DOES CAR-T THERAPY OVERCOME TP53-DRIVEN RESISTANCE IN LYMPHOMA? A SYSTEMATIC REVIEW OF CLINICAL OUTCOMES

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INTRODUCTION

TP53 alterations, including mutations and 17p deletions, are among the most powerful adverse prognostic factors in non-Hodgkin lymphoma (NHL), conferring resistance to chemotherapy, early relapse, and inferior survival. Chimeric antigen receptor T-cell (CAR-T) therapy has transformed the treatment landscape of relapsed/refractory (R/R) B-cell lymphomas; however, its ability to overcome TP53-driven disease biology remains incompletely defined.

METHODS

We conducted a systematic review of studies published through March 2026, identified through major medical databases including PubMed/MEDLINE, Embase, and Web of Science evaluating clinical outcomes of CAR-T therapy in TP53-mutated NHL. Eligible studies included prospective trials, retrospective cohorts, and case reports involving large B-cell lymphoma, mantle cell lymphoma, CNS lymphoma, and Burkitt lymphoma, and reporting response rates, progression-free survival (PFS), overall survival (OS), and prognostic modifiers. A qualitative synthesis was performed because of study heterogeneity.

RESULTS

Across the 23 included studies, TP53 alterations were present in approximately 30%–50% of CAR-T treated populations, reflecting enrichment in high-risk disease. CAR-T therapy demonstrated preserved efficacy, with overall response rates ranging from 50% to 85% and complete response rates of 30%–80% in TP53-mutated patients.

However, survival outcomes were heterogeneous. Several studies identified TP53 alterations as an independent predictor of inferior response depth and reduced survival, with median PFS of approximately 6–14 months and shorter OS compared with TP53 wild-type patients.

In contrast, other studies showed no significant impact of TP53 status, suggesting partial mitigation of TP53-associated risk. Importantly, co-occurring genomic alterations, particularly MYC, ARID1A, and DDX3X, consistently defined subgroups with markedly poor outcomes, indicating that composite genomic profiles drive resistance more than TP53 alone.

Dual-target CAR-T strategies and combination approaches, including CAR-T with autologous stem cell transplantation or BTK inhibitors, were associated with improved response durability.

Emerging evidence highlights the prognostic value of dynamic biomarkers, particularly TP53-mutated circulating tumor DNA, which strongly predicts relapse and outperforms baseline genomic status.

CONCLUSION

CAR-T therapy partially overcomes the adverse prognostic impact of TP53 alterations in NHL, achieving meaningful responses even in high-risk disease. However, durability remains limited in genomically complex cases. Integration of combination strategies, optimized CAR-T constructs, and molecular monitoring is essential to improve long-term outcomes in TP53-mutated lymphoma.

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Table 1. Comprehensive Summary of Studies Evaluating CAR-T Outcomes in TP53-Mutated Lymphoma

Ref	Study	Disease	N (Total / TP53+)	CAR-T Strategy	ORR / CR (%)	Survival Outcomes	TP53 Impact	Key Message
1	Shouval et al.	LBCL	153 / ~37%	CD19	CR 34 vs 65	1y OS 44 vs 76%	Adverse	TP53 independently predicts poor OS
2	Wei et al.	Aggressive B-NHL	123 / 60	CD19/CD22 ± ASCT	ORR 87 / CR 45	PFS 14.8 mo, OS 56% (2y)	Neutral	ASCT + CAR-T improves outcomes
3	Xue et al.	DLBCL	73 / NR	CD19	Similar	NR	Context-dependent	TP53 + DE → poor prognosis
4	Li et al.	Pediatric B-NHL	89 / 66%	CD19	ORR 85	OS 12.6 mo	Trend	ARID1A + TP53 → high-risk
5	Ponpaczy et al.	DLBCL	170 / 34.5%	CD19	NR	OS NS	Neutral	CAR-T mitigates TP53 effect
6	Liu et al.	LBCL	195 / 53	CD19	ORR 56 / CR 39	PFS 6.9 mo, OS 12.1 mo	Partial	Improves survival vs chemo
7	Zhou et al.	B-NHL	79 / NR	CD19	CR ↓ (33 vs 68)	OS NS	Partial	ctDNA > TP53 baseline
8	Mao et al.	B-NHL	122 / 59	CD19/CD22 ± ASCT	High	5y OS 70% (combo)	Neutral	ASCT + dual CAR-T best
9	Wang et al.	B-NHL	38 / 44.7%	CD19/CD22	ORR 72 / CR 50	PFS 8.8 mo	Neutral	Dual CAR-T overcomes TP53
10	Shi et al.	DLBCL	105 / >15%	CD19	CR ↓	OS ↓	Adverse	TP53 = key genomic predictor
11	Gao et al.	DLBCL	83 / 40	CD19	ORR ~56	OS 24.5 mo	Adverse	TP53 independent OS predictor
12	Sheng et al.	LBCL	139 / 52	CD19	Similar	NS	Neutral	Depends on CAR construct
13	Zheng et al.	DLBCL	172 / 58	CD19	ORR 51 / CR 17	OS 14.2 mo	Partial	TP53 alone not predictive
14	Chen et al.	B-NHL	40 / 100%	CD19/CD22	ORR 92 vs 7	PFS NR vs 3 mo	Dynamic	ctDNA strongest predictor
15	Cai et al.	DLBCL	Case	CD19 + ASCT	CR achieved	OS >28 mo	Overcome	ASCT improves CAR-T outcomes
16	Gong et al.	LBCL	Case	CD19	CR achieved	Durable	Overcome	Debulking improves response
17	Li et al.	CNS lymphoma	61 / 39.5%	CD19	ORR 64	OS 14 mo	Neutral	CAR-T effective in CNSL
18	Wang M et al	MCL	68 / 6	CD19	CR 100%	PFS NR	Neutral	Excellent responses
19	Wang Y et al	MCL	189 / ~48%	CD19	High	PFS ↓	Adverse	Inferior durability
20	Minson et al	MCL	20 / 9	CD19 + Ibrutinib	CR 80	PFS 75% (1y)	Neutral	Ibrutinib improves CAR-T
21	Koroleva et al.	MCL	Case	CD19	CR achieved	MRD– 40 mo	Overcome	Early CAR-T effective
22	Zhou et al.	Burkitt	Case	CD19	CR achieved	OS >30 mo	Overcome	Durable remission
23	Zhang et al.	Burkitt	Case	CD19/CD22 + ASCT	CR achieved	OS >4y	Overcome	Sequential CAR-T strategy

Abbreviations: ASCT, autologous stem cell transplantation; B-NHL, B-cell non-Hodgkin lymphoma; CAR-T, chimeric antigen receptor T-cell therapy; CR, complete response; CRR, complete response rate; CNSL, central nervous system lymphoma; DE, double expression (MYC/BCL2); DLBCL, diffuse large B-cell lymphoma; LBCL, large B-cell lymphoma; MCL, mantle cell lymphoma; mo, months; NR, not reported or not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; y, year.