Genetic Determinants of CAR T-Cell Therapy Outcomes: A Comparative Analysis of DLBCL and Glioblastoma

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INTRODUCTION

Chimeric Antigen Receptor T-cell (CAR T) therapy is a form of immunotherapy that modifies a patient's own T cells to recognize and destroy cancer cells. The process involves extracting T cells, engineering them to express receptors, expanding them in the lab, and infusing them back into the patient. This approach has shown promise in hematologic malignancies, especially B-cell cancers. In relapsed or refractory diffuse large B-cell lymphoma (DLBCL), for example, CAR T-cell therapy has demonstrated a complete response (CR) rate of 54%, with 40% of patients maintaining remissions beyond two years (1). However, the success of CAR T therapy is far more limited in other solid tumors (2). Since CAR T cells typically target CD19, a surface protein expressed on B cells, genetic mutations in immunoglobulin-related genes like IGHV2-70, which are involved in B-cell receptor formation, may influence both disease progression and response to CAR T-cell therapy (3).

DLBCL, the most common type of non-Hodgkin lymphoma, accounts for 30–40% of all cases globally. It is an aggressive cancer of mature B cells, often presenting with rapidly growing lymph nodes and systemic symptoms. While first-line treatment with the R-CHOP regimen, Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone, cures approximately 60–70% of patients, a significant proportion either relapse or fail to respond (4). The consistent expression of CD19 on malignant B cells makes DLBCL an ideal candidate for CD19-directed CAR T therapies, such as Yescarta and Kymriah, both of which are FDA-approved for use in relapsed or refractory DLBCL. Yescarta showed an overall response rate of 82% and complete response rate of 54% in real-world data (5). Immune checkpoint inhibitors (ICIs) have been explored in DLBCL as well, particularly PD-1 blockade with nivolumab or pembrolizumab, but results have been limited, with single-agent response rates typically under 40% (6). Ongoing trials are evaluating ICIs efficacy in combination with chemotherapy or other immunotherapies. Genetically, DLBCL is heterogeneous, and it can be categorized into subtypes like germinal center B-cell-like (GCB) and activated B-cell-like (ABC), each with distinct molecular pathways and treatment responses (7).

In contrast to DLBCL where CAR T-cell therapy has shown success, other solid tumors pose unique challenges. Among solid tumors, glioblastoma (GBM) stands out as a particularly aggressive cancer, making it an important candidate for investigation. GBM is a highly aggressive primary brain tumor with a median survival time of only 15 to 18 months despite standard treatment involving surgical resection, radiation, and chemotherapy with temozolomide (8). GBM poses significant therapeutic challenges due to its extensive heterogeneity in genetic profiles and the tumor ecosystem, its resistance to treatment, and the presence of the blood-brain barrier, which limits drug and immune cell access. While CAR T therapy has been tested in GBM, mainly targeting EGFRvIII, clinical trials have shown limited efficacy, with no sustained responses and median progression-free survival of only 1.3 months (7). Immune checkpoint inhibitors have also been developed and tested for GBM, especially PD-1 and

CTLA-4 inhibitors like nivolumab and ipilimumab, but they have not been effective, due to low tumor mutational burden, poor T-cell infiltration, and an immunosuppressive environment (9). However, unlike in melanoma or non-small cell lung cancer, ICIs have failed to significantly improve survival in GBM (10).

CAR T-cell therapy is significantly more effective in DLBCL than in GBM. In DLBCL, complete response rates reach up to 54%, with many patients achieving long-term remission, largely due to uniform CD19 expression, better CAR T-cell expansion, and a less immunosuppressive tumor environment. In contrast, GBM exhibits poor CAR T efficacy, with low response rates and short progression-free survival. This is due to antigen heterogeneity (e.g., variable EGFRvIII or IL13Rα2 expression), immune evasion mechanisms, and physical barriers like the blood-brain barrier (7). Additionally, the GBM microenvironment contains suppressive myeloid cells that hinder CAR T-cell activity (11). While these tumor-level and microenvironmental challenges play a major role, underlying genetic differences between DLBCL and GBM may further influence treatment response, shaping both tumor behavior and susceptibility to CAR T-cell therapy. These differences suggest that genetics may be critical to understanding why CAR T-cell therapy is more successful in DLBCL than GBM.

To our knowledge, no head-to-head genomic studies have compared CAR T-cell factors in DLBCL versus GBM. We aim to investigate whether genetic differences between DLBCL and GBM can help explain the contrast in CAR T-cell therapy effectiveness. We hypothesize that specific mutations in GBM may hinder CAR T efficacy but these are not present in DLBCL. By using publicly available datasets from cBioPortal and other sources, this study offers insights that could guide the development of future CAR T therapies for solid tumors.

METHODS

To allow for proper comparison between cBioPortal patient datasets and clinical trial populations used in CAR-T studies, where individual genetic information is unavailable, for diffuse large B-cell lymphoma (DLBCL) and glioblastoma (GBM), a matching process was designed based on available demographic and clinical data in both datasets. This process involved extracting summary statistics of patient characteristics from the trials, defining a distance function of the patient characteristics, and selecting subsamples from cBioPortal that closely matched the clinical trial populations based on the distance function.

Clinical Trial Reference Statistics

Trial demographic and disease characteristics were extracted from published studies (1, 12-24) and standardized. For continuous variables (e.g., age, Karnofsky score), weighted medians were calculated. For categorical variables (e.g., sex, disease stage), sample-size proportions were used. Separate standardization was used for DLBCL and GBM. Patients were excluded if more than 50% of the characteristics are missing. Pediatric GBM patients were also excluded due to known differences in genetic profiles between adult and pediatric GBM patients (25). Patient age was assumed to be reported at the beginning of the trials.

To quantify similarity between a subsample and its corresponding clinical trial population, a distance function was defined. This function accounts for both categorical and continuous variables after scaling and standardizing the data.

An algorithm was implemented to identify the optimal subset from the cBioPortal dataset that minimized the defined distance to the clinical trial reference statistics. At each iteration: A candidate subsample of size “n” was drawn without replacement. The distance to the clinical trial reference was computed. The best subsample for each “n” was noted. This process was repeated across a range of “n” values, and the overall best subsample was selected as the one with the lowest distance.

Mutation data for Diffuse large B-cell lymphoma (DLBCL) and Glioblastoma (GBM) was downloaded from cBioPortal. Both the complete group and subsampled datasets were processed. The following metrics were computed for each group after removing synonymous mutations:

Top-10 most frequently mutated genes

Distribution of mutation types (e.g., SNP, DEL, INS)

Distribution of variant classifications (e.g., missense, nonsense, frameshift)

For both DLBCL and GBM, three data frames were constructed:

For each patient, overall survival time, progression-free survival time and event status (death/progression) were compiled. Available overall survival or progression-free survival was included.

Patient-level clinical features were compiled:

DLBCL: Diagnosis age, sex, stage III/IV status, and International Prognostic Index (IPI) score.

GBM: Diagnosis age, sex, stage, Karnofsky performance score.

For each patient, mutation status (0 = absent, 1 = present) was determined for the top 10 most frequently mutated genes in each cancer type, based on the cBioPortal dataset.

The mutation matrix and patient characteristics were merged based on patient IDs. To ensure equal weighting of characteristics, continuous variables were scaled by subtracting the mean (of the entire dataset for a cancer) and dividing by the standard deviation (of the entire dataset for a cancer) within each iteration. Mutation columns were also scaled to match continuous variables. The final dataset (merged survival, characteristics, and mutations) was prepared for Cox Modeling.

Cox proportional hazards models were made separately for DLBCL and GBM datasets using the lifelines Python package (26). The models included both clinical variables and genetic mutation statuses. Hazard ratios (HRs), 95% confidence intervals, and p-values were computed for each predictor.

RESULTS

Patient Matching

To perform joint analysis of genetic mutations and CAR T therapy treatment outcomes on the same individuals, we matched subsets of cBioPortal patients in terms of patient characteristics with patients who underwent CAR T clinical trials. This is because cBioPortal provides individual-level genetic mutations from many patients, but most patients did not go through clinical trials. The existing clinical trials tend to be small and typically do not make individual-level genetic mutations available. By minimizing demographic and clinical differences between subsampled patient cohorts in cBioPortal and the overall populations within the clinical trials, we aim to approximate the CAR T treatment outcome of the subsampled cBioPortal patients for each cancer.

Using distance-based matching (Figures 1-2, Equation 1-2), minimal distances were achieved: 2.697 for DLBCL and 2.836 for GBM. This yielded subsample sizes of n = 74 for DLBCL and n = 80 for GBM. Distributions of patient characteristics (Figure 1) are not significantly different between matched and full cohorts (DLBCL IPI score: p=0.59; GBM Karnofsky score: p=0.13).

Table 1.

Reference Statistics for DLBCL

Characteristic	Statistic	% Missing
Median Age	60 years	21.5%
Stage III/IV	80.4%	17.1%
IPI High-Risk (Score 3–5)	50.5%	13.1%
Ann Arbor Stage III–IV	68%	23.0%
Male Sex	66%	10.3%

*Statistic column was calculated after removing patients missing more than 50% of characteristics.

Summary of diffuse large B-cell lymphoma (DLBCL) patient populations from CAR T-cell therapy clinical trials. Median age, sex distribution, stage III/IV status, and International Prognostic Index (IPI) scores are shown. Percent missing was calculated after removing patients missing 50% or more of characteristics.

Table 2.

Reference Statistics for GBM

Characteristic	Statistic	% Missing
Median Age	52.7 years	2.5%
Stage III/IV	80.8%	20.2%
Male Sex	51.9%	27.3%
Karnofsky Performance Score	80.8	37.1%

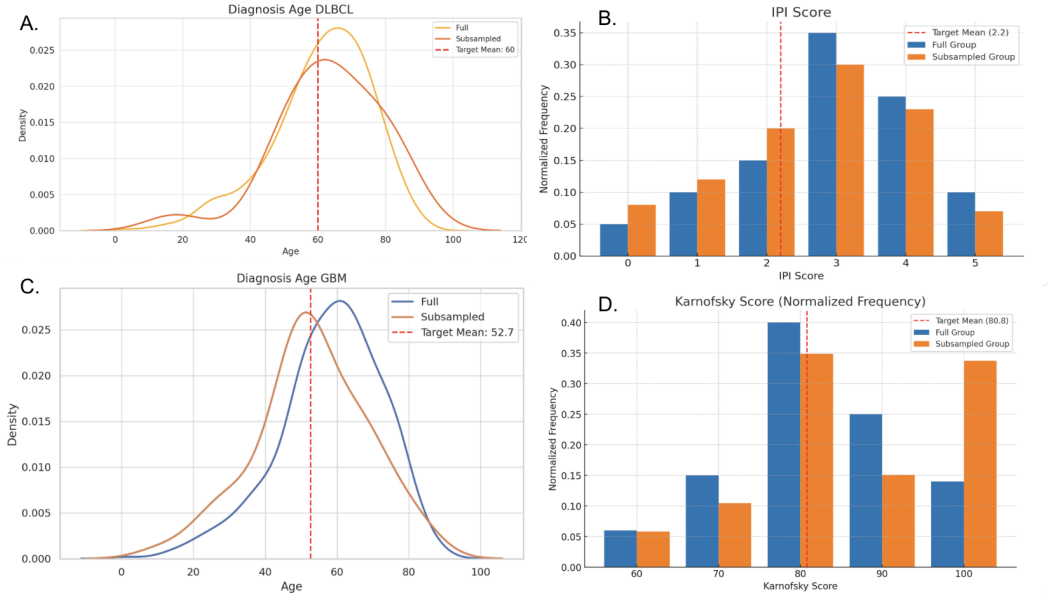
*Statistic column was calculated after removing patients missing more than 50% of characteristics.

Summary of glioblastoma (GBM) patient populations from CAR T-cell therapy clinical trials. Median age, sex distribution, tumor stage, and Karnofsky performance score are listed. Percent missing was calculated after removing patients missing 50% or more of characteristics.

Trial reference statistics guided subsampling of cBioPortal patients to approximate clinical trial populations.

Patient characteristics in histograms:

Figure 1.



Distributions of patient characteristics between subsampled and full cohorts are aligned. (A) Age at diagnosis in diffuse large B-cell lymphoma (DLBCL), (B) age at diagnosis in glioblastoma

(GBM), (C) International Prognostic Index (IPI) scores in DLBCL, and (D) Karnofsky performance scores in GBM. Distance-based matching minimized differences between cBioPortal subsamples and clinical trial reference populations (minimal distance = 2.697 for DLBCL; 2.836 for GBM), yielding matched sample sizes of n = 74 (DLBCL) and n = 80 (GBM). Wilcoxon rank-sum tests showed no significant differences in age distributions (DLBCL p = 0.59; GBM p = 0.13).

Top 10 Genes

Identifying the most frequently mutated genes in each cancer type provides insights into potential drivers of disease progression and resistance to CAR T-cell therapy.
After removing synonymous mutations, the dataset contained 2,346 unique mutated genes in DLBCL and 1,857 in GBM. The top 10 most frequently mutated genes were (Table 3-4). SNPs made up most of the mutations in the full cohort and the subsampled cohort for each cancer (Table 5-6).

Table 3.

Top 10 Mutated Genes in DLBCL

Gene	Full Data	Full Data %	Subsampled Data	Subsampled Data %
PIM1	241	24%	21	28%
BCL2	232	23%	17	22%
PCLO	184	18%	14	18%
IGLL5	143	14%	13	17%
FAT4	140	14%	10	13%
CSMD3	138	14%	10	13%
BTG1	138	14%	10	13%
SGK1	123	12%	8	11%
KMT2D	113	11%	8	11%
IGHV2-70	93	9%	6	8%

The ten most frequently mutated genes identified in diffuse large B-cell lymphoma (DLBCL) patients (total of 2,346 unique mutated genes). Most common mutations included PIM1, BCL2, PCLO, IGLL5, FAT4, CSMD3, BTG1, SGK1, KMT2D, IGHV2-70.

Table 4.

Top 10 Mutated Genes in GBM

Gene	Full Data	Full Data %	Subsampled Data	Subsampled Data %
TP53	142	21%	23	29%
PTEN	129	19%	13	16%
EGFR	117	17%	14	17%
TTN	117	17%	11	14%
NF1	71	11%	9	11%
MUC16	66	10%	6	8%
PIK3R1	49	7%	12	15%
FLG	48	7%	9	11%
PIK3CA	46	7%	6	8%
RYR2	42	6%	3	4%

The ten most frequently mutated genes identified in glioblastoma (GBM) patients (total of 1,857 unique mutated genes after excluding synonymous mutations). Frequent mutations occurred in TP53, PTEN, EGFR, TTN, NF1, MUC16, PIK3R1, FLG, PIK3CA, RYR2.

*Note that the top genes are those with the most number of mutations within the entire patient cohort in cBioPortal (or the subsampled patient cohort). For patients with multiple mutations in the same gene, each mutation was counted individually.

Table 3a.

DLBCL_Variant_Classifications

Variant_Classification	Full Data	Subsampled Data
Missense_Mutation	30241	486.0
Nonsense_Mutation	1910	44.0
Splice_Site	948	12.0
Frame_Shift_Del	719	6.0
Frame_Shift_Ins	531	6.0

Breakdown of mutation classes in the DLBCL dataset for full and subsampled data. SNPs made up the majority of mutations, with insertions and deletions comprising smaller proportions, similar across full and subsampled cohorts.

Table 3b.

GBM_Variant_Classifications

Variant_Classification	Full Data	Subsampled Data
Missense_Mutation	14783	168.0
Nonsense_Mutation	946	10.0
Frame_Shift_Del	817	5.0
Splice_Site	446	4.0
In_Frame_Del	289	2.0

Breakdown of mutation classes in the GBM dataset for full and subsampled data. SNPs made up the majority of mutations, with insertions and deletions comprising smaller proportions, similar across full and subsampled cohorts.

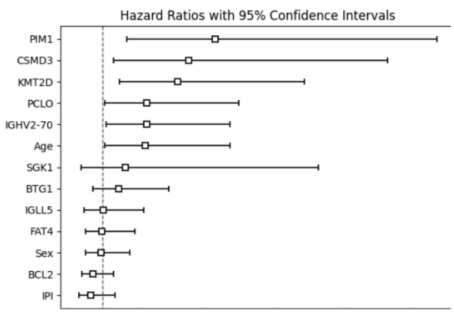
Survival Analysis

To test the hypothesis of whether distinct genetic features are associated with CAR T therapy in DLBCL and GBM, we conducted a survival analysis to associate the presence or absence of mutations in top 10 most mutated genes and the clinical factors (e.g., age) with survival outcomes in DLBCL and GBM,

DLBCL

Figure 2a.

	coef	exp(coef)	se(coef)	coef lower 95%	coef upper 95%	exp(coef) lower 95%	exp(coef) upper 95%	cmp to	z	p	-log2(p)
PIM1	1.45	4.28	0.47	0.54	2.37	1.71	10.69	0.00	3.11	<0.005	9.08
BCL2	-0.32	0.73	0.30	-0.92	0.28	0.40	1.32	0.00	-1.05	0.29	1.76
PCLO	0.83	2.29	0.39	0.06	1.60	1.06	4.96	0.00	2.11	0.03	4.84
IGLL5	0.03	1.03	0.39	-0.73	0.79	0.48	2.21	0.00	0.08	0.94	0.09
FAT4	-0.01	0.99	0.35	-0.69	0.67	0.50	1.95	0.00	-0.03	0.98	0.03
CSMD3	1.25	3.49	0.50	0.28	2.23	1.32	9.27	0.00	2.51	0.01	6.38
BTG1	0.38	1.47	0.35	-0.30	1.07	0.74	2.93	0.00	1.09	0.27	1.87
SGK1	0.51	1.66	0.75	-0.97	1.98	0.38	7.25	0.00	0.67	0.50	0.99
KMT2D	1.16	3.19	0.39	0.40	1.92	1.49	6.85	0.00	2.98	<0.005	8.42
IGHV2-70	0.82	2.28	0.37	0.10	1.55	1.11	4.70	0.00	2.24	0.03	5.31
Age	0.81	2.24	0.38	0.06	1.55	1.07	4.71	0.00	2.13	0.03	4.91
IPI	-0.42	0.66	0.37	-1.15	0.32	0.32	1.37	0.00	-1.11	0.27	1.91
Sex	-0.04	0.96	0.32	-0.67	0.59	0.51	1.80	0.00	-0.12	0.90	0.15

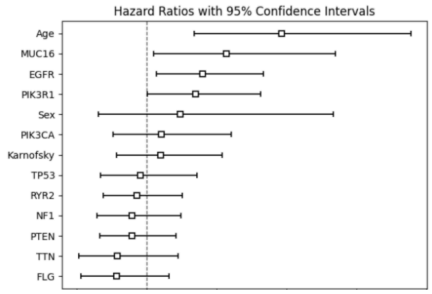


Hazard ratios (HRs), 95% confidence intervals, and p-values for predictors of survival in DLBCL (n = 74). Significant risk factors included mutations in PIM1 (HR > 2, $p < 0.05$), CSMD3 (HR > 2, $p < 0.05$), KMT2D (HR > 2, $p < 0.05$), PCLO (HR > 2, $p < 0.05$), and IGHV2-70 (HR > 2, $p < 0.05$). Age was also a strong clinical predictor (HR = 2.24 per unit increase, $p < 0.01$).

GBM

Figure 2b.

	coef	exp(coef)	se(coef)	coef lower 95%	coef upper 95%	exp(coef) lower 95%	exp(coef) upper 95%	cmp to	z	p	−log2(p)
TP53	-0.05	0.95	0.18	-0.40	0.31	0.67	1.36	0.00	-0.27	0.79	0.34
PTEN	-0.11	0.90	0.15	-0.41	0.19	0.66	1.21	0.00	-0.72	0.47	1.08
EGFR	0.34	1.40	0.14	0.07	0.61	1.07	1.83	0.00	2.44	0.01	6.10
TTN	-0.24	0.79	0.22	-0.67	0.20	0.51	1.22	0.00	-1.06	0.29	1.78
NF1	-0.11	0.90	0.17	-0.44	0.22	0.64	1.25	0.00	-0.65	0.51	0.96
MUC16	0.45	1.57	0.21	0.05	0.85	1.05	2.35	0.00	2.19	0.03	5.13
PIK3R1	0.30	1.35	0.15	0.01	0.59	1.01	1.81	0.00	1.99	0.05	4.44
FLG	-0.24	0.78	0.20	-0.64	0.15	0.53	1.16	0.00	-1.22	0.22	2.18
PIK3CA	0.10	1.10	0.19	-0.28	0.47	0.76	1.60	0.00	0.51	0.61	0.71
RYR2	-0.08	0.93	0.15	-0.38	0.23	0.69	1.25	0.00	-0.49	0.62	0.69
Age	0.68	1.97	0.20	0.29	1.06	1.34	2.89	0.00	3.44	<0.005	10.75
Karnofsky	0.09	1.10	0.17	-0.25	0.43	0.78	1.54	0.00	0.54	0.59	0.76
Sex	0.21	1.24	0.32	-0.42	0.85	0.65	2.33	0.00	0.65	0.51	0.96



Hazard ratios (HRs), 95% confidence intervals, and p-values for predictors of survival in GBM (n = 80). Significant risk factors included mutations in MUC16 (HR ≈ 1.97, $p < 0.05$), EGFR (HR ≈ 1.97, $p < 0.05$), and PIK3R1 (HR ≈ 1.97, $p < 0.05$). Age at diagnosis was also a significant predictor, with older patients experiencing substantially higher risk of death.

In DLBCL, mutations in PIM1, CSMD3, KMT2D, PCLO, and IGHV2-70 are associated with significantly increased hazard ratios (Table 4a), indicating a higher risk of death and lower efficacy of CAR T therapy. Age is an important clinical predictor. The model shows that for every unit increase in age, the hazard increases by a factor of 2.24, confirming age as a relevant variable in DLBCL prognosis.

In GBM, MUC16, EGFR, and PIK3R1 had high HRs (Table 4b), showing an association with worse CAR T therapy outcomes, increasing risk by a factor of 1.97. Age was also a statistically significant predictor of poorer prognosis, indicating that older patients face a significantly higher risk of death.

Age at diagnosis remained a negative prognostic factor in both cancers. This trend is also generally observed across many cancer types, where advanced age is associated with poorer outcomes, potentially due to immunosenescence and changes in the tumor microenvironment that impair T-cell function and reduce CAR-T efficacy (27).

The PI3K/AKT/mTOR pathway is represented in both datasets through genes such as PTEN, PIK3CA, PIK3R1, and SGK1. This pathway promotes cell survival and proliferation, and its disruption has been shown to reduce CAR T-cell infiltration and contribute to resistance against immune-mediated killing (28).

Receptor tyrosine kinase (RTK) and MAPK signaling pathways are affected by mutations in EGFR, NF1, and PIM1. These pathways enhance tumor growth and contribute to the formation of an immune-suppressive tumor microenvironment (29).

CONCLUSIONS

Discussion

In this study, we tested the hypothesis that genetic differences between diffuse large B-cell lymphoma (DLBCL) and glioblastoma (GBM) help explain why CAR T-cell therapy is effective in some cancers but not others. Using publicly available datasets from cBioPortal, we analyzed mutation and clinical data from 74 DLBCL patients and 80 GBM patients, selected through distance-based patient matching to reflect clinical trial populations. We identified the top 10 most frequently mutated genes in each cancer type and conducted a survival analysis to determine which genetic mutations were associated with worse prognosis.

In DLBCL, mutations in key genes play significant roles in disease progression. PIM1 mutations cause gain-of-function or constitutive kinase activation, enhancing cell proliferation and survival (11). Mutations in PCLO disrupt normal cellular communication (30). CSMD3 mutations impair tumor suppressor activity due to loss-of-function (31). KMT2D mutations affect histone methylation and transcriptional control, altering gene expression (32). Mutations in IGHV2-70 impact immunoglobulin structure and function, disrupting B-cell receptor signaling (33).

In GBM, mutations in several critical genes influence tumor progression. EGFR mutations are typically gain-of-function, driving uncontrolled cell proliferation (34). Disruption of mucin functions by MUC16 mutations may affect immune evasion and cell signaling (35). PIK3R1 mutations impair inhibitory control of the PI3K pathway, leading to AKT activation and increased cell survival (36). Hotspot mutations in PIK3CA result in gain-of-function, activating PI3K signaling and promoting cell survival and growth.

Age at diagnosis remained a negative prognostic factor in both cancers. This is also generally true in most cancers. which could influence the immune microenvironment and T-cell function, indirectly affecting CAR-T efficacy (27).

The genetic differences between DLBCL and GBM provide important clues as to why CAR T-cell therapy is highly effective in one but not the other. In DLBCL, the most frequently mutated genes, PIM1, BCL2, and KMT2D, are involved in B-cell development, survival, and epigenetic regulation (37). Several mutations, including those in IGLL5 and IGHV2-70, affect immunoglobulin genes, which are closely tied to the cancer's origin in the immune system (38). These features make DLBCL well-suited for CAR T-cell therapies that target B-cell antigens like CD19, which are expressed on the surface of malignant cells (39). In contrast, GBM frequently has mutations in TP53, PTEN, EGFR, and NF1, which activate growth-promoting pathways such as RTK/MAPK and PI3K/AKT (34). These mutations drive rapid tumor progression and create conditions that prevent immune cell activity. For example, PTEN mutations have been associated with reduced T-cell infiltration and resistance to immunotherapy (40), while EGFR mutations contribute to immune evasion (41). GBM's location within the brain also limits immune cell access due to the blood-brain barrier and presents a challenge for CAR T-cell therapies (41).

This is an active research area. In DLBCL, FDA-approved CAR T therapies such as axicabtagene ciloleucel (axi-cel), tisagenlecleucel (tisa-cel), and lisocabtagene maraleucel (liso-cel) target CD19, a B-cell surface antigen expressed in nearly all malignant B cells. Consistent with our findings, multiple genes related to B-cell functions, such as IGHV2-70, IGLL5, and PIM1, were identified in the DLBCL top gene and survival analysis. On the other hand, developing CAR T therapies for GBM is more challenging, as our study highlighted recurrent alterations in the PI3K/AKT/mTOR pathway (PIK3R1, PIK3CA, PTEN, SGK1) and the RTK/MAPK pathway (EGFR, NF1, PIM1). Likely due to the complexity and redundancy of these pathways, existing CAR T therapies that focus on targets such as EGFRvIII and IL13Rα2 have shown only limited effects. However, these antigens are often variably expressed, contributing to the limited efficacy of CAR T therapy in GBM. To overcome this limitation, researchers have begun testing multi-targeted strategies. In a study, researchers tested intraventricular CARv3-TEAM-E T cells, targeting EGFRvIII and wild-type EGFR, in three recurrent glioblastoma patients. Treatment caused no severe toxicities, induced rapid tumor regression in all, but responses were short-lived in two. Activity was observed even without EGFRvIII expression (42).These results suggest that while promising strategies are emerging, a better genetic understanding of GBM will be critical for identifying stable and broadly effective CAR T-cell targets.

Limitations

This study has several limitations: First, data availability was limited, particularly regarding clinical variables, which restricted the ability to fully match patients across groups. Additionally, the sample size for both DLBCL and GBM was relatively small, and this also caused a small number of mutations in the dataset after subsampling. Since the analysis was not based on patients from a single controlled trial, the comparison between cancer types is indirect. Some patient demographic data, such as race, was incomplete or missing altogether. Some of the studies were done in areas with the majority of patients being one race. Also, the cohort was mainly made up of patients with recurrent or refractory cancer as CAR-T is generally used as a second or third line treatment in most cancers. As a result, the representativeness of the cohort is limited, and the findings may not fully reflect the broader population of patients with DLBCL or GBM.
The long-term goal is to develop predictive models that use a patient's genetic profile to determine the likelihood of response to CAR T therapy. Cancer treatment decisions will significantly benefit from reliable tools that predict patient responses. For recurrent or refractory tumors, CAR T-cell therapy is often a last-resort option: one that is extremely costly but can produce remarkable, durable remissions in select patients. The long-term goal of this line of research is to develop predictive models that integrate a patient’s genetic profile to estimate the likelihood of response to CAR T therapy. Such models would help clinicians identify patients most likely to benefit, while sparing others from unnecessary toxicity and expense.

Developing these tools requires overcoming key limitations. Currently, the lack of genomic and clinical data directly linked to CAR T clinical trial participants makes it difficult to establish precise correlations between genetic mutations and therapeutic efficacy. In this study, we addressed this gap by designing a method to approximate trial populations through patient matching and by analyzing mutational patterns that may influence outcomes. While indirect, this

approach provides a foundational dataset and highlights genetic features that could be incorporated into future predictive models. Ultimately, by combining mutation profiles with clinical trial data, these tools could transform patient selection, optimize resource use, and improve overall outcomes in CAR T-cell therapy.

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