months despite resection and chemoradiation therapy (Shergalis et al., 2018; Ostrom et al., 2021). The incidence rate of GBM ranges from 3.19 to 4.17 cases per 100,000 person-years and has slowly been increasing (Razavi et al., 2016; Batash et al., 2016; Batash et al., 2017; Fabbro-Peray et al., 2019; Lin, 2021). There are no known risk factors for GBM, other than prior exposure of CNS to ionizing radiation (Wu et al., 2021). The 5-year survival rate is 6.8 % based on the Central Brain Tumor Registry of United States Statistical Report published in 2021 (Wu, 2021).

Due to recent research by the World Health Organization, there has been a change in the classification of CNS tumors (Louis et al., 2021). GBM is presently a reference to astrocytic tumors containing isocitrate dehydrogenase (IDH) - wildtype (wt); this is understood based on O6-methylguanine-DNA methyltransferase (MGMT) methylation status. The IDH-wt GBM is synonymous with the prior classification for primary GBM (Hanif et al., 2017). A separate entity as of 2021, the IDH-mutant (mut) tumors, synonymous with secondary GBM, comes from lower-grade and less aggressive tumors (Louis et al., 2021). Approximately 80% of GBM tumors are IDH-wt, rapidly developing *de novo* without precursor lesions such as lower-grade gliomas prevalent in IDH-mut tumor (Hanif et al., 2017). IDH-wt GBM often occurs in elderly populations, with an average age of 64 (Tamimi & Juweid, 2017). Conversely, IDH-mut GBM has an average age of 45 and is associated with a better prognosis and reduced necrosis (Tamimi & Juweid, 2017).

Standard treatment consists of maximal surgical resection with adjuvant chemoradiotherapy (Xu et al., 2020). Magnetic Resonance Imaging (MRI), having higher resolutions and contrast, is a vital component of resection due to its role in tumor margin identification (Barone et al., 2014). To have a concrete diagnosis, the tumor must be removed through microsurgery; if such practices are not possible, an open biopsy is sufficient (Weller et al., 2017). Gross total resection is ideal as a larger extent of resection is positively associated with survival time (Lacroix et al., 2001; Sanai

& Berger, 2008; Stummer et al., 2008). Maximal surgical resection aims to maintain neurological function and increase survival (Ellingson et al., 2018).

The standard post-surgical treatment regimen for six weeks of temozolomide (TMZ) and radiation followed by adjuvant TMZ for five days every 28 days for six cycle (Stupp et al., 2005). For those 70 and below, regardless of methylation status, concurrent and monthly adjuvant TMZ with radiation therapy is used as the treatment; however, unmethylated tumors receive few benefits from TMZ (Batash et al., 2017; Davis, 2016). Alternative drugs, such as irinotecan, are being explored, yet no strong contenders exist (Batash et al., 2017; Davis, 2016). For those above 70 years, toxicity and side effects of treatments must be considered (Batash et al., 2017; Davis, 2016). Those with good performance on the Karnofsky Performance Status scale benefit from hypo-fractionated radiation (Minniti et al., 2019). For those with poor performance, single-modality treatment is preferred to avoid adverse effects in relation to comorbidities (Minniti et al., 2019). See Table 1.

Considering the lack of innovation in treatment, increasing incidence rate, and highly malignant nature of GBM, GBM is a topic of importance and this research aimed to understand and analyze the current and future trends of the GBM clinical trial landscape.

GBM reoccurs in most scenarios, even in the light of maximal surgical resection and chemoradiotherapy (Wu et al., 2021). This is partly due to how infiltrative GBM is, making complete resection difficult, and the hypoxic brain regions ideal for glioma-initiating cells (GIC); GICs are a distinct subgroup of cells that self-renew, causing more resistant tumors (Wu et al., 2021). Genetic modeling of GBM in mice has shown that the tumor is most likely derived from neural stem cell astrocytes and oligodendrocyte precursor cells (Wu et al., 2021). GBM's epigenetic mutations assist in classifying the tumors' behavior, ranging from metabolism to prognosis to proliferation patterns: telomerase reverse transcriptase mutation and cyclin-dependent kinase inhibitor 2A deletion (Wang et al., 2018; Delgado-Martín & Medina, 2020).

Further, GBM treatment is complex due to the genetic diversity of the tumor and its location within the blood-brain barrier (Wu et al., 2021). Tumor heterogeneity, in the form of genetic and epigenetic markers, complicates targeted therapy, as GBM IDH-WT tumors are classified as mesenchymal, classical, proneural, and neural (Ramón et al., 2020; Verhaak et al., 2010 ; Behnan et al., 2019). Respectively, the defining characteristics are the presence of the neurofibromin 1 tumor suppressor gene, epidermal growth factor receptor amplification, and tumor protein p53 mutation (Verhaak et al., 2010). The blood barrier in GBM poses a challenge: the typical selective boundary composed of blood vessels becomes excessively permeable (Daneman & Prat, 2015).

There is a lack of concrete evidence for promising alternatives to TMZ, increasing reliance on it despite possible toxic effects (Minniti et al., 2019). Despite abundant research, there have been no treatment approvals since the 2015 approval of Tumor Treating Fields (TTFields) as a device for GBM treatment (Fisher & Adamson, 2021). Further, there's been minimal changes to the standard of care following the approval of bevacizumab as adjuvant therapy since 2005 (Fisher & Adamson, 2021).

Methods

The records of all 424,545 trials registered at ClinicalTrials.gov were downloaded on July 19, 2022 and a SQL database was created to enable further analysis. The database was queried for "Glioblastoma" and "Glioblastoma Multiforme." Of the 424,545 trials registered at ClinicalTrials.gov, an initial 1,728 trials were identified. We then selected trials registered within the last 10 years, between January 1st, 2012, to July 19, 2022, yielding 1,001 results. A further selection of Interventional trials resulted in 894 trials, and of these, 433 were identified after selecting for phases II, III, and IV. From the 433 trials, those suspended, terminated, withdrawn, and unknown trials were removed. Subsequently, 336 trials (19.44%) were selected for analysis.

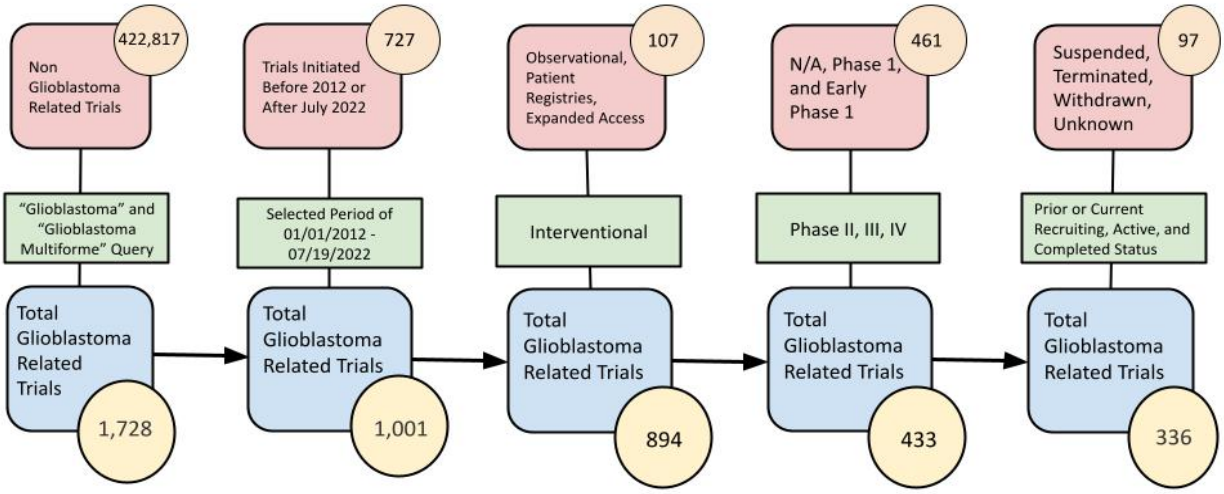

Figure 1. Method Depiction

Trials were then divided into systemic and localized therapy, determined by intervention type: interventions involving biological compounds, drugs, or a combination were classified as systemic therapy, while radiation therapy, procedure, and other devices were classified as localized therapy. Funding was categorized as either academia, industry, national, or other and determined by the clinical trial's primary sponsor.

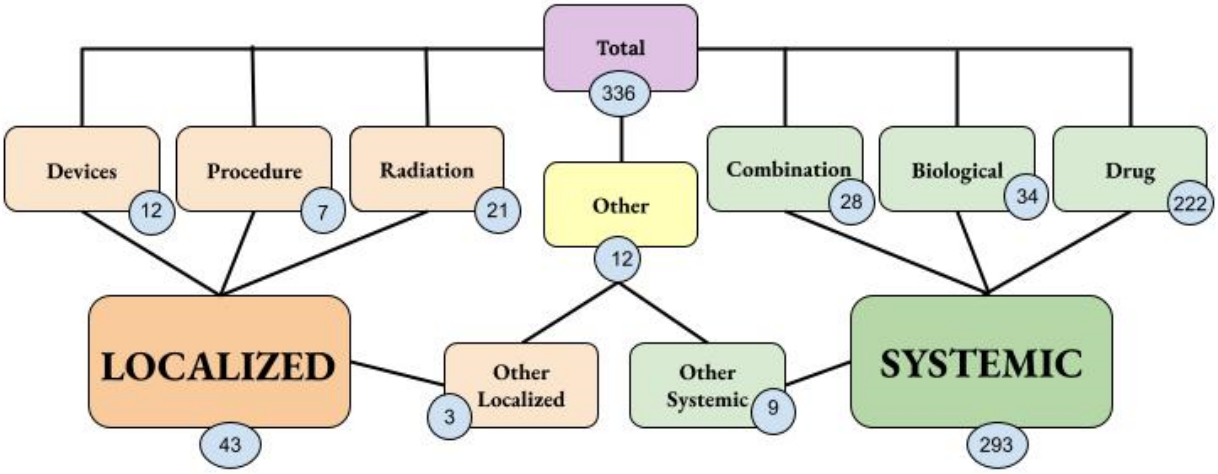

Figure 2. Depiction of Localized versus Systemic Therapy

Results

Of 336 eligible trials identified, 89.58% (n=301) were open-label. The interventional model was primarily a single group (46.73%, n=157) and parallel (42.56%, n=143). The allocation of subjects was non-randomized in 20.54% (n=69) and randomized in 32.74% (n=110) of trials, while the remaining (n=157) was registered as non-applicable. Most trials were phase II (58.93%, n=198) or phase I/II (30.36%, n=102). Approximately 11.31% (n=38) of trials had an enrollment of over 201 participants, with 48.21% (n=162) having 0-50 participants, 41.37% (n=139) of trials were recruiting, while 48.81% (n=164) either completed or active.

36 trials (10.71%) were registered in 2018, followed by 27 trials (8.04%) in 2019 and 36 trials (10.71%) in 2020. In 2021, 33 trials (9.82%) were registered. Most trials were initiated in 2022 (32.4%, n=109). Academia funded 44.94% (n=151) trials, followed by industry at 36.31% (n=122). National funding consisted of 9.52% (n=32) of trials.

87.20% (n=293) of trials observed systemic therapy, while 12.80% (n=43) observed localized therapy. Devices were tested in 3.57% (n=12) of trials, while 2.08% (n=7) of trials tested procedures. Biological interventions were utilized in 10.12% (n=34) of trials, while drugs were in 66.07% (n=222) of trials. Combinations were analyzed in 8.33% (n=28), as was radiation in 6.25% (n=21). The remaining 3.57% (n=12) of trials' interventions were classified as other. Evaluated trials were primarily systemic approaches (n=293, 87.20%). 251 unique systemic agents were identified. Of these agents, 36.25% (n=91) were registered in the WHO/ACT/DDD database, while 63.75% (n=160) were not. 86.06% (n=216) of the identified agents were small molecules that were chemically derived, while 13.94% (n=13.94) were biological agents. Of the 251 unique agents, protein kinase inhibitors consisted of 35.46% (n=89), monoclonal antibodies 10.36% (n=26), antineoplastics and alkylating agents consisted of 18.33% (n=46), and immunotherapies 13.15% (n=33). See Table 4.

Three trials evaluated SonoCloud-9, 66.6% of which utilized carboplatin as an adjuvant drug and were conducted with IDH-mut GBM. In the IDH-WT and non-differentiated GBM setting, two trials examined SonoCloud-9: one with TMZ and the other with MRI-guided laser ablation. Exablate BBBD, dTMS, TTFields, and NoTTF-100A were observed devices in the IDH-mut GBM setting. Four trials analyzed imaging, all of which were in the IDH-WT setting. 75% (n=3) analyzed MRI. Of these, 66.67% focused on MRI as a guide for analyzing therapy. There were five notable trials concerning treatment procedures, one of which analyzed laser interstitial thermal therapy (LITT) and skull remodeling. 40% (n=2) were in the IDH-WT setting, 40% (n=2) in the IDH-mut, and the remaining 20% (n=1) of trials in an undefined setting.

Table 1. These are quantitative values of the variables that were analyzed.

Variable	**n**	**%**	**Variable**	**n**	**%**
Masking			Enrollment		
Quadruple	9	2.68	0-50	162	48.21
Triple	9	2.68	51-100	87	25.89
Open Label	301	89.58	101-200	49	14.58
Single Blind	6	1.79	201-300	15	4.46
Double Blind	11	3.27	301+	23	6.85
Model			Phase		
Sequential Assignment	32	9.52	Phase I/II	102	30.36
Single Group Assignment	157	46.73	Phase II	198	58.93
Parallel	143	42.56	Phase II/III	8	2.38
Factorial	1	0.30	Phase III	25	7.44
Crossover	3	0.89	Phase IV	3	0.89
Status			Funding		
Completed	92	27.38	Governmental:	32	9.52
Active, Not Completed	72	21.43	Industry	122	36.31
Not Yet Recruiting	33	9.82	Academic	151	44.94
Recruiting	139	41.37	Other	31	9.23
Intervention Classification			WHO/ACT/DDD Status		
Biologicals	35	13.94	not registered	160	63.75
Small Molecule	216	86.06	registered	91	36.25

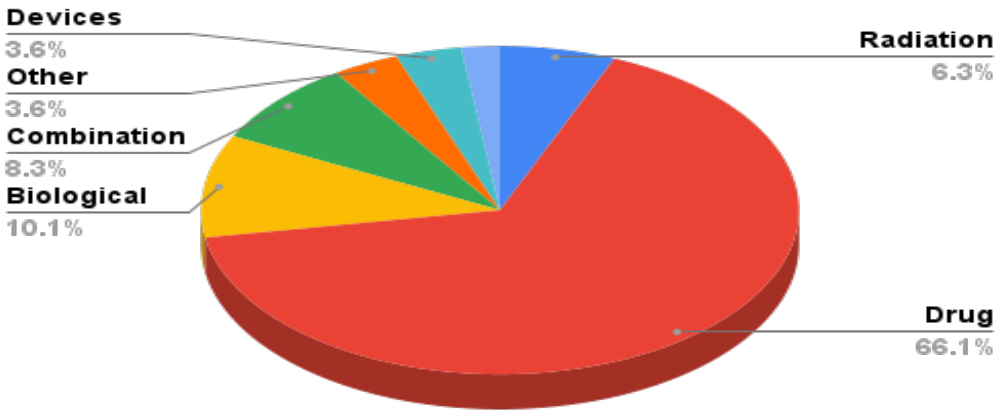

Figure 3. Pie Chart of the Interventions Type

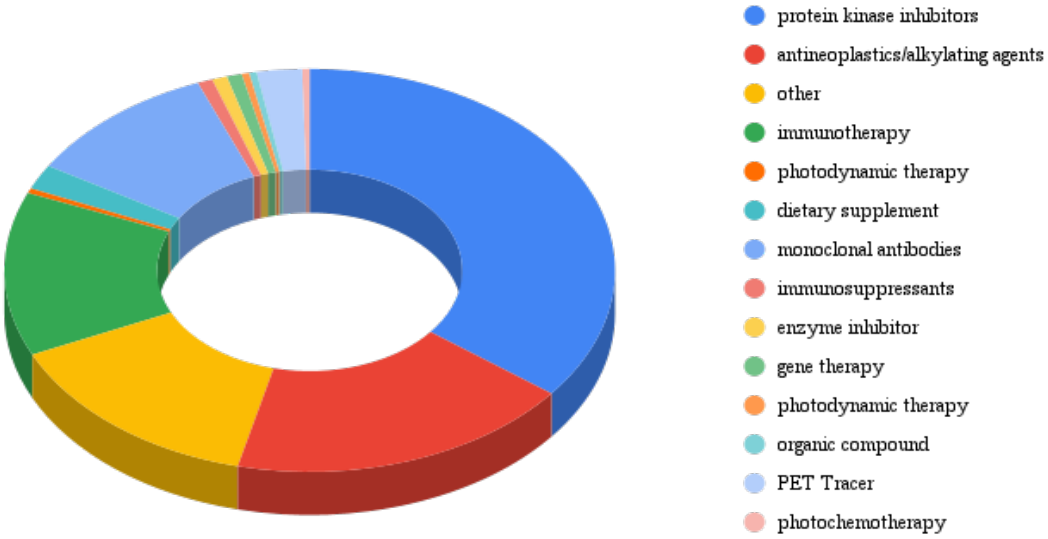

Figure 4. Pie Chart of the Molecular Classifications

Table *2*. These are quantitative values of the molecular classifications that were analyzed.

Variable	n	%
Photodynamic Therapy	1	0.40
Organic Compound	1	0.40
Photochemotherapy	1	0.40
Immunosuppressants	2	0.80
Enzyme Inhibitor	2	0.80
Gene Therapy	2	0.80
Dietary Supplement	5	1.99
PET Tracer	6	2.39
Monoclonal Antibodies	26	10.36
Immunotherapy	33	13.15
Other	36	14.34
Alkylating Agents	46	18.33
Protein Kinase Inhibitors	89	35.46

Discussion

This paper analyzed IDH-mut and IDH-WT glioblastoma trials registered between January 1st, 2012, and July 19th, 2022. There has been an increasing trend in trials throughout the analyzed period, primarily in Phase II trials. This trend is typically attributed to the failure of investigative trials to demonstrate interventions with medical promise, prompting increased initiation of trials (Cihoric et al., 2017). Further, of the observed trials registered at ClinicalTrials.gov, study terminations, withdrawals, and suspensions affected 18.24% (n=79) of trials fitting the specified criteria. Difficulty in accruing participants is the primary reason for such terminations (Shah et al., 2022). Thereby, it is appropriate to set reasonable enrollment targets to combat overestimation and utilize suitable recruitment and inclusion strategies (Shah et al., 2022). A challenge for conducting successful clinical trials includes eligible participants being few in number, which is applicable to GBM trials as 23 (6.85%) had 301 or more participants (Shah et al., 2022)).

An overwhelming majority of trials (n=301, 89.58%) were open label, wherein both the participant and researcher know the treatment being received. A mere 3.27% (n=11) of trials were double-blinded, in which both participant and researcher are unaware of the treatment being received. Traditionally, double-blinded placebos have been used in the clinical setting, as they aim to eliminate placebo responses (Ballou et al., 2017). However, as they need to be more transparent, it is associated with a history of questioned ethics (Ballou et al., 2017). Open-label placebos are yet to be supported in clinical practice (Ballou et al., 2017). There was a sharp increase in trials registered in 2022. Before the increase, a relatively stable number of trials were initiated from 2017 to 2021. Substantially fewer trials were initiated in earlier years.

Funding for GBM clinical trials, similar to other oncological clinical trials, was primarily from academia (44.94%, n=151) and industry (36.63%, n=122) (Cihoric et al., 2017). However, these were primarily systemic therapies, presenting a gap in localized therapy trials. Localized therapies are important as the process of treating GBM must be refined. A mere 12.80% (n=43) of trials in the observed period focused on surgery, imaging, and radiotherapy. Of these, academia consisted of the sponsor for most trials, and the need for more focus on these crucial modalities by industry is a basis for concern. Commercial or industry, sponsored trials are crucial to the field as they are responsible for new drugs (del Álamo et al., 2022). However, there is substantial evidence that industry-funded trials prioritize commercial concerns (del Álamo et al., 2022). This hinders the collaboration between academia and industry in light of agreements where funders can block or stall publications (del Álamo et al., 2022). Academia-funded trials are focused on refining current treatments. These trials further face a lack of funding and platforms and insufficient resources and plan (del Álamo et al., 2022). Overall, the minimal funding by the industry limits the movement of interventions toward the market.

Maximal surgical resection is a vital competent of the standard treatment. Of the few trials focused on surgery as a point of intervention, stereotactic radiosurgery, and skull remodeling were the most common. Though a highly precise technique utilized promise for localized IDH-mut GBM, there is a lack of benefits of upfront stereotactic radiosurgery but found implications of improved survivals when in conjunction with bevacizumab (Bunevicius & Sheehan, 2021).

Many radiotherapy trials analyzed the impact of new drugs in conjunction with radiation therapy, such as atorvastatin, plerixafor, and valganciclovir. Further, one such trial observed the impact of dose-intensified radiotherapy. Concerning the variety of treatments, depending on classification, dose variation is of importance. However, dose escalation was studied in 7 clinical trials, with only two completed studies. Further, these trials were primarily concerned with high-grade gliomas and advanced solid tumors. Five trials concerning radiotherapy analyzed hypo-fractioned radiotherapy. Of these, only one was completed (NCT02968940). With an enrollment of six participants, the trial found 83.33% (n=5) to have experienced a severe adverse event.

It is suggested that the subventricular zone is a topic of interest. NCT02177578 observed the role of neural progenitor cells in this region in relation to IDH-mut GBM. However, it is still in the patient accrual process. Of the 11 imaging conferenced trials, much focused on contrast MRI and adverse effects. MRI findings that are increasing in sub-acuity indicate pseudo-progression, a treatment-related asymptomatic effect (Thust et al., 2018).

The most targeted receptor was the epidermal growth factor receptor, followed by the T cell receptor. Receptor tyrosine kinases, whose pathways drive malignant cancers. These are either upregulated or mutated, making them the crucial targets of inhibitive therapies, such as erlotinib and cediranib (Robinson et al., 2000). Some observed in trials include apatinib, axitinib, dabrafenib, encorafenib.

Alkylating agents were examined in the trial. TMZ, a small molecular alkylating agent, is the most common chemotherapeutic drug for GBM that forms O6-methylgaunine, which promotes apoptosis and radiosensitivity. Methyl guanine methyl transferase reverses the alkylation damage that TMZ causes due to the transfer of methyl groups to DNA. However, TMZ has hematologic toxic properties. MGMT understanding assists with the development of target therapies (Chakravarti et al., 2000)). Other alkylating agents were carmustine (BCNU), carboplatin, and lomustine.

Monoclonal antibodies observed include daratumumab, atezolizumab, and avelumab. Bevacizumab is a monoclonal antibody that inhibits vascular endothelial, initiating blood vessel growth; it has been found to improve progression-free GBM survival, but not newly diagnosed (Ameratunga et al., 2018). Immunotherapies are less successful with GBM than other cancers (W. Wu, J.L. Klockow, M. Zhang, F. Lafortune, E. Chang, L. Jin, Y. Wu, H. E. Daldrup-Link. Glioblastoma Multiforme (GBM): An overview of current therapies and mechanisms of resistance HHS public access. Pharmacol Res. 171, 105780 (2021)). Checkpoint inhibitors, are monoclonal antibodies that interrupt the binding of regulatory receptors on T cells, the ones that include nivolumab, and pembrolizumab (Wu et al., 2021). Vaccines are another type of immunotherapy: peptide vaccines and cell-based vaccines (Wu et al., 2021). Peptide vaccines are amino acid chains that encompass tumor-specific antigens (TSA), which are mutations in tumor cells that are absent in normal somatic cells (Wu et al., 2021). GBM has very low levels of mutation lending to few TSA. Cell-based vaccines are derived from peripheral blood that is pulsed with TAA (Wu et al., 2021)). Further, CAR T cells bind to tumor antigens without process (Jena et al., 2010). Immunotherapy, including monoclonal antibodies, was commonly observed in many trials; these include poly-adenosine diphosphate ribose polymerase inhibitor, pamiparib-290, napabucasin, and autologous lymphoid effector cells specific against tumor cells technology.

Conclusion

Of the clinical trials registered between January 2012 and July 2022, the majority are in Phase II, primarily sponsored by academic sources and focused on systemic therapies. These insinuate the need for more experimental academic-driven trials and industry-sponsored localized therapy trials, with reasonable participant accrual goals and encouragement of unrepresented enrollment.

Limitations

This analysis has limitations. The possibility of an error during the classification of trials and interventions is the main one. Further, ClinicalTrials.gov is not guaranteed to have provided all criteria necessary. Nonetheless, this paper is valuable for its up-to-date analysis of the current landscape of GBM clinical trials.

Acknowledgments

I would like to thank Little Rock Central High School for providing me with any resources I utilized and my faculty advisor, Mrs. Lee Conrad.

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