








Impact of *TP53* mutations on the efficacy of CAR-T cell therapy in cancer

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Abstract

The efficacy of chimeric antigen receptor (CAR)-T therapy may not match initial expectations due to the influence of multiple circumstances, some of which cannot be predicted. CAR-T treatment groups include high-risk patients, particularly those with *TP53* mutations. A significant body of research has demonstrated that mutations in the *TP53* gene play a pivotal role in cancer development and progression. Any aberration in the *TP53* gene in cancer is invariably associated with complications and a poor prognosis. Moreover, mutations in the *TP53* gene have been observed to correlate with resistance to conventional chemotherapy, prompting the use of alternative therapeutic approaches, including CAR-T therapy. However, there is a possibility that abnormalities in the *TP53* gene may affect patients after CAR-T cell administration reducing the efficacy of therapy. This review examines the link between *TP53* mutations in cancer and the efficacy of CAR-T therapy, as well as the potential implications of this aspect in therapeutic planning.

Keywords

TP53, mutation, CAR-T, immunotherapy, cancer

Introduction

A significant advancement in the treatment of recurrent/refractory (R/R) hematologic malignancies has been the introduction of chimeric antigen receptor (CAR)-T cell therapy. CAR-T therapy has demonstrated remarkable efficacy for this type of cancer, which is often less responsive to alternative therapeutic approaches. The safety and efficacy of CAR-T therapy have been demonstrated to be superior to conventional chemotherapy. Moreover, CAR-T cells, which are classified as advanced therapy medicinal products (ATMPs), have the potential to be approved as orphan pharmaceuticals. At the present time, CAR-T cells have already successfully completed the preclinical trial stage and are currently being used in

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clinical settings to treat a number of hematologic and rare diseases for which they have been specifically approved (Table 1) [1]. However, their efficacy in treating the majority of solid tumors remains uncertain, and their wide utilization is significantly limited. There are several challenges associated with the infiltration of CAR-T cells into solid tumors and their subsequent activation within these complex environments. The immunosuppressive nature of the tumor microenvironment (TME) further complicates the use of CAR-T cells in the treatment of malignant neoplasms. The selection of antigens represents a pivotal and intricate process in ensuring the optimal functioning of CAR-T cells. This is due to the fact that tumor cells possess the capacity to downregulate antigens, a phenomenon known as antigen escape, through the application of CAR-T cell selection pressure [2].

Furthermore, a study on mice showed that *TP53* mutations in chronic lymphocytic leukemia (CLL) lead to a high tumor burden, reduce T cell transplantation efficacy, and lead to diminished effectiveness of anti-CD19 CAR-T cell treatment [18]. Normally, the wild-type p53 protein functions as an oncosuppressor by inhibiting tumor growth. However, often disruption in its activity leads to protein malfunction and inactivation. In cancer, *TP53* gene mutations have been repeatedly linked to a worse prognosis, more aggressive disease development, and resistance to treatment. Multiple studies have provided evidence of the correlation between mutations or deletions in the *TP53* gene in CLL and the development of resistance to chemoimmunotherapy, along with a significantly deteriorated prognosis of the disease [19–21]. Consequently, the objective of this study is to assess the efficacy of CAR-T therapy in individuals with *TP53* mutations.

CAR-T cells (general background)

Approved CAR-T cell products contain a CAR consisting of an antibody-like antigen binding domain, a surface co-stimulatory factor, a T cell receptor (TCR), and a co-receptor signaling domain [22]. In a conventional CAR, the antigen-binding domain is typically composed of an antibody-derived scFv (single chain variable fragment). Nevertheless, there exist alternative options, such as nanobodies, which are truncated versions of scFv and consist of heavy-chain variable domains (VHHs), native receptors, and small peptides, including peptide-centric [23] and specific peptide enhanced affinity receptor (SPEAR) [24]. The functions of the antigen-binding domain are influenced by various factors such as the total number of CAR domains, which can vary depending on the specific construct design (e.g., dual CAR-T cells have two domains). In addition, important parameters include the type of protein used to derive the antigen-binding domain, its affinity and/or avidity for the antigen, and the combined affinity of several various CAR constructs on a single CAR-T cell surface. Each of these features results in different cell properties and behaviors which together may affect the safety and efficacy profile of CAR-T cells in patient's body [25].

The architecture of CARs is continuously being revised and is now in its fifth generation. The first iteration of CAR comprises solely an extracellular domain that selectively identifies antigens and an intracellular CD3 ζ signaling domain. However, its ability to target tumors is severely restricted due to the lack of co-stimulatory signals. Second-generation CARs have incorporated an intracellular motif containing a co-stimulatory receptor signaling domain into their structure (Figure 1). Second-generation CAR-T cells are capable of proliferating and releasing cytokines to exert anti-tumor effects even without the presence of external co-stimulatory molecules. Third-generation CAR is equipped with two co-stimulatory domains, specifically engineered to enhance the cytotoxicity of CAR-T cells. Fourth-generation CARs include additional molecular components to facilitate the expression of functional transgenic proteins, such as interleukins or suicide molecules, thereby improving the cytotoxicity and safety of CAR-T cells. The advanced fifth-generation CARs employ an adaptor-specific recognition domain to substitute the tumor-specific scFv extracellular structural domain used in earlier generations of CAR-T cells. This recognition domain binds to an adapter molecule targeting a tumor-specific target, such as the split, universal, and programmable (SUPRA) CAR system [26] and the biotin-binding immune receptor (BBIR) CAR [27].

In summary, incremental changes in CAR configurations that happened with each successive generation have led to significant improvements of CAR-T cell therapy safety and efficacy. Currently,

Table 1. Approved CAR-T cell therapies

| Trade name (generic name) | Target | Indication | Approval year | Company | Clinical study |
|--------------------------------------|--------|--|---------------|------------------------------|------------------------------|
| Kymriah (tisagenlecleucel) | CD19 | Patients under the age of 25 with B-cell ALL that is refractory or in second or subsequent relapse | 2017 | Novartis | ELIANA trial [3] |
| | | Adults with R/R LBCL after two or more lines of systemic therapy (including DLBCL-NOS, HGBCL, and DLBCL arising from FL) | 2018 | | JULIET trial [4] |
| | | Adults with R/R FL after two or more lines of systemic therapy | 2022 | | ELARA trial [5] |
| Yescarta (axicabtagene ciloleucel) | CD19 | Adults with R/R LBCL (including PMBCL, HGBCL, and DLBCL arising from FL) after two or more lines of systemic therapy | 2017 | Gilead Sciences | ZUMA-1 trial [6] |
| | | Adults with R/R FL after two or more lines of systemic therapy | 2021 | | ZUMA-5 trial [7] |
| | | Patients with R/R LBCL and within a maximum of 12 months following first-line chemoimmunotherapy | 2022 | | ZUMA-7 trial [8] |
| Tecartus (brexucabtagene autoleucel) | CD19 | Adults with R/R mantle cell lymphoma | 2020 | Gilead Sciences | ZUMA-2 trial [9] |
| | | Adult patients with R/R B-cell precursor ALL | 2021 | | ZUMA-3 trial [10] |
| Breyanzi (lisocabtagene maraleucel) | CD19 | Adults with R/R LBCL who have previously received 2 or more systemic therapies | 2021 | Bristol Myers Squibb | TRANSCEND NHL 001 trial [11] |
| | | Adults with R/R LBCL: <ul style="list-style-type: none"> Refractory to first-line chemoimmunotherapy Relapse within 12 months after first-line chemoimmunotherapy | 2022 | | TRANSFORM trial [12] |
| | | Adults with R/R CLL and SLL, who have received at least 2 prior therapies, including a BTK inhibitor and B-cell lymphoma 2 inhibitor venetoclax | 2024 | | TRANSCEND CLL 004 trial [13] |
| Carteyva (relmacabtagene autoleucel) | CD19 | Adults with R/R LBCL after two or more lines of systemic therapy | 2021 | JW Therapeutics | RELIANCE trial [14] |
| Abecma (idecabtagene vicleucel) | BCMA | Patients with R/R multiple myeloma after three or more previous lines of therapy including a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 antibody | 2021 | Bristol Myers Squibb | KarMMa trial [15] |
| Carvykti (ciltacabtagene autoleucel) | BCMA | Patients with multiple myeloma: <ul style="list-style-type: none"> After three or more previous lines of therapy Double-refractory to a proteasome inhibitor and an immunomodulatory drug, and had received a proteasome inhibitor, immunomodulatory agent, and anti-CD38 antibody | 2022 | Janssen Pharmaceuticals | CARTITUDE-1 trial [16] |
| ARI-0001 | CD19 | Patients aged > 25 years with R/R ALL | 2021 | Hospital Clinic of Barcelona | CART19-BE-01 trial [17] |

ALL: acute lymphoblastic leukemia; BCMA: B-cell maturation antigen; BTK: Bruton tyrosine kinase; CAR: chimeric antigen receptor; CLL: chronic lymphocytic leukemia; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; HGBCL: high-grade B-cell lymphoma; LBCL: large B-cell lymphoma; NOS: not otherwise specified; PMBCL: primary mediastinal B-cell lymphoma; R/R: recurrent/refractory; SLL: small lymphocytic lymphoma

second-generation CAR-T cells, which exhibit compromised efficacy and side effect profiles, are employed in clinical practice. The growing number of CAR-T cell therapies approved by regulatory authorities over recent years (Table 1) is indicative of the successful application of these therapies.

CAR-T in clinical practice

CAR-T cell immunotherapy has already demonstrated significant clinical efficacy for a number of hematological malignancies, including acute lymphoblastic leukemia (ALL), diffuse large B-cell lymphoma

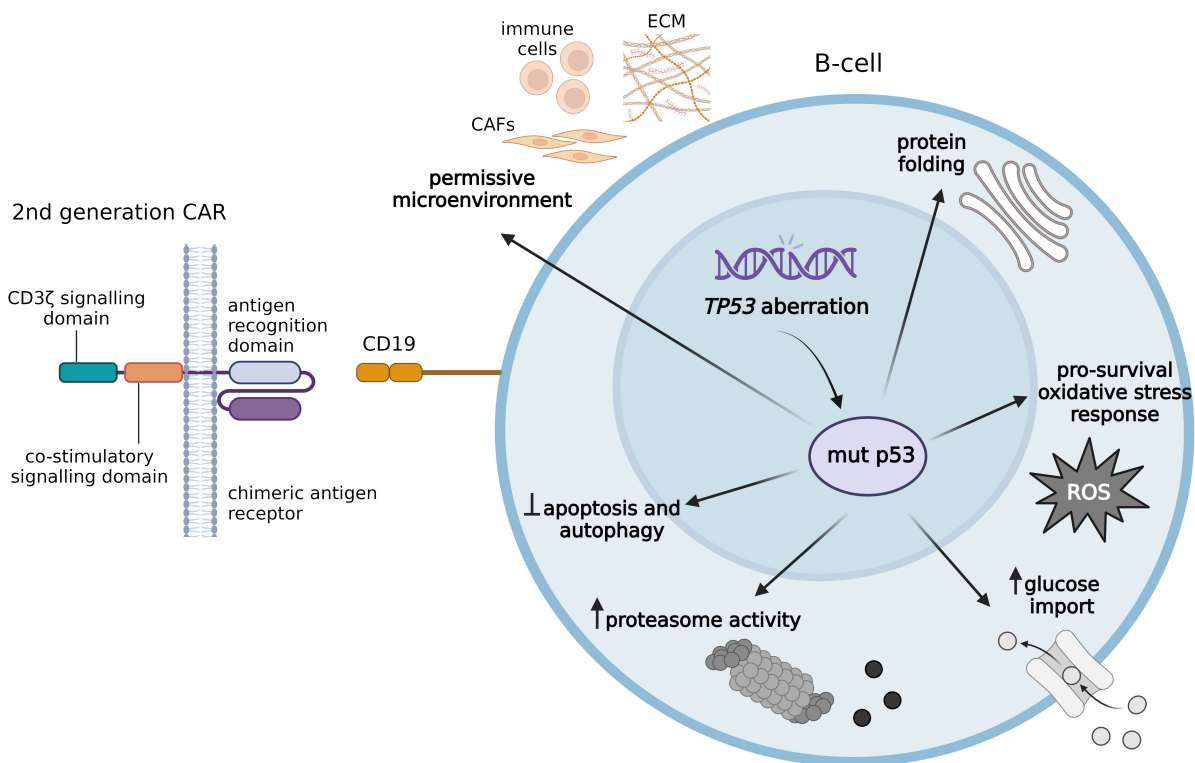


Figure 1. Second-generation CAR-T recognizes CD19 on the target B-cell. The presence of mut p53 protein promotes tumor progression, increases tumor aggressiveness, and is likely to reduce the efficacy of CAR-T cells. mut p53 induces a pro-survival response to oxidative stress, assists in protein folding, and increases proteasome activity. mut p53 protein resists autophagic cell death and prevents apoptosis. It promotes anabolic growth by increasing glucose uptake and facilitating the Warburg effect. mut p53 protein influences the environment by stimulating angiogenesis and triggering the release of proinvasive secretome. CAFs: cancer-associated fibroblasts; CAR: chimeric antigen receptor; ECM: extracellular matrix; mut p53: mutant p53; ROS: reactive oxygen species. Created in BioRender. Mirgayazova, R. (2024) <https://BioRender.com/r03q792>

(DLBCL), LBCL, and multiple myeloma (MM). CAR-T cell-based therapy has been approved by relevant organizations for the treatment of the aforementioned and some other diseases (Table 1). Most recently, in March 2024, the Food and Drug Administration (FDA) approved Breyanzi for the treatment of patients with R/R CLL and small lymphocytic lymphoma (SLL) who have received at least two prior therapies, including a Bruton tyrosine kinase (BTK) inhibitor and the B-cell lymphoma 2 inhibitor venetoclax [13].

However, in contrast to the impressive clinical outcomes demonstrated in hematological malignancies, the effectiveness of CAR-T treatment in solid tumors has been mostly disappointing so far. There is currently a limited number of suitable antigens that can be effectively targeted by CAR-T cells in solid tumors. Overexpressed proteins such as mesothelin (MSLN) and epithelial cell adhesion molecule (EpCAM) are prominently present on the surface of tumor cells, including breast, prostate, and stomach cancers. These proteins could serve as promising targets for the development of CAR-T cell therapies against solid tumors [28].

TME contains immunosuppressive components that impede the infiltration and efficacy of CAR-T cells. These include tumor-associated macrophages (TAMs), regulatory T (Treg) cells, myeloid-derived suppressor cells (MDSCs), and tumor-associated fibroblasts (TAFs). Moreover, various cytokines such as transforming growth factor beta (TGF-β), IL-4, and IL-10 can facilitate migration of immune cells that suppress the immune response, thereby indirectly inhibiting CAR-T cells. In addition, several inherent features of tumors, such as faulty blood vessels and a dense extracellular matrix (ECM) that contains cancer-associated fibroblasts (CAFs) and inappropriately expressed adhesion molecules, contribute to the insufficient movement and penetration of CAR-T cells within the tumor. While several stroma-targeting drugs have been reported [29], it is important to note that these targets may also be present in healthy tissues. CAR-T therapy specifically targeting CAFs has been demonstrated to recognize and attack malignant multipotent bone marrow stromal cells (BMSCs) [30]. However, this therapy has been associated with severe bone toxicity and cachexia, leading to deadly outcomes.

In the phase I clinical research conducted by Ahmed et al. [31], autologous modified virus-specific T (VST) cells that target cytomegalovirus, Epstein-Barr virus, or adenovirus were used to improve the persistence of systemically administered CAR-T cells that target HER2. This clinical trial included a cohort of 17 individuals diagnosed with progressing glioblastoma multiforme (GBM) who were administered with one or several infusions of autologous anti-HER2 CAR-VST cells without preceding lymphodepletion. The presence of CAR-T cells was observed in the peripheral blood for a duration of 12 months, which surpasses the duration observed in another study [32, 33]. The median overall survival (OS) was 11.1 months from the initial T cell infusion and 24.5 months from the time of diagnosis, demonstrating the clinical advantage. In addition, Hegde et al. [34] have effectively developed bispecific CAR-T cells that specifically target IL13R α 2 and HER2. These multi-targeted CAR-T cells have the potential to address the issue of antigen escape and offer promising prospects for the future application of CAR-T in glioma treatment [34]. In phase I clinical trial conducted by Brown et al. [35] three patients with recurrent GBM (rGBM) were administered a total of 12 regional doses of CAR-T cells targeting IL13R α 2 (NCT00730613). Despite the limited sample size, a group of 3 patients who experienced GBM recurrence achieved a median OS time of 10.9 months. In recent preclinical investigations the inclusion of Nivolumab, a monoclonal antibody that targets programmed cell death protein 1 (PD-1), has been found to enhance the ability of anti-GD2 CAR-T cells to destroy cancer cells. Additionally, in new nonobese diabetic/severe combined immunodeficient (NOD/SCID) mice model of GBM, the combination of anti-GD2 CAR-T cells with Nivolumab was shown to increase the animals' survival [36].

In addition, the activation of CAR-T cells leads to the production of various cytokines, such as IL-1, IL-2, IL-4, IL-6, IL-8, IL-10, and tumor necrosis factor alpha (TNF α) resulting in cytokine release syndrome (CRS)—a dangerous potentially fatal side effect [37].

Some individuals treated with CAR-T therapy may also experience immune effector cell-associated neurotoxicity syndrome (ICANS) [38]. While CAR-T cell activity can be enhanced by inflammatory cytokines like IL-2, it is important to note that systemic IL-2 administration can lead to the development of severe capillary leak syndrome and ultimately result in organ failure. Allen et al. [39] developed therapeutic T cells with engineered cytokine circuits based on tumor-specific synthetic Notch (synNotch) receptor that stimulates the production of IL-2. In immune-excluded tumor models such as pancreatic cancer and melanoma, the use of modified synNotch \rightarrow IL-2 induction circuits resulted in a strong infiltration of CAR-T or TCR-T cells into TME. These findings open up the potential avenue for using CAR-T therapy to treat solid tumors [39].

Mutated *TP53* in cancer

The *TP53* gene, also known as the tumor protein p53 gene, is located on the short arm of chromosome 17 and encodes a protein p53 that plays a critical role as tumor suppressor. The p53 protein is involved in the regulation of cell cycle, deoxyribonucleic acid (DNA) repair, cellular senescence, maintaining genomic stability, and inducing apoptosis, all of which are important mechanisms for preventing the initiation and progression of cancer. The *TP53* gene is activated in response to a variety of cellular stresses and can induce cell cycle arrest for the purpose of DNA repair or, if the damage is irreparable, it can initiate programmed cell death [40].

The *TP53* gene consists of 11 exons that encode for a protein with several functional domains, including the transactivation domain, DNA-binding domain, oligomerization domain, and regulatory domain. These domains allow the p53 protein to interact with various cellular components and carry out its tumor-suppressing functions. Upon activation by cellular stress signals, such as DNA damage or oncogene activation, p53 undergoes post-translational modifications that lead to its stabilization and activation. Subsequently, activated p53 translocates to the nucleus and binds to specific DNA sequences to modulate the expression of its target genes.

In addition, the *TP53* gene has the highest frequency of genetic alterations in human tumors [41]. *TP53* mutations primarily lead to the inactivation of normal p53 functions, which is advantageous for cancer

development because it prevents cells from undergoing natural tumor-suppressor responses such as senescence and apoptosis. In addition, cancer cells appear to acquire advantageous properties by exclusively retaining the mutant variant of the p53 protein. Mutant p53 has the ability to reorganize the transcriptomes and proteomes of tumor cells by forming new associations with transcriptional regulators, enzymes, and other cellular proteins [42, 43]. Specific missense mutations in p53 have been found to disrupt key cellular pathways, promote cancer cell growth and survival, facilitate invasion, migration, metastasis, and resistance to chemotherapy [44, 45]. Some reports suggest that mutant p53 plays a role in adapting to stressful conditions that occur during tumor development. These conditions include DNA damage caused by excessive cell growth, oxidative and proteotoxic stress, changes in nutrient levels, physical constraints, signals from surrounding tissues, and the body's immune response against the tumor [46]. Mutant p53 has been shown to improve protein folding [47] and increase proteasome activity [48] in human breast, lung, and pancreatic cancer cell lines. It also resists autophagic cell death in breast cancer [49] and inhibits therapy-induced apoptosis in head and neck cancer [50]. The mutant protein increases glucose uptake, which contributes to the Warburg effect in mice lacking the *TP53* gene [51]. In addition, mutant p53 has been found to regulate the extracellular environment by promoting angiogenesis in breast cancer [52], increasing cancer-promoting inflammation in the colon of p53 knockout mice [53], and stimulating the production of a proinvasive secretome in human lung tumors and their derived cell lines [54] (Figure 1).

The presence of mutated p53 in tumors has been shown to significantly alter the TME, promoting immune evasion through the modulation of myeloid cells and T cells. It has been demonstrated that mutant p53 can influence the polarization of TAMs, skewing them towards an M2-like phenotype that supports tumor growth and suppresses anti-tumor immunity [55]. This M2 polarization is associated with increased production of immunosuppressive factors such as IL-10 and TGF- β , which further impede T cell activation and proliferation. Furthermore, mutant p53 has been shown to enhance the recruitment of MDSCs, which inhibit T cell function and promote an immunosuppressive microenvironment [56].

Ghosh et al. [57] demonstrated that mutant p53 has the effect of disrupting the activity of the cytoplasmic DNA sensing pathway, specifically the cyclic GMP-AMP synthase-stimulator of interferon genes-TANK-binding kinase 1-interferon regulatory factor 3 (cGAS-STING-TBK1-IRF3) axis, which is crucial for triggering the innate immune response. In contrast to wild-type p53, mutant p53 binds to TBK1, preventing the formation of a vital trimeric complex comprising TBK1, the endoplasmic reticulum-resident STING, and IRF3. This complex is essential for the activation, nuclear translocation, and transcriptional function of IRF3. The impairment of innate immune signaling caused by mutant p53 leads to altered cytokine production, which in turn facilitates immune evasion. Furthermore, mutant p53 impairs IRF3-induced apoptosis. It is worth noting that reactivating TBK1 signaling can circumvent the effects of mutant p53, resulting in the revival of immune cell functionality and the elimination of cancer cells. These findings have significant implications for the development of new treatments. Strategies that reactivate TBK1 could potentially restore immune surveillance and target tumors with mutant p53.

It has been demonstrated that *TP53* mutations are more prevalent in cancerous tissues than in healthy ones. In the context of cancer, it is crucial to recognize that mutations and deletions that arise in the *TP53* gene are common genetic events that are associated with adverse clinical manifestations and a poor prognosis. It has been observed that *TP53* mutations are found in some high-risk metastatic malignancies, including esophageal adenocarcinoma, ovarian serous carcinoma, and small cell lung carcinoma. These mutations occur with a high frequency (85–98%) in these cancers [58]. Additionally, a comparative study of primary and metastatic samples demonstrated that *TP53* mutations are significantly more frequent in secondary and metastatic lesions [59]. These observations are in excellent agreement with earlier studies that have noted that the development of high-grade glioblastoma from a previous low-grade astrocytoma is associated with the specific growth of individual *TP53*-mutant cells that were already present in the previous cancer [60].

Somatic *TP53* mutations in cancer are found in all regions of the gene but with a marked concentration at specific sites. DNA-binding and transactivation domains carry markedly more mutations in hotspots (the *TP53* Database R20, July 2019: <https://tp53.isb-cgc.org>) [61].

In addition, several single nucleotide variations (SNVs) have been identified in a significant number of patients, ranging from hundreds to thousands. It has been observed that germline *TP53* mutations are present in individuals diagnosed with Li-Fraumeni syndrome, a disorder characterized by an increased susceptibility to cancer throughout life.

It is also noteworthy that there are additional genes linked to the *TP53* pathway that may exhibit mutations or copy number variations, both of which are similarly correlated with an unfavorable prognosis. The Catalogue Of Somatic Mutations In Cancer (COSMIC) database [62] provides data indicating that 15 genes involved in the *TP53* pathway undergo recurrent alterations. These genes include *TP53* regulators such as *MDM2* and *CDKN2A*, as well as downstream effectors including *CCND1* and *PTEN* [63]. The function of p53 is suppressed in some virus-associated malignancies. For example, in cervical cancer, the HPV E6 oncoprotein destroys the p53 protein [64]. The p53 protein plays a critical role in these cancers, although the *TP53* gene itself is not mutated. Notably, some rare cancers, such as childhood ALL and testicular seminoma, have a high chance of cure despite initial malignancy and metastasis. In contrast to metastatic disseminated adult malignancies, these tumors exhibit the wild-type *TP53* gene [65]. The collective data presented herein provide evidence in favor of the argument that a majority of cell types found in advanced or metastatic malignancies exhibit *TP53* abnormalities, resulting in the presence of non-functional p53 protein.

Inactivation of p53 functions or its downstream pathway is a common feature of human tumors that often correlates with increased malignancy, poor patient survival, and resistance to treatment [66, 67]. Several studies indicate that *TP53* mutations confer chemoresistance to lung cancer cells in vitro and in vivo [68, 69]. In CLL the presence of mutant *TP53* variants is associated with poor prognosis, advanced disease stage, rapid progression, chemoresistance, and reduced OS [70].

In their research, Roselle et al. [71] emphasized the substantial impact of the human and great ape-specific p53 isoform, $\Delta 133p53\alpha$, in enhancing the efficacy of CAR-T cell therapy for CLL patients who had not responded to previous treatments. Despite lacking a transactivation domain, $\Delta 133p53\alpha$ is capable of forming heterooligomers with full-length p53, thus influencing the p53-mediated stress response [72]. The study demonstrated that the sustained expression of $\Delta 133p53\alpha$ enhances the anti-tumor efficacy of CD19-targeted CAR-T cells and mitigates dysfunction in scenarios involving high tumor loads and metabolic stress. The researchers discovered that CAR-T cells expressing $\Delta 133p53\alpha$ exhibit a robust metabolic profile, enabling them to perform effector functions and proliferate even in nutrient-deprived environments. This is partly due to the upregulation of essential biosynthetic processes and enhanced mitochondrial function. These results highlight the potential advantages of targeting the p53 pathway to enhance CAR-T cell therapies [71].

Mutant *TP53* variants have been identified as strong prognostic markers for patients receiving standard first-line treatment in CLL. Preclinical evidence indicates that *TP53*-mutated CLL leads to early disease onset, high tumor burden, and ineffective T cell engraftment in a mouse model, resulting in suboptimal efficacy of anti-CD19 CAR-T cells [18]. Clinical trials of anti-CD19 CAR-T cells have shown limited complete remissions in cases carrying the del17p gene (*TP53* gene locus) [73].

Determining *TP53* status may be of a great prognostic value for the optimal decision-making in chemo/radiation therapy. For instance, it is well known that tumors containing the mutant *TP53* are more resistant to ionizing radiation than those with the wild-type *TP53*. The frequent inactivation of *TP53* in human tumors suggests that the restoration of the abrogated *TP53* pathway is an attractive tumor cell-specific strategy for treating cancers.

TP53 mutations affect CAR-T therapy

Mutations in the *TP53* gene lead to genomic instability, tumor cell clonal evolution, growth, and survival [73]. These mutations are also associated with dysregulation of pathways related to CAR-T cell cytotoxicity resulting in poor prognosis and potential drug resistance [74]. In preclinical studies, it has been demonstrated that mutations in the *TP53* gene have a negative impact on the duration of CAR-T cell persistence, resulting in a reduction in the long-term efficacy of anti-CD19 CAR-T cell therapy in the context of cancer treatment [18].

The efficacy of treatment with anti-CD19 CAR-T cells in patients with *TP53* mutations was evaluated by Zhang et al. [75] in a recent study. A total of 102 patients with B-ALL, of whom 11 had mutations in the *TP53* gene, participated in the study. The researchers observed that the OS and leukemia-free survival (LFS) rates at six months were significantly lower in patients with *TP53* mutations than in patients without mutations (OS: 51.9% vs. 89.0%; LFS: 42.4% vs. 82.6%; Figure 2). Five out of 11 patients experienced a relapse with a median duration of 56 days, 7 patients died (1 patient due to infection and 4 due to relapse). Patients with *TP53* mutations may experience a higher rate and earlier onset of relapse due to rapid mutations in leukemic blasts, enhanced proliferation, and evasion of CAR-T cell cytotoxicity. Authors demonstrate that CAR-T cell treatment followed by consolidative allogeneic hematopoietic stem cell transplantation (allo-HSCT) has superior LFS and OS.

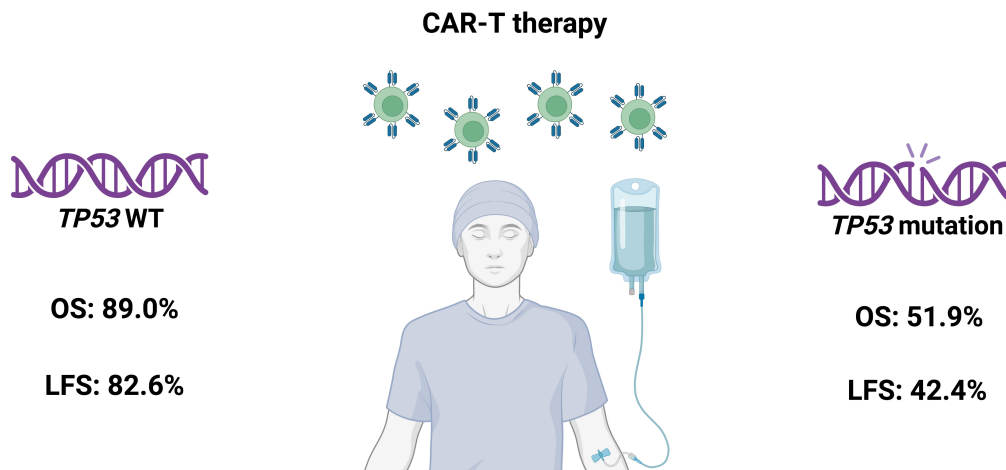


Figure 2. The impact of CAR-T therapy on patient survival. The OS and LFS at 6 months after CAR-T therapy are much lower in the group with *TP53* mutation compared to the group with WT *TP53* [75]. CAR: chimeric antigen receptor; LFS: leukemia-free survival; OS: overall survival; WT: wild-type. Created in BioRender. Mirgayazova, R. (2024) <https://BioRender.com/n41y197>

Porpaczy et al. [76] investigated the impact of *TP53* mutations on the OS of patients with R/R DLBCL following CAR-T therapy. R/R DLBCL is associated with a poor prognosis, and *TP53* mutations in DLBCL are recognized as indicators of poor outcomes and are often associated with treatment resistance. A total of 170 patients with DLBCL and high-grade B-cell lymphoma who were treated at an Austrian medical center between 2000 and 2021 were enrolled in the study. In this study, 29 out of 170 patients underwent CAR-T cell treatment, and *TP53* mutations were detected in 10 out of 29 patients (35%) in the CAR-T cell treatment group and in 31 out of 141 patients (22%) in the conventional treatment group. The presence of *TP53* mutations was identified as a distinct factor that negatively impacts OS among the 141 patients who did not receive CAR-T cell treatment. However, this correlation was not observed in the cohort of patients who underwent CAR-T cell therapy. The researchers concluded that the presence of *TP53* mutations did not influence the clinical outcomes of patients with DLBCL who received CAR-T cell therapy and proposed that a comprehensive assessment in larger cohorts is necessary.

In a retrospective study conducted by Gao et al. [77], the effect of *TP53* mutations in R/R DLBCL on the clinical picture after CAR-T therapy was investigated. Authors evaluated the impact of CAR-T cell therapy on patients with *TP53* mutations and found that these patients had a median OS of 24.5 months and a

median LFS of 6.8 months following CAR-T treatment. There were no significant differences in the objective remission rate (ORR) and LFS between patients with wild-type and mutated *TP53* after CAR-T therapy. However, patients with *TP53* mutations had significantly poorer OS. Concurrent mutations of chromosome 17 and those found on exon 5 of the *TP53* gene were associated with a more unfavorable prognosis. Additionally, individuals with dual mutations in *TP53* and *DDX3X* were identified as a subgroup with a critically poor prognosis.

Xue et al. [78] conducted a retrospective analysis involving 73 patients in China diagnosed with R/R DLBCL who underwent CD19 CAR-T therapy (Axi-cel or Relma-cel) following a chemotherapy regimen of fludarabine and cyclophosphamide. The findings indicated that patients with R/R DLBCL exhibiting both double-expression (*MYC* > 40% and *BCL2* > 50%) and *TP53* mutations generally experience a worse clinical outcome post-CAR-T treatment, even when combined with additional therapies. Conversely, the study demonstrated that CAR-T therapy was an effective treatment option for patients with either *TP53* mutations or double-expression status, with outcomes comparable to those observed in patients without these genetic alterations.

Eder et al. [79] reported on a 64-year-old male patient diagnosed with LBCL who experienced two relapses after standard-of-care treatment. Next-generation sequencing identified a clonal population with *TP53* mutations. The patient received CAR-T cell therapy as a third-line treatment resulting in complete remission. However, this therapy also led to the proliferation of *TP53*-mutated cells and the development of therapy-induced myelodysplasia with a complex abnormal chromosomal structure. The authors suggest that this case could be considered a typical example of clonal hematopoietic expansion in a patient undergoing CAR-T cell treatment, especially in the presence of *TP53*-mutated clones.

CAR-T cell therapy has shown promise as a viable treatment for R/R Burkitt's lymphoma with *TP53* mutation, a condition that often has low remission rates when treated with traditional chemoimmunotherapy [80]. Here, the patient with Burkitt's lymphoma achieved complete remission and prolonged disease-free period after receiving a combination of anti-CD19 and anti-CD22 CAR-T cells, followed by autologous hematopoietic stem cell therapy (ASCT).

Shouval et al. [81] demonstrated that *TP53* alterations represent a valuable prognostic indicator in LBCL patients receiving anti-CD19 CAR-T therapy. Gene expression profiling indicates that *TP53* mutations are associated with a TME that suppresses the immune system and impairs apoptotic signaling, potentially reducing the effectiveness of CAR-T therapy.

Mueller et al. [82] conducted a study to assess the efficacy of CAR-T therapy in treating *TP53*-mutant acute myeloid leukemia/myelodysplastic neoplasms (AML/MDS), which are known to be resistant to chemotherapy and have a poor prognosis. The study demonstrated that AML cells with *TP53* mutations exhibited heightened resistance to CAR-T cell therapy in vitro. The proliferation and viability of CAR-T cells were found to be significantly reduced when co-cultured with *TP53*-mutant AML blasts, in comparison to those with wild-type *TP53*. The live-cell imaging results demonstrated that *TP53*-mutant cells were eliminated at a slower rate, which had an adverse effect on the effectiveness of CAR-T cells. The survival rates of immunocompromised mice with *TP53*-mutant AML who received CAR-T cell treatment were lower than those of mice with wild-type AML. Gene expression analysis indicated an upregulation of the mevalonate pathway in *TP53*-mutant cells, alongside a downregulation of the Wnt pathway in CAR-T cells. Pharmacological intervention targeting these pathways restored the susceptibility of *TP53*-mutant AML cells to CAR-T cell-mediated cytotoxicity. Furthermore, CAR-T cells engineered using CRISPR/Cas9 to enhance Wnt signaling demonstrated improved effectiveness against *TP53*-mutant AML cells.

Conclusions

Currently, there is a limited number of studies focused on understanding the correlation between patient's *TP53* mutational status and the efficacy of CAR-T therapy due to the fact that the presence of *TP53* mutations is not yet universally tested in all cancers. The available clinical information indicates that *TP53* mutations have an impact on the outcomes of patients with B-cell malignancies treated with CAR-T cell

therapy. Patients with *TP53* mutations often exhibit lower survival rates and higher rates of relapse compared to those without the mutation.

Mutations of *TP53* gene correlate with poor prognosis following CAR-T therapy. Mutant p53 may be responsible for the poor efficacy of CAR-T cell therapy as a result of alterations to the TME and the influence of key signaling pathways involved in the immune response. The presence of mutant p53 has been observed to enhance the recruitment of Tregs and MDSCs, both of which contribute to an immunosuppressive environment that impairs the efficacy of CAR-T cell therapy. The additional effect of mutant p53 is to disrupt the expression of pro-inflammatory cytokines and chemokines, which further limits the ability of CAR-T cells to infiltrate and persist in tumors.

However, using combination of anti-CD19 and anti-CD22 CAR-T cells, and in some cases following allo-HSCT transplantation allows achieving complete remission for patients with *TP53* mutations. Furthermore, pharmacological intervention targeting the mevalonate pathway and the Wnt pathway has been shown to restore the susceptibility of *TP53*-mutant AML cells to CAR-T therapy. Also, genetically modified CAR-T cells, engineered to enhance Wnt signaling, have shown promising results in treating *TP53*-mutant tumors. Additional studies and a larger patient sample size are necessary for a more in-depth analysis. Overall, further research is needed to fully understand the impact of *TP53* mutations on the response to CAR-T cell therapy. This will enable the development of more efficient treatment protocols and the enhancement of early genetic diagnostics.

Abbreviations

ALL: acute lymphoblastic leukemia

allo-HSCT: allogeneic hematopoietic stem cell transplantation

AML: acute myeloid leukemia

CAFs: cancer-associated fibroblasts

CAR: chimeric antigen receptor

CLL: chronic lymphocytic leukemia

DLBCL: diffuse large B-cell lymphoma

DNA: deoxyribonucleic acid

GBM: glioblastoma multiforme

IRF3: interferon regulatory factor 3

LBCL: large B-cell lymphoma

LFS: leukemia-free survival

MDSCs: myeloid-derived suppressor cells

OS: overall survival

R/R: recurrent/refractory

scFv: single chain variable fragment

STING: stimulator of interferon genes

synNotch: synthetic Notch

TAMs: tumor-associated macrophages

TBK1: TANK-binding kinase 1

TCR: T cell receptor

TGF- β : transforming growth factor beta

TME: tumor microenvironment

Treg: regulatory T

VST: virus-specific T

Declarations

Author contributions

RM: Conceptualization, Writing—original draft, Supervision. RK: Writing—original draft. MF and VC: Visualization. EB: Writing—review & editing, Funding acquisition. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

Not applicable.

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References

1. Giorgioni L, Ambrosone A, Cometa MF, Salvati AL, Magrelli A. CAR-T State of the Art and Future Challenges, A Regulatory Perspective. *Int J Mol Sci.* 2023;24:11803. [DOI] [PubMed] [PMC]
2. Sterner RC, Sterner RM. CAR-T cell therapy: current limitations and potential strategies. *Blood Cancer J.* 2021;11:69. [DOI] [PubMed] [PMC]
3. Laetsch TW, Myers GD, Baruchel A, Dietz AC, Pulsipher MA, Bittencourt H, et al. Patient-reported quality of life after tisagenlecleucel infusion in children and young adults with relapsed or refractory B-cell acute lymphoblastic leukaemia: a global, single-arm, phase 2 trial. *Lancet Oncol.* 2019;20:1710–8. [DOI] [PubMed] [PMC]
4. Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, et al.; JULIET Investigators. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *N Engl J Med.* 2019;380:45–56. [DOI] [PubMed]
5. Fowler NH, Dickinson M, Dreyling M, Martinez-Lopez J, Kolstad A, Butler J, et al. Tisagenlecleucel in adult relapsed or refractory follicular lymphoma: the phase 2 ELARA trial. *Nat Med.* 2022;28:325–32. [DOI] [PubMed]

6. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. *N Engl J Med.* 2017;377:2531–44. [DOI] [PubMed] [PMC]
7. Jacobson CA, Chavez JC, Sehgal AR, William BM, Munoz J, Salles G, et al. Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial. *Lancet Oncol.* 2022;23:91–103. [DOI] [PubMed]
8. Locke FL, Miklos DB, Jacobson CA, Perales MA, Kersten MJ, Oluwole OO, et al.; All ZUMA-7 Investigators and Contributing Kite Members. Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma. *N Engl J Med.* 2022;386:640–54. [DOI] [PubMed]
9. Wang M, Munoz J, Goy A, Locke FL, Jacobson CA, Hill BT, et al. KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma. *N Engl J Med.* 2020;382:1331–42. [DOI] [PubMed] [PMC]
10. Shah BD, Ghobadi A, Oluwole OO, Logan AC, Boissel N, Cassaday RD, et al. KTE-X19 for relapsed or refractory adult B-cell acute lymphoblastic leukaemia: phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study. *Lancet.* 2021;398:491–502. [DOI] [PubMed]
11. Abramson JS, Palomba ML, Gordon LI, Lunning MA, Wang M, Arnason J, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. *Lancet.* 2020;396:839–52. [DOI] [PubMed]
12. Kamdar M, Solomon SR, Arnason J, Johnston PB, Glass B, Bachanova V, et al.; TRANSFORM Investigators. Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma (TRANSFORM): results from an interim analysis of an open-label, randomised, phase 3 trial. *Lancet.* 2022;399:2294–308. [DOI] [PubMed]
13. Siddiqi T, Maloney DG, Kenderian SS, Brander DM, Dorritie K, Soumerai J, et al. Lisocabtagene maraleucel in chronic lymphocytic leukaemia and small lymphocytic lymphoma (TRANSCEND CLL 004): a multicentre, open-label, single-arm, phase 1–2 study. *Lancet.* 2023;402:641–54. [DOI] [PubMed]
14. Zhu J, Ying Z, Song Y, Yang H, Guo Y, Li W, et al. Clinical Response of CD19 CAR-T Cells (relmacabtagene autoleucel, relma-cel) in Adults with Heavily-Pre-Treated Relapsed/Refractory (r/r) Large B-Cell Lymphoma in China. *Blood.* 2020;136:39–40. [DOI]
15. Munshi NC, Anderson LD Jr, Shah N, Madduri D, Berdeja J, Lonial S, et al. Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma. *N Engl J Med.* 2021;384:705–16. [DOI] [PubMed]
16. Berdeja JG, Madduri D, Usmani SZ, Jakubowiak A, Agha M, Cohen AD, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. *Lancet.* 2021;398:314–24. [DOI] [PubMed]
17. Ortiz-Maldonado V, Frigola G, Español-Rego M, Balagué O, Martínez-Cibrián N, Magnano L, et al. Results of ARI-0001 CART19 Cells in Patients With Chronic Lymphocytic Leukemia and Richter's Transformation. *Front Oncol.* 2022;12:828471. [DOI] [PubMed] [PMC]
18. Mancikova V, Peschelova H, Kozlova V, Ledererova A, Ladungova A, Verner J, et al. Performance of anti-CD19 chimeric antigen receptor T cells in genetically defined classes of chronic lymphocytic leukemia. *J Immunother Cancer.* 2020;8:e000471. [DOI] [PubMed] [PMC]
19. Stilgenbauer S, Schnaiter A, Paschka P, Zenz T, Rossi M, Döhner K, et al. Gene mutations and treatment outcome in chronic lymphocytic leukemia: results from the CLL8 trial. *Blood.* 2014;123:3247–54. [DOI] [PubMed]
20. Zenz T, Eichhorst B, Busch R, Denzel T, Häbe S, Winkler D, et al. *TP53* mutation and survival in chronic lymphocytic leukemia. *J Clin Oncol.* 2010;28:4473–9. [DOI] [PubMed]

21. Gonzalez D, Martinez P, Wade R, Hockley S, Oscier D, Matutes E, et al. Mutational status of the *TP53* gene as a predictor of response and survival in patients with chronic lymphocytic leukemia: results from the LRF CLL4 trial. *J Clin Oncol*. 2011;29:2223–9. [DOI] [PubMed]
22. De Marco RC, Monzo HJ, Ojala PM. CAR T Cell Therapy: A Versatile Living Drug. *Int J Mol Sci*. 2023;24:6300. [DOI] [PubMed] [PMC]
23. Ma Q, Garber HR, Lu S, He H, Tallis E, Ding X, et al. A novel TCR-like CAR with specificity for PR1/HLA-A2 effectively targets myeloid leukemia *in vitro* when expressed in human adult peripheral blood and cord blood T cells. *Cytotherapy*. 2016;18:985–94. [DOI] [PubMed] [PMC]
24. Ramachandran I, Lowther DE, Dryer-Minnerly R, Wang R, Fayngerts S, Nunez D, et al. Systemic and local immunity following adoptive transfer of NY-ESO-1 SPEAR T cells in synovial sarcoma. *J Immunother Cancer*. 2019;7:276. [DOI] [PubMed] [PMC]
25. Labanieh L, Mackall CL. CAR immune cells: design principles, resistance and the next generation. *Nature*. 2023;614:635–48. [DOI] [PubMed]
26. Cho JH, Collins JJ, Wong WW. Universal Chimeric Antigen Receptors for Multiplexed and Logical Control of T Cell Responses. *Cell*. 2018;173:1426–38.e11. [DOI] [PubMed] [PMC]
27. Urbanska K, Lanitis E, Poussin M, Lynn RC, Gavin BP, Kelderman S, et al. A universal strategy for adoptive immunotherapy of cancer through use of a novel T-cell antigen receptor. *Cancer Res*. 2012;72:1844–52. [DOI] [PubMed] [PMC]
28. Yan T, Zhu L, Chen J. Current advances and challenges in CAR T-Cell therapy for solid tumors: tumor-associated antigens and the tumor microenvironment. *Exp Hematol Oncol*. 2023;12:14. [DOI] [PubMed] [PMC]
29. Valkenburg KC, de Groot AE, Pienta KJ. Targeting the tumour stroma to improve cancer therapy. *Nat Rev Clin Oncol*. 2018;15:366–81. [DOI] [PubMed] [PMC]
30. Tran E, Chinnasamy D, Yu Z, Morgan RA, Lee CC, Restifo NP, et al. Immune targeting of fibroblast activation protein triggers recognition of multipotent bone marrow stromal cells and cachexia. *J Exp Med*. 2013;210:1125–35. [DOI] [PubMed] [PMC]
31. Ahmed N, Brawley V, Hegde M, Bielamowicz K, Kalra M, Landi D, et al. HER2-Specific Chimeric Antigen Receptor-Modified Virus-Specific T Cells for Progressive Glioblastoma: A Phase 1 Dose-Escalation Trial. *JAMA Oncol*. 2017;3:1094–101. [DOI] [PubMed] [PMC]
32. Goff SL, Morgan RA, Yang JC, Sherry RM, Robbins PF, Restifo NP, et al. Pilot Trial of Adoptive Transfer of Chimeric Antigen Receptor-transduced T Cells Targeting EGFRvIII in Patients With Glioblastoma. *J Immunother*. 2019;42:126–35. [DOI] [PubMed] [PMC]
33. Liu Z, Zhou J, Yang X, Liu Y, Zou C, Lv W, et al. Safety and antitumor activity of GD2-Specific 4SCAR-T cells in patients with glioblastoma. *Mol Cancer*. 2023;22:3. [DOI] [PubMed] [PMC]
34. Hegde M, Mukherjee M, Grada Z, Pignata A, Landi D, Navai SA, et al. Tandem CAR T cells targeting HER2 and IL13R α 2 mitigate tumor antigen escape. *J Clin Invest*. 2016;126:3036–52. [DOI] [PubMed] [PMC]
35. Brown CE, Badie B, Barish ME, Weng L, Ostberg JR, Chang WC, et al. Bioactivity and Safety of IL13R α 2-Redirected Chimeric Antigen Receptor CD8⁺ T Cells in Patients with Recurrent Glioblastoma. *Clin Cancer Res*. 2015;21:4062–72. [DOI] [PubMed] [PMC]
36. Zhang G, Zhao Y, Liu Z, Liu W, Wu H, Wang X, et al. GD2 CAR-T cells in combination with Nivolumab exhibit enhanced antitumor efficacy. *Transl Oncol*. 2023;32:101663. [DOI] [PubMed] [PMC]
37. Norelli M, Camisa B, Barbiera G, Falcone L, Purevdorj A, Genua M, et al. Monocyte-derived IL-1 and IL-6 are differentially required for cytokine-release syndrome and neurotoxicity due to CAR T cells. *Nat Med*. 2018;24:739–48. [DOI] [PubMed]
38. Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. *Biol Blood Marrow Transplant*. 2019;25:625–38. [DOI] [PubMed]

39. Allen GM, Frankel NW, Reddy NR, Bhargava HK, Yoshida MA, Stark SR, et al. Synthetic cytokine circuits that drive T cells into immune-excluded tumors. *Science*. 2022;378:eaba1624. [DOI] [PubMed] [PMC]
40. Lozano G, Levine AJ, editors. *The p53 Protein: From Cell Regulation to Cancer*. Cold Spring Harbor Laboratory Press; 2016.
41. Kandath C, McLellan MD, Vandin F, Ye K, Niu B, Lu C, et al. Mutational landscape and significance across 12 major cancer types. *Nature*. 2013;502:333–9. [DOI] [PubMed] [PMC]
42. Mantovani F, Walerych D, Sal GD. Targeting mutant p53 in cancer: a long road to precision therapy. *FEBS J*. 2017;284:837–50. [DOI] [PubMed]
43. Kim MP, Lozano G. Mutant p53 partners in crime. *Cell Death Differ*. 2018;25:161–8. [DOI] [PubMed] [PMC]
44. Walerych D, Napoli M, Collavin L, Del Sal G. The rebel angel: mutant p53 as the driving oncogene in breast cancer. *Carcinogenesis*. 2012;33:2007–17. [DOI] [PubMed] [PMC]
45. Walerych D, Lisek K, Del Sal G. Mutant p53: One, No One, and One Hundred Thousand. *Front Oncol*. 2015;5:289. [DOI] [PubMed] [PMC]
46. Raja DS, Paramaguru G, Bhuvanesh NS, Reibenspies JH, Renganathan R, Natarajan K. Effect of terminal N-substitution in 2-oxo-1,2-dihydroquinoline-3-carbaldehyde thiosemicarbazones on the mode of coordination, structure, interaction with protein, radical scavenging and cytotoxic activity of copper(II) complexes. *Dalton Trans*. 2011;40:4548–59. [DOI] [PubMed]
47. Vogiatzi F, Brandt DT, Schneikert J, Fuchs J, Grikscheit K, Wanzel M, et al. Mutant p53 promotes tumor progression and metastasis by the endoplasmic reticulum UDPase ENTPD5. *Proc Natl Acad Sci U S A*. 2016;113:E8433–42. [DOI] [PubMed] [PMC]
48. Walerych D, Lisek K, Sommaggio R, Piazza S, Ciani Y, Dalla E, et al. Proteasome machinery is instrumental in a common gain-of-function program of the p53 missense mutants in cancer. *Nat Cell Biol*. 2016;18:897–909. [DOI] [PubMed]
49. Rodriguez OC, Choudhury S, Kolukula V, Vietsch EE, Catania J, Preet A, et al. Dietary downregulation of mutant p53 levels via glucose restriction. *Cell Cycle*. 2012;11:4436–46. [DOI] [PubMed] [PMC]
50. Bergamaschi D, Gasco M, Hiller L, Sullivan A, Syed N, Trigiante G, et al. p53 polymorphism influences response in cancer chemotherapy via modulation of p73-dependent apoptosis. *Cancer Cell*. 2003;3:387–402. [DOI] [PubMed]
51. Zhang C, Liu J, Liang Y, Wu R, Zhao Y, Hong X, et al. Tumour-associated mutant p53 drives the Warburg effect. *Nat Commun*. 2013;4:2935. [DOI] [PubMed] [PMC]
52. Fontemaggi G, Dell’Orso S, Trisciuglio D, Shay T, Melucci E, Fazi F, et al. The execution of the transcriptional axis mutant p53, E2F1 and ID4 promotes tumor neo-angiogenesis. *Nat Struct Mol Biol*. 2009;16:1086–93. [DOI] [PubMed]
53. Cooks T, Pateras IS, Tarcic O, Solomon H, Schetter AJ, Wilder S, et al. Mutant p53 prolongs NF-κB activation and promotes chronic inflammation and inflammation-associated colorectal cancer. *Cancer Cell*. 2013;23:634–46. [DOI] [PubMed] [PMC]
54. Yeudall WA, Vaughan CA, Miyazaki H, Ramamoorthy M, Choi MY, Chapman CG, et al. Gain-of-function mutant p53 upregulates CXC chemokines and enhances cell migration. *Carcinogenesis*. 2012;33:442–51. [DOI] [PubMed]
55. Cooks T, Pateras IS, Jenkins LM, Patel KM, Robles AI, Morris J, et al. Mutant p53 cancers reprogram macrophages to tumor supporting macrophages via exosomal miR-1246. *Nat Commun*. 2018;9:771. [DOI] [PubMed] [PMC]
56. Blagih J, Buck MD, Vousden KH. p53, cancer and the immune response. *J Cell Sci*. 2020;133:jcs237453. [DOI] [PubMed]
57. Ghosh M, Saha S, Bettke J, Nagar R, Parrales A, Iwakuma T, et al. Mutant p53 suppresses innate immune signaling to promote tumorigenesis. *Cancer Cell*. 2021;39:494–508.e5. [DOI] [PubMed] [PMC]

58. Zehir A, Benayed R, Shah RH, Syed A, Middha S, Kim HR, et al. Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. *Nat Med.* 2017;23:703–13. [DOI] [PubMed] [PMC]
59. Robinson DR, Wu YM, Lonigro RJ, Vats P, Cobain E, Everett J, et al. Integrative clinical genomics of metastatic cancer. *Nature.* 2017;548:297–303. [DOI] [PubMed] [PMC]
60. Sidransky D, Mikkelsen T, Schwechheimer K, Rosenblum ML, Cavanee W, Vogelstein B. Clonal expansion of p53 mutant cells is associated with brain tumour progression. *Nature.* 1992;355:846–7. [DOI]
61. de Andrade KC, Lee EE, Tookmanian EM, Kesserwan CA, Manfredi JJ, Hatton JN, et al. The *TP53* Database: transition from the International Agency for Research on Cancer to the US National Cancer Institute. *Cell Death Differ.* 2022;29:1071–3. [DOI] [PubMed] [PMC]
62. Futreal PA, Coin L, Marshall M, Down T, Hubbard T, Wooster R, et al. A census of human cancer genes. *Nat Rev Cancer.* 2004;4:177–83. [DOI] [PubMed] [PMC]
63. Stracquadanio G, Wang X, Wallace MD, Grawenda AM, Zhang P, Hewitt J, et al. The importance of p53 pathway genetics in inherited and somatic cancer genomes. *Nat Rev Cancer.* 2016;16:251–65. [DOI] [PubMed] [PMC]
64. Scheffner M, Werness BA, Huibregtse JM, Levine AJ, Howley PM. The E6 oncoprotein encoded by human papillomavirus types 16 and 18 promotes the degradation of p53. *Cell.* 1990;63:1129–36. [DOI] [PubMed]
65. Mansur MB, deSouza NM, Natrajan R, Abegglen LM, Schiffman JD, Greaves M. Evolutionary determinants of curability in cancer. *Nat Ecol Evol.* 2023;7:1761–70. [DOI] [PubMed]
66. Munro AJ, Lain S, Lane DP. P53 abnormalities and outcomes in colorectal cancer: a systematic review. *Br J Cancer.* 2005;92:434–44. [DOI] [PubMed] [PMC]
67. Vousden KH, Lu X. Live or let die: the cell's response to p53. *Nat Rev Cancer.* 2002;2:594–604. [DOI] [PubMed]
68. Vogt U, Zaczek A, Klinke F, Granetzny A, Bielawski K, Falkiewicz B. *p53* Gene status in relation to ex vivo chemosensitivity of non-small cell lung cancer. *J Cancer Res Clin Oncol.* 2002;128:141–7. [DOI] [PubMed]
69. Higashiyama M, Kodama K, Yokouchi H, Takami K, Doi O, Kobayashi H, et al. Immunohistochemical p53 protein status in nonsmall cell lung cancer is a promising indicator in determining in vitro chemosensitivity to some anticancer drugs. *J Surg Oncol.* 1998;68:19–24. [DOI] [PubMed]
70. Gruber M, Wu CJ. Evolving understanding of the CLL genome. *Semin Hematol.* 2014;51:177–87. [DOI] [PubMed] [PMC]
71. Roselle C, Horikawa I, Chen L, Kelly AR, Gonzales D, Da T, et al. Enhancing chimeric antigen receptor T cell therapy by modulating the p53 signaling network with $\Delta 133p53\alpha$. *Proc Natl Acad Sci U S A.* 2024;121:e2317735121. [DOI] [PubMed] [PMC]
72. Horikawa I, Park KY, Isogaya K, Hiyoshi Y, Li H, Anami K, et al. $\Delta 133p53$ represses p53-inducible senescence genes and enhances the generation of human induced pluripotent stem cells. *Cell Death Differ.* 2017;24:1017–28. [DOI] [PubMed] [PMC]
73. Mancikova V, Smida M. Current State of CAR T-Cell Therapy in Chronic Lymphocytic Leukemia. *Int J Mol Sci.* 2021;22:5536. [DOI] [PubMed] [PMC]
74. Shouval R, Alarcon Tomas A, Fein JA, Flynn JR, Markovits E, Mayer S, et al. Impact of *TP53* Genomic Alterations in Large B-Cell Lymphoma Treated With CD19-Chimeric Antigen Receptor T-Cell Therapy. *J Clin Oncol.* 2022;40:369–81. [DOI] [PubMed] [PMC]
75. Zhang X, Lu XA, Yang J, Zhang G, Li J, Song L, et al. Efficacy and safety of anti-CD19 CAR T-cell therapy in 110 patients with B-cell acute lymphoblastic leukemia with high-risk features. *Blood Adv.* 2020;4:2325–38. [DOI] [PubMed] [PMC]

76. Porpaczy E, Wohlfarth P, Königsbrügge O, Rabitsch W, Skrabs C, Staber P, et al. Influence of *TP53* Mutation on Survival of Diffuse Large B-Cell Lymphoma in the CAR T-Cell Era. *Cancers (Basel)*. 2021; 13:5592. [DOI] [PubMed] [PMC]
77. Gao F, Hu K, Zheng P, Shi H, Ke X. Characteristics and prognosis of rrDLBCL with *TP53* mutations and a high-risk subgroup represented by the co-mutations of *DDX3X-TP53*. *Cancer Med*. 2023;12:10267–79. [DOI] [PubMed] [PMC]
78. Xue B, Liu Y, Zhou J, Zhou L, Ye S, Lu Y, et al. CD19 CAR-T treatment shows limited efficacy in r/r DLBCL with double expression and TP53 alterations. *Cytotherapy*. 2024;26:1465–71. [DOI] [PubMed]
79. Eder LN, Martinovic D, Mazzeo P, Ganster C, Hasenkamp J, Thomson J, et al. Fatal Progression of Mutated TP53-Associated Clonal Hematopoiesis following Anti-CD19 CAR-T Cell Therapy. *Curr Oncol*. 2023;30:1146–50. [DOI] [PubMed] [PMC]
80. Zhang Q, Zhu X, Liu B, Zhang Y, Xiao Y. Case report: Sandwich therapy of CAR-T combined with ASCT: Sequential CAR-T cell therapy with ASCT after remission with CAR-T therapy caused long-term survival in a patient with relapsed/refractory Burkitt's lymphoma with TP53 mutations. *Front Immunol*. 2023;14:1127868. [DOI] [PubMed] [PMC]
81. Shouval R, Alarcon Tomas A, Fein JA, Flynn J, Markovits E, Mayer S, et al. *TP53* and CD19-Directed Chimeric Antigen Receptor T-Cell (CAR-T) Therapy in Large B-Cell Lymphoma. *Blood*. 2021;138:710. [DOI]
82. Mueller J, Schimmer RR, Koch C, Schneiter F, Fullin J, Lysenko V, et al. Targeting the mevalonate or Wnt pathways to overcome CAR T-cell resistance in *TP53*-mutant AML cells. *EMBO Mol Med*. 2024;16: 445–74. [DOI] [PubMed] [PMC]