MAGIERA, Michał, SIKORA, Miłosz, CZWAŁGA, Piotr, and KOPROWSKA, Patrycja. Emerging Directions in CAR-T Cell Therapy: Solid Tumors. Quality in Sport. 2026;49:67441. eISSN 2450-3118.
https://doi.org/10.12775/QS.2026.49.67441
https://apcz.umk.pl/QS/article/view/67441

The journal has been awarded 20 points in the parametric evaluation by the Ministry of Higher Education and Science of Poland. This is according to the Annex to the announcement of the Minister of Higher Education and Science dated 05.01.2024, No. 32553. The journal has a Unique Identifier: 201398. Scientific disciplines assigned: Economics and Finance (Field of Social Sciences); Management and Quality Sciences (Field of Social Sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).
The authors declare that there is no conflict of interest regarding the publication of this paper.
Received: 13.12.2025. Revised: 16.12.2025. Accepted: 04.01.2026. Published: 05.01.2026.

Emerging Directions in CAR-T Cell Therapy: Solid Tumors

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ABSTRACT

Background. CAR-T therapy represents a breakthrough in immuno-oncology, enabling tumor elimination independently of the MHC system. This strategy has achieved spectacular clinical success in hematology (ALL, DLBCL), primarily by targeting CD19 and BCMA antigens. However, adapting this technology to solid tumors, which account for approximately 90% of cancer cases, remains a challenge. Given the rising incidence in an aging population, overcoming the barriers limiting CAR-T efficacy in this group has become a critical research priority.

Aim. The aim of the study was to summarize the current state of knowledge, challenges and emerging strategies for the use of CAR-T therapy in the treatment of solid tumors, based on the latest literature reports.

Materials and methods. A literature review was conducted using PubMed, Google Scholar, and Web of Science databases, focusing primarily on articles published between 2023 and 2025, alongside relevant historical context. The search utilized the following keywords: CAR-T cells, immunotherapy, tumor microenvironment, breast cancer, lung cancer, and solid tumor. The analysis included only English-language publications.

Results. The analysis tracks CAR evolution from 1st to 5th generation, emphasizing costimulation and TRUCK systems. In solid tumors (e.g., TNBC, NSCLC), efficacy is hindered by the immunosuppressive microenvironment (TME), antigen heterogeneity, and physical barriers. Key strategies to overcome these include combination with checkpoint inhibitors, CRISPR/Cas9 editing, Dual-CAR systems, and cytokine induction.

Conclusions. CAR-T technology extends beyond hematology, showing promising potential in solid tumors, autoimmune diseases, and neurodegenerative disorders. New modification strategies overcome microenvironmental barriers in solid tumors, while CAR-T and CAR-Tregs effectively restore immune homeostasis in autoimmunity. This therapy is evolving into a versatile platform with broad translational significance.

Keywords: CAR-T cells, immunotherapy, tumor microenvironment, breast cancer, lung cancer, solid tumor

Introduction

Therapy utilizing T lymphocytes genetically modified to express chimeric antigen receptors (CAR-T) constitutes one of the greatest achievements in modern immuno-oncology. Based on genetic engineering, the patient's lymphocytes acquire the ability to eliminate target cells independently of Major Histocompatibility Complex (MHC) antigen recognition strategies [1]. This unique mechanism has paved the way for breakthrough clinical successes in hemato-oncology, including the treatment of acute lymphoblastic leukemia (ALL), diffuse large B-cell lymphoma (DLBCL), and multiple myeloma (MM). The foundation of CAR-T efficacy in these indications lies in targeting CD19 and BCMA antigens, which are characterized by high density on the surface of tumor cells while maintaining minimal expression in other tissues, translating into a favorable therapeutic index [2].

Despite spectacular results in the treatment of hematological malignancies, adapting this technology to solid tumors—which account for approximately 90% of all cancers in adults—remains a challenge. It is noteworthy that while tumor development is influenced by numerous factors, ranging from genetic to environmental, age remains the single strongest and non-modifiable risk factor. The demographic trend observed in recent decades, characterized by an increase in average life expectancy, is leading to a rapid rise in the number of elderly patients requiring oncological care. Epidemiological data indicate that over 80% of solid tumors are diagnosed in patients over the age of 50, and 60% in those over 60, making these cancers more than ten times more frequent than in younger populations. In the face of an aging society and the growing number of elderly patients requiring care, the scientific community faces the necessity of intensifying research into improving treatment methods for solid tumors, including overcoming the barriers limiting the efficacy of CAR-T therapy in this patient group [3].

Materials and methods

The work is based mainly on articles from recent years, i.e., 2023–2025, taking into account some historical materials. The purpose of the literature review was to gather comprehensive knowledge on the current landscape, challenges, and emerging strategies for applying CAR-T cell therapy in the treatment of solid tumors . A comprehensive search was conducted in PubMed, Google Scholar, and Web of Science databases using the following keywords: CAR-T cells, immunotherapy, tumor microenvironment, breast cancer, lung cancer, solid tumor. The analysis primarily focused only on articles published in English.

Results

CAR-T Therapy

The foundation of CAR-T therapy is the genetic modification of the patient's T lymphocytes to express a chimeric antigen receptor (CAR). As indicated by Sadelain et al., the key advantage of this strategy is the ability of CAR-T constructs to directly select native surface antigens, rendering therapeutic efficacy independent of antigen presentation mechanisms, which are often impaired in tumor cells.

The functionality of the receptor stems from its modular structure, which integrates an extracellular binding domain (scFv, most commonly derived from a monoclonal antibody) responsible for antigen binding, a hinge domain, a transmembrane part, and intracellular signaling pathways (CD3ζ). The introduction of the appropriate genetic construct—usually via viral vectors—into T lymphocytes allows for the generation of CAR-T cells capable of direct activation upon contact with a tumor antigen [1].

The evolution of CAR technology has concentrated on optimizing the persistence and potency of the immune response, leading to the distinction of five generations of receptors differing in the number and type of activation signals. First-generation constructs, based solely on the CD3ζ signaling domain, demonstrated limited clinical efficacy due to low in vivo persistence. A breakthrough came with the second generation, which was equipped with a single costimulatory domain. The choice of this domain determines the lymphocyte activity profile: the use of 4-1BB (CD137) promotes long-term cell survival and persistence, while CD28 strongly stimulates proliferation and rapid cytokine secretion. Further development in molecular engineering resulted in subsequent generations with enhanced functionality. The third generation combines the advantages of both costimulatory pathways (e.g., CD28 and 4-1BB in a single receptor), while the fourth generation, known as TRUCKs, is capable of the inducible release of transgenic cytokines (e.g., IL-12), allowing for the modulation of the hostile tumor microenvironment. The fifth generation integrates three synergistic signals: TCR activation, costimulation, and a cytokine-binding domain (e.g., a fragment of the IL-2 receptor), which autonomously activates the JAK-STAT3/5 pathway, providing cells with the highest proliferative and cytotoxic potential [4].

Solid Tumors

Prostate cancer is the most frequently diagnosed malignancy in the male population. Although surgical interventions, radiotherapy, and hormonal therapy can be effective in treating early localized tumors, many patients inevitably develop metastatic castration-resistant prostate cancer (mCRPC), for which current treatments offer limited long-term survival.

Canadian guidelines from 2025 emphasize treatment personalization based on the tumor's molecular profile and prior exposure to drugs during the hormone-sensitive phase (mHSPC). The standard of care for mCRPC has evolved toward strict personalization, making therapy selection dependent on the genomic profile of the tumor (testing for HRR/BRCA mutations). The management algorithm relies on the sequential use of androgen receptor pathway inhibitors (ARPI), taxane chemotherapy, PARP inhibitors, and radioligands ([177Lu]Lu-PSMA-617) [5]. Despite a wide range of pharmacological options, the inevitable progression of the disease remains a major challenge, justifying the search for new strategies to overcome multidrug resistance. In this context, CAR-T technology appears as a strategy with higher therapeutic potential, capable of more effectively overcoming the tumor's complex defense mechanisms [6].

In light of recent analyses published by Kwon and Joung, prostate cancer is classified as an immunologically "cold" tumor. This phenotype is characterized by low immunogenicity, limited infiltration by tumor-infiltrating lymphocytes (TILs), and the presence of a strongly suppressive tumor microenvironment (TME), dominated by populations of regulatory T cells (Tregs), tumor-associated macrophages (TAMs), and myeloid-derived suppressor cells (MDSCs).

In this view, CAR-T therapy is perceived not only as a tool for direct cytotoxicity but as the foundation of a strategy aimed at transitioning the tumor from "cold" to "hot". Although the engineering of lymphocytes targeting specific surface antigens (mainly PSMA) enables precise recognition of tumor cells independently of the MHC system, antigen expression alone does not guarantee therapeutic success. A key challenge remains the survival of modified cells in the hostile TME, where monotherapy encounters barriers in the form of local inhibitory signals. In response to these limitations, authors point to the necessity of implementing combination strategies—particularly the integration of CAR-T cells with immune checkpoint inhibitors—which may effectively unlock the effector potential of lymphocytes and overcome tumor resistance mechanisms [7].

As signaled by M.L. Calabrò et al., a significant barrier to therapeutic efficacy is the expression of PD-L1 ligands on prostate cancer cells (often induced as a resistance mechanism), which leads to the rapid exhaustion and deactivation of CAR-T lymphocytes via the PD-1 pathway. To prevent this, the authors postulate a two-pronged approach. The first pillar involves combination therapies, consisting of the simultaneous administration of CAR-T lymphocytes and systemic anti-PD-1/PD-L1 monoclonal antibodies (e.g., pembrolizumab). In preclinical

studies, this strategy demonstrates a synergistic effect, effectively restoring the cytotoxic function of lymphocytes.

The second, more advanced approach is intrinsic genetic blockade. This involves engineering the CAR-T lymphocytes themselves to autonomously secrete PD-1 blocking scFv fragments (autocrine checkpoint blockade) or to have the PD-1 receptor gene permanently disabled (e.g., via CRISPR/Cas9 genome editing). Consequently, these cells become intrinsically resistant to inhibitory signals originating from the tumor. These combined efforts, supplemented by metabolic adaptation to hypoxic conditions, constitute a comprehensive strategy aimed at maintaining long-term persistence and functionality of CAR-T cells within the dense tumor tissue [8].

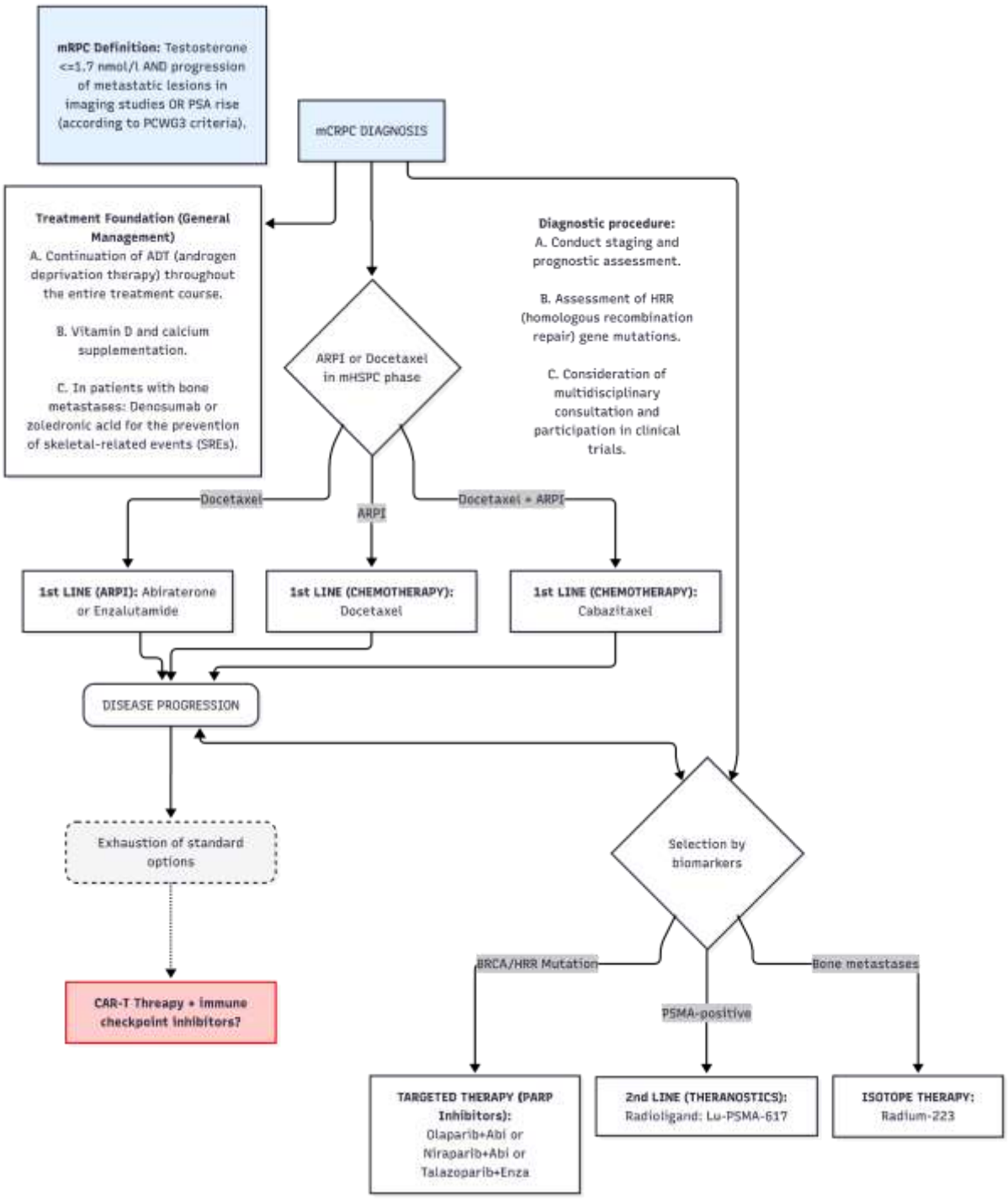

Figure 1. Management algorithm in mCRPC.

Accordingly, breast cancer is the most common malignancy in the female population. It is a disease entity with a complex etiology and high molecular heterogeneity, traditionally classified based on the expression of estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2). Although the introduction of targeted therapies (e.g., trastuzumab) and hormone therapy has significantly improved prognosis in luminal and

HER2-positive subtypes, triple-negative breast cancer (TNBC) remains a significant clinical challenge.

TNBC, accounting for approximately 25% of all diagnoses, is characterized by the absence of the aforementioned receptors, an aggressive clinical course, a high proliferative index, and a tendency toward early distant metastasis (mainly to the lungs and brain). Due to the lack of viable targets for standard molecular therapies, chemotherapy remains the basis of systemic treatment; however, it is often associated with high toxicity and the phenomenon of multidrug resistance (MDR) [9].

Given the limited efficacy of conventional treatment methods for advanced TNBC and recurrent forms of other subtypes, the scientific community's attention is focused on immuno-oncological strategies. Consequently, CAR-T technology appears as a promising tool capable of precisely directing lymphocyte cytotoxicity against tumor cells, with the potential to overcome the immune tolerance characteristic of this cancer.

Despite spectacular successes in in vitro and in vivo animal model studies, the translation of results to the clinical setting encounters significant obstacles. Clinical efficacy in breast cancer is currently lower than in hematological malignancies, due to factors such as:

- Antigenic heterogeneity: Based on the phenomenon of a mosaic of tumor cells with varying levels of antigen expression, resulting in the survival of antigen-negative populations, antigen escape, and disease recurrence due to the CAR-T elimination of high-expression cells (e.g., HER2+).
- Impaired infiltration: The dense connective tissue stroma (desmoplasia), characteristic of breast cancer, constitutes a physical barrier hindering CAR-T lymphocyte penetration into the tumor interior.
- "On-target, off-tumor" toxicity: There is a risk of attack on healthy tissues (e.g., lungs or heart) that exhibit trace amounts of the targeted antigen, posing a serious challenge in designing safe receptors [10].

The future of CAR-T therapy in breast cancer lies in structural modifications and combination therapies. Alongside strategies increasing the migratory potential of lymphocytes, e.g., through the expression of chemokine receptors, it is becoming crucial to implement multi-target systems (Dual-CAR) to prevent tumor escape and ensure survival in a suppressive microenvironment. Overcoming resistance requires a shift from monotherapy to complex combination strategies—combining CAR-T not only with immune checkpoint inhibitors but also with oncolytic viruses or drugs modifying the tumor stroma. Supplementing these methods with local administration

allows for the minimization of systemic toxicity while maximizing the effect at the disease site. These possibilities are presented in Figure 2 [10, 11].

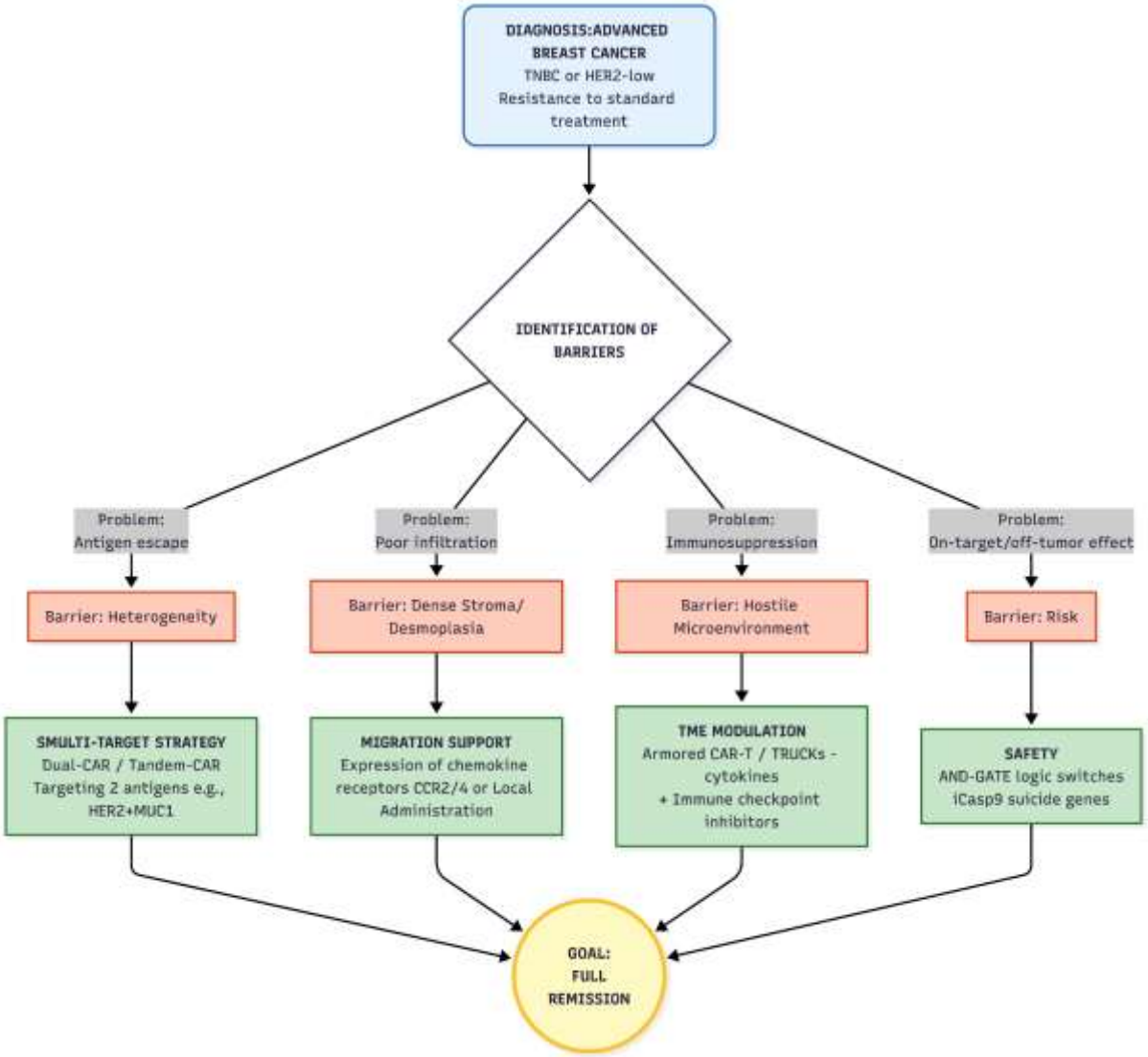

Figure 2. Barriers to CAR-T treatment in breast cancer and potential modifications.

Lung cancer remains the leading cause of cancer deaths worldwide, histologically dominated by non-small cell lung cancer (NSCLC), which accounts for approximately 85% of all diagnoses [12].

Although the introduction of immune checkpoint inhibitors (ICI) targeting the PD-1/PD-L1 axis and CTLA-4 has revolutionized treatment standards and significantly extended overall patient survival, a substantial percentage of patients exhibit primary resistance or develop acquired resistance during therapy. Radiotherapy, chemotherapy, antiangiogenic drugs, and TME modulators can synergistically enhance immunotherapy by regulating the tumor immune process, including the release of tumor antigens, presentation, and infiltration of TME immune

cells. However, these synergistic effects are uncontrolled and unpredictable. Facing the exhaustion of available pharmacological options, the development of new therapeutic strategies for advanced stages of the disease has become an urgent clinical need [13].

The extrapolation of clinical successes achieved in hemato-oncology has provided the impetus for implementing CAR-T technology in the field of thoracic malignancies, particularly NSCLC. Unlike lymphoid malignancies, the application of CAR-T lymphocytes in NSCLC encounters specific barriers resulting from the dense, desmoplastic architecture of the tumor and a strongly immunosuppressive microenvironment. Offering a unique ability to recognize tumor cells independently of the Major Histocompatibility Complex (MHC), cell therapy enables the detection of tumor cells "invisible" to classical T lymphocytes, as one of the main mechanisms of lung cancer escape from immune surveillance is precisely the downregulation of antigen presentation by MHC.

To overcome these barriers, clinical and preclinical studies have identified a broad spectrum of molecular targets, among which the epidermal growth factor receptor (EGFR), mesothelin (MSLN), MUC1 glycoprotein, prostate stem cell antigen (PSCA), HER2 receptor, and ROR1 receptor hold the greatest promise. Significantly, studies indicate that targeting these antigens allows not only for the reduction of tumor mass but also for the elimination of cell subpopulations resistant to current pharmacological treatment, which should theoretically prevent disease recurrence [14, 15].

Particular attention in the context of lung cancer is paid to the safety profile, which differs from that observed in leukemias. In addition to the classic cytokine release syndrome (CRS), a specific and dangerous complication is—analogous to prostate and breast cancer—"on-target, off-tumor" toxicity. This results from the fact that many lung cancer antigens (such as EGFR or HER2) undergo low, physiological expression on healthy epithelial tissues, including in the lung parenchyma itself outside the tumor foci. An attack by modified lymphocytes on these structures can lead to fulminant pneumonia, edema, and in extreme cases, acute respiratory distress syndrome (ARDS) [16]. Therefore, current research strategies focus not only on increasing cell potency (e.g., via IL-7/CCL19 secretion) but primarily on precisely tuning their affinity so that they attack only cells with pathologically high antigen overexpression, sparing healthy tissues [17, 18].

Other common solid tumors and their potential CAR-T treatment are presented in Table 1.

Cancer (Type) Colorectal Cancer	**Antigen (Targets)** CEA, GUCY2C, TAG-72	**Cancer (Type)** Gastric Cancer	**Antigen (Targets)** HER2, CEA, MUC1, EpCAM, CLDN 18.2, MSLN, NKG2D, FOLR1
CAR-T Application Overcoming the immunosuppressive tumor microenvironment, limiting toxicity; engineering cells capable of autocrine secretion of checkpoint blockers (scFv anti-PD-1), logic gating to increase specificity, and regional administration (intraperitoneal).		**CAR-T Application** Application of 4th generation CAR-T (TRUCK) secreting cytokines (e.g., IL-7, IL-12, IL-15) for remodeling the immunosuppressive tumor microenvironment (TME), use of multi-specific receptors, and combination with checkpoint blockade (anti-PD-1) or regional administration.	
Drawbacks and Main Challenge "On-target" toxicity: These antigens are also present in the healthy intestine, which may lead to severe colitis. Physical barrier: Difficulty in penetrating large tumor masses [19].		**Drawbacks and Main Challenge** Tumor heterogeneity: Not all cancer cells express the antigen, leading to tumor escape. Helicobacter pylori may reduce therapeutic efficacy. Mucosal damage: Risk of damage to healthy gastric tissue [20, 21].	
Cancer (Type) Pancreatic Cancer	**Antigen (Targets)** MSLN, CEA, Claudin 18.2, PSCA	**Cancer (Type)** Liver Cancer (HCC)	**Antigen (Targets)** Glypican-3 (GPC3), AFP, NKG2DL, MUC1, EpCAM, CLD18, CD147, CD133, c-MET, HBs antigen
CAR-T Application Overcoming antigenic heterogeneity and the immunosuppressive microenvironment of pancreatic cancer; induction of mesothelin expression (sensitization to CAR-T), tumor stroma remodeling via the		**CAR-T Application** Overcoming microenvironmental barriers through engineering cells releasing cytokines (IL-7, CCL19) in "7x19 CAR-T" systems, targeting multiple antigens (e.g., GPC3/TGFβ), local administration (intraperitoneal/intra-	

use of an engineered oncolytic virus HSV-1 (HSV-MSLN).	arterial), and combination with checkpoint inhibitors and anti-angiogenic drugs.
Drawbacks and Main Challenge Desmoplasia (fibrosis): The tumor is surrounded by a dense "shell" through which CAR-T cells cannot penetrate. Hypoxia: Lack of oxygen within the tumor leads to T-cell death [22, 23].	**Drawbacks and Main Challenge** Immunosuppression: The liver naturally tolerates foreign proteins, leading to rapid T-cell deactivation (exhaustion phenomenon). Hepatitis: Risk of exacerbating organ failure [24].
Cancer (Type) Glioblastoma	**Antigen (Targets)** B7-H3, EGFRvIII, and IL13Rα2, HER2
CAR-T Application Treatment of glioblastoma (GBM) using tandem CAR (TanCART) targeting EGFRvIII and IL-13Rα2; prevention of tumor antigen escape via "OR" logic gating.	
Drawbacks and Main Challenge Antigen escape: The tumor changes its profile very rapidly (ceases production of the targeted protein). Cerebral edema: An inflammatory reaction within the closed intracranial space is highly dangerous (neurotoxicity) [25, 26].	

Table 1. CAR-T therapy in selected solid tumors.

Conclusions

The successes of CAR-T therapy in hematology have spurred intensive research into expanding its applications to other fields of medicine. A growing body of data suggests that CAR-T cells may play a significant role in the therapy of solid tumors, autoimmune diseases, and selected neurodegenerative disorders.

In the case of solid tumors, strategies improving T-cell migration and tumor microenvironment modulation are successively addressing challenges resulting from antigenic heterogeneity and the physical and immunological barriers of the tumor. Conversely, in autoimmune diseases,

CAR-T (anti-CD19) and CAR-Tregs therapy demonstrate the ability to permanently restore immune homeostasis, as confirmed in the treatment of systemic lupus erythematosus (SLE). In light of these observations, CAR-T technology is transforming from a therapy with a limited range of indications into an immunotherapeutic platform with broad translational potential.

Disclosure

Conceptualization: Michał Magiera, Miłosz Sikora
Methodology: Patrycja Koprowska, Piotr Czwałga
Software: not applicable.
Check: Michał Magiera, Piotr Czwałga, Miłosz Sikora, Patrycja Koprowska
Formal analysis: Miłosz Sikora
Investigation: Michał Magiera
Resources: Miłosz Sikora
Writing-rough preparation: Michał Magiera, Piotr Czwałga
Writing-review and editing: Miłosz Sikora, Patrycja Koprowska
Visualization: Piotr Czwałga, Miłosz Sikora
Supervision: Michał Magiera, Patrycja Koprowska
Project administration: Michał Magiera
Receiving funding: not applicable.

All authors have read and agreed with the published version of the manuscript.

Funding Statement: Not applicable.
Institutional Review Board Statement: Not applicable.
Informed Consent Statement: Not applicable.

Data Availability Statement: The authors confirm that the data supporting this study are available in the article's references.
Conflict of Interest: Authors declare no conflict of interest.

References

1. Sadelain M, Brentjens R, Rivière I. The basic principles of chimeric antigen receptor design. Cancer Discov. 2013;3(4):388-398. doi:10.1158/2159-8290.CD-12-0548
2. Bogacz A, Bukowska A, Bukowska M, et al. Modern immunotherapy using CAR-T cells in haemato-oncology and solid tumors. Acta Haematol Pol. 2024;55(1):34-41. doi:10.5603/ahp.97189
3. Radecka B, Czech J, Siedlaczek A, Maczkiewicz M, Jagiełło-Gruszfeld A, Duchnowska R. Chemotherapy compliance in elderly patients with solid tumors: a real-world clinical practice data. Oncol Clin Pract. 2023;19(4):217-223. doi:10.5603/OCP.2022.0009
4. Zugasti I, Espinosa-Aroca L, Fidyt K, et al. CAR-T cell therapy for cancer: current challenges and future directions. Sig Transduct Target Ther. 2025;10(1):210. doi:10.1038/s41392-025-02269-w
5. Saad F, So AI, Aprikian A, et al. 2025 Canadian Urological Association-Canadian Uro-oncology Group Guideline: Metastatic castration-resistant prostate cancer (Update). Can Urol Assoc J 2025;19(8):E276-89. http://dx.doi.org/10.5489/cuaj.9341
6. Kulasegaran T, Oliveira N. Metastatic Castration-Resistant Prostate Cancer: Advances in Treatment and Symptom Management. Curr Treat Options Oncol. 2024;25(7):914-931. doi:10.1007/s11864-024-01215-2
7. Kwon WA, Joung JY. Immunotherapy in Prostate Cancer: From a "Cold" Tumor to a "Hot" Prospect. Cancers (Basel). 2025;17(7):1064. doi:10.3390/cancers17071064
8. Calabrò ML, Ettari R, Di Chio C, De Luca F, Previti S, Zappalà M. CAR-T Cell Therapy for Prostate Cancer: Current Advances and Future Perspectives. Biomedicines. 2025;13(10):2545. doi:10.3390/biomedicines13102545
9. Błaszczak E, Miziak P, Odrzywolski A, Baran M, Gumbarewicz E, Stepulak A. Triple-Negative Breast Cancer Progression and Drug Resistance in the Context of Epithelial-Mesenchymal Transition. Cancers (Basel). 2025;17(2):228. doi:10.3390/cancers17020228
10. Niu Z, Wu J, Zhao Q, Zhang J, Zhang P, Yang Y. CAR-based immunotherapy for breast cancer: peculiarities, ongoing investigations, and future strategies. Front Immunol. 2024;15:1385571. doi:10.3389/fimmu.2024.1385571
11. Rebaudi F, De Franco F, Goda R, et al. The landscape of combining immune checkpoint inhibitors with novel Therapies: Secret alliances against breast cancer. Cancer Treat Rev. 2024;130:102831. doi:10.1016/j.ctrv.2024.102831

12. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021: 71: 209-249. https://doi.org/10.3322/caac.21660
13. Zhou S, Yang H. Immunotherapy resistance in non-small-cell lung cancer: From mechanism to clinical strategies. Front Immunol. 2023;14:1129465. doi:10.3389/fimmu.2023.1129465
14. Trudu L, Rovesti G, Neri G, et al. CAR-T for Lung Cancers: Challenges and Innovations. Lung Cancer. 2025;207:108711. doi:10.1016/j.lungcan.2025.108711
15. Tan J, Zhu L, Shi J, et al. Evaluation of drug resistance for EGFR-TKIs in lung cancer via multicellular lung-on-a-chip. Eur J Pharm Sci. 2024;199:106805. doi:10.1016/j.ejps.2024.106805
16. Liu H, Ma Y, Yang C, et al. Severe delayed pulmonary toxicity following PD-L1-specific CAR-T cell therapy for non-small cell lung cancer. Clin Transl Immunology. 2020;9(10):e1154. doi:10.1002/cti2.1154
17. Li F, Zhao S, Wei C, et al. Development of Nectin4/FAP-targeted CAR-T cells secreting IL-7, CCL19, and IL-12 for malignant solid tumors. Front Immunol. 2022;13:958082. doi:10.3389/fimmu.2022.958082
18. Flugel CL, Majzner RG, Krenciute G, et al. Overcoming on-target, off-tumour toxicity of CAR T cell therapy for solid tumours. Nat Rev Clin Oncol. 2023;20(1):49-62. doi:10.1038/s41571-022-00704-3
19. Ouladan S, Orouji E. Chimeric Antigen Receptor-T Cells in Colorectal Cancer: Pioneering New Avenues in Solid Tumor Immunotherapy. J Clin Oncol. 2025;43(8):994-1005. doi:10.1200/JCO-24-02081
20. Qi C, Liu C, Peng Z, et al. Claudin-18 isoform 2-specific CAR T-cell therapy (satri-cel) versus treatment of physician's choice for previously treated advanced gastric or gastro-oesophageal junction cancer (CT041-ST-01): a randomised, open-label, phase 2 trial. Lancet. 2025;405(10494):2049-2060. doi:10.1016/S0140-6736(25)00860-8
21. Bębnowska D, Grywalska E, Niedźwiedzka-Rystwej P, et al. CAR-T Cell Therapy-An Overview of Targets in Gastric Cancer. J Clin Med. 2020;9(6):1894. doi:10.3390/jcm9061894
22. Aboalela MA, Abdelmoneim M, Matsumura S, et al. Enhancing mesothelin CAR T cell therapy for pancreatic cancer with an oncolytic herpes virus boosting CAR target antigen

expression. Cancer Immunol Immunother. 2025;74(7):202. doi:10.1007/s00262-025-04039-7

23. Guirguis DA, Hasan F, Morris N, et al. Tumor tough, therapy smarter: Rethinking CAR-T for pancreatic cancer. Semin Oncol. 2025;52(6):152411. doi:10.1016/j.seminoncol.2025.152411
24. Ozer M, Goksu SY, Akagunduz B, George A, Sahin I. Adoptive Cell Therapy in Hepatocellular Carcinoma: A Review of Clinical Trials. Cancers (Basel). 2023;15(6):1808. doi:10.3390/cancers15061808
25. Schmidts A, Srivastava AA, Ramapriyan R, et al. Tandem chimeric antigen receptor (CAR) T cells targeting EGFRvIII and IL-13Rα2 are effective against heterogeneous glioblastoma. Neurooncol Adv. 2022;5(1):vdac185. doi:10.1093/noajnl/vdac185
26. Agosti E, Garaba A, Antonietti S, et al. CAR-T Cells Therapy in Glioblastoma: A Systematic Review on Molecular Targets and Treatment Strategies. Int J Mol Sci. 2024;25(13):7174. Published 2024 Jun 29. doi:10.3390/ijms25137174