UNDERGRADUATE RESEARCH IN NATURAL AND CLINICAL SCIENCE AND TECHNOLOGY (URNCST) JOURNAL
Read more URNCST Journal articles and submit your own today at: https://www.urncst.com

REVIEW OPEN ACCESS

Targeting the Tumor Microenvironment: A Review of Macrophage Immunotherapies Across Cancer Types

Catherine Rohner, BSc Student [1]*

[1] Department of Health Sciences and Technology, ETH Zürich, Switzerland 8092

*Corresponding Author: crohner64@gmail.com

Abstract

Introduction: Macrophage immunotherapy is a promising approach to cancer treatment, leveraging the ability to target tumor-associated macrophages (TAMs) within the tumor microenvironment (TME). TAMs, often in an M2-like phenotype, contribute to immune evasion and tumor progression. This review synthesizes clinical trials of macrophage immunotherapy, including strategies to either deplete or reprogram M2-like TAMs to boost anti-tumor immunity.

Methods: This review systematically analyzes research conducted between January 2010 and April 2024. Literature was sourced from PubMed using terms like "macrophage cancer immunotherapy" and "tumor-associated macrophage immunotherapy." The studies reviewed include clinical trials and primary research involving TAM-targeting strategies across different cancer types.

Results: A total of 37 clinical trials were selected for this review, focusing on TAM-targeting therapies across 25 cancer types. The majority of studies examined solid tumors, including breast cancer, prostate cancer, and melanoma, alongside hematological malignancies. The therapeutic strategies investigated included monoclonal antibodies (mAbs), cytokine-based therapies, immune checkpoint inhibitors (ICIs), and oncolytic viruses. Notably, mAbs targeting CSF-1R showed a 45% increase in T-cell infiltration, and GM-CSF cytokine therapies successfully reprogrammed TAMs to an M1-like phenotype, enhancing anti-tumor immune responses. ICIs also demonstrated encouraging results, particularly in "hot" tumors, with progression-free survival (PFS) reaching up to 36 months.

Discussion: The reviewed trials underline the potential of TAM-targeting therapies in reshaping the TME and enhancing immune activation, especially in TAM-rich tumors. mAbs targeting CSF-1R and TREM2, along with GM-CSF reprogramming, were particularly effective in reducing TAM populations and promoting T-cell activity. Despite these promising outcomes, challenges remain due to the complexity of TAM biology and cancer-specific differences. Combination therapies, such as pairing CSF-1R inhibitors with ICIs, have shown potential to enhance efficacy by addressing multiple immune suppression mechanisms in the TME.

Conclusion: TAM-targeted therapies offer a promising approach in cancer immunotherapy by reprogramming the TME and restoring immune surveillance. However, challenges like TAM plasticity and tumor heterogeneity remain. Future trials should focus on refining combination therapies, standardizing biomarkers for patient stratification, and using advanced profiling technologies to enhance TAM-targeted treatments and improve outcomes.

Keywords: tumor-associated macrophages (TAMs); cancer immunotherapy; tumor microenvironment; macrophage polarization; immune checkpoint inhibitors; cytokine therapy; monoclonal antibodies

Introduction

Immunotherapy has revolutionized cancer treatment by activating the body's immune system to target tumors, offering promising outcomes for malignancies resistant to traditional therapies such as chemotherapy and radiation. Immune checkpoint inhibitors (ICIs), oncolytic viruses (OVs), and personalized vaccines exemplify the field's success in overcoming tumor-induced immune suppression, even in advanced disease settings. However, the tumor microenvironment (TME) remains a significant barrier to effective treatment, actively promoting tumor progression and immune evasion. Within this context, tumor-associated macrophages (TAMs) have emerged as critical players in cancer progression and as compelling targets for therapeutic intervention [1, 2].

Macrophages, derived from circulating monocytes, play key roles in immune surveillance, tissue repair, and host defense [3]. Their plasticity allows them to adapt to environmental signals, resulting in distinct phenotypes: M1-like macrophages with pro-inflammatory, tumor-suppressive functions, and M2-like macrophages with immunosuppressive, tumor-promoting roles. In the TME,

TAMs are predominantly M2-like, facilitating angiogenesis, immune evasion, and metastasis through the secretion of cytokines like interleukin-10 (IL-10) and growth factors such as vascular endothelial growth factor (VEGF) [3]. This dual functionality positions TAMs as both obstacles and opportunities in cancer immunotherapy. Strategies targeting TAMs aim to either deplete the M2-like population or reprogram them into the tumor-suppressive M1-like phenotype [1, 4]. For example, mAbs targeting colony-stimulating factor 1 receptor (CSF-1R) reduce M2-like TAM density, while cytokine therapies like granulocyte-macrophage colony-stimulating factor (GM-CSF) polarize TAMs to the M1-like state, enhancing anti-tumor immune responses [5, 6].

Despite promising preclinical advances, the efficacy of TAM-targeted therapies varies widely across cancer types and TME landscapes, raising critical questions: What are the determinants of success or failure in TAM-targeted therapies? How can clinical outcomes be better predicted? And what factors are essential for optimizing therapeutic design?

By synthesizing data from 37 clinical trials, the review aims to provide insights into the tumor-specific factors and mechanisms that influence the efficacy of TAM-targeted strategies. Understanding these dynamics not only bridges gaps between preclinical promise and clinical reality but also informs the design of future trials. Furthermore, advancements in biomarkers and profiling technologies, such as single-cell RNA sequencing and spatial transcriptomics, provide opportunities for refining TAM-targeted therapies. This review highlights their potential to guide personalized interventions and improve outcomes in treatment-resistant malignancies.

Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [7]. A comprehensive search strategy was implemented using PubMed to identify relevant studies published between January 2010 and April 2024. The Boolean query, "macrophage cancer immunotherapy" OR "tumor-associated macrophage immunotherapy", was used to retrieve articles, with filters applied to include only peer-reviewed primary research published in English. Studies were deemed eligible if they investigated macrophage-targeted therapies within the TME, focused on macrophages as standalone therapeutic targets or in combination with other treatments, and involved human subjects diagnosed with cancer. Studies were excluded if they centered on non-cancer diseases, non-human models, reviews, meta-analyses, or if macrophages were not the primary focus.

Titles and abstracts were screened, followed by full-text assessments to confirm eligibility. Key data points, including study phase, cancer type, therapeutic modality, and primary outcomes, were systematically extracted and recorded in an Excel spreadsheet to ensure structured data organization and facilitate analysis, as shown in Table 1. Any uncertainties during study selection or data extraction were addressed through iterative review and discussions, ensuring alignment with the review objectives.

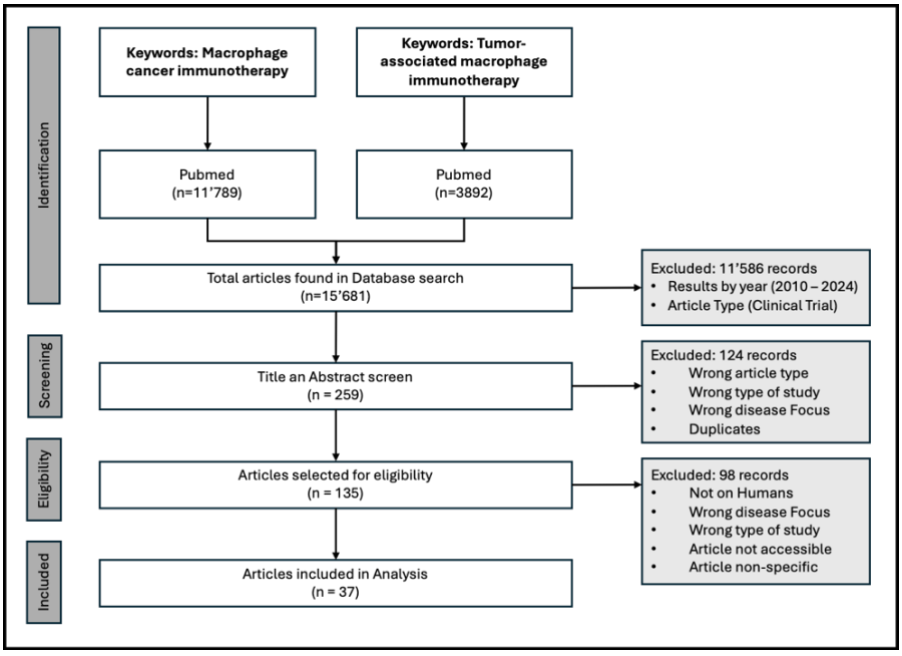

Figure 1. Flow Diagram of Study Selection Process. This figure was created using Microsoft PowerPoint.

DOI Link: https://doi.org/10.26685/urncst.700

Table 1. Summary of Macrophage-Targeted Immunotherapy Clinical Trials

Study	Size	Phase	Cancer Type	Therapy Strategy	Therapeutic Agent
Beckermann et al., 2024 [1]	17	Ib	Renal Cell Carcinoma	Combination Checkpoint Inhibitors with Monoclonal Antibodies	PY314, Pembrolizumab
Hashimoto et al., 2021 [4]	36	I	Advanced hepatocellular carcinoma (HCC)	Combination Immunomodulatory Drugs with Multi-Kinase Inhibitor	MTL-CEBPA, Sorafenib
Andtbacka et al., 2016 [5]	436	III	Melanoma	Combination Cytokines with Oncolytic Viruses	Talimogene Laherparepvec, GM-CSF
Autio et al., 2020 [8]	34	I	Breast and Prostate Cancer	Monoclonal Antibodies	LY3022855
Borazanci et al., 2022 [9]	41	I	Solid Tumors	Monoclonal Antibodies	MSC-1
Yarchoan et al., 2020 [10]	17	II	Colorectal Cancer	Combination Chemotherapeutic Agents with Checkpoint Inhibitors and Vaccine	GVAX Colon Vaccine, Cyclophosphamide, Pembrolizumab
Amaria et al., 2022 [11]	30	II	Melanoma	Combination Checkpoint Inhibitors	Relatlimab, Nivolumab
Song et al., 2022 [12]	70	II	Classical Hodgkin Lymphoma	Checkpoint Inhibitor	Tislelizumab
Ye et al., 2021 [13]	113	II	Urothelial Carcinoma	Checkpoint Inhibitor	Tislelizumab
Barqawi et al., 2021 [14]	20	II	Prostate Cancer	Combination Cytokines with Treatment	GM-CSF, Cryotherapy
Lawson et al., 2015 [15]	815	III	Melanoma	Combination Cytokines with Vaccine	Peptide Vaccine, GM-CSF
Garcia et al., 2011 [16]	61	I/II	Renal cell carcinoma	Combination Cytokines	GM-CSF, IL-2, IFN-α
Rosenblatt et al., 2011 [17]	36	II	Multiple myeloma	Combination Cell Transplant with Vaccine	Dendritic Cell/Tumor Fusion Cell Vaccine, Autologous Stem Cell Transplant
Yu et al., 2010 [18]	226	III	Neuroblastoma	Combination Cytokines with Monoclonal Antibodies and Retinoids	Anti-GD2 Antibody, GM-CSF, IL-2, Isotretinoin
sRodrigues et al., 2023 [19]	16	I	Cervical Cancer	Combination Checkpoint Inhibitor with Treatment	Nivolumab, Chemoradiotherapy
Byrne et al., 2021 [20]	16	I	Resectable pancreatic ductal adenocarcinoma (PDAC) Pancreatic Cacner	Combination Monoclonal Antibodies with Treatment	Selicrelumab, Chemotherapy
Domingo-Musibay et al., 2017 [21]	9	I	Melanoma	Combination Cytokines with Treatment	Percutaneous Thermal Ablation, GM-CSF
Kolstad et al., 2015 [22]	14	I	Follicular lymphoma	Combination Cytokines with Treatment	Radiotherapy, Rituximab, Immature Autologous Dendritic Cells, GM-CSF

LaMarche et al., 2024 [25]	6	Ib	NSCLC	Combination Checkpoint Inhibitor with Monoclonal Antibodies	Dupilumab, PD-(L)1 Blockade
Liao et al., 2017 [26]	21	I/II	Ovarian Cancer, peritoneal, or fallopian tube cancer	Combination Chemotherapeutic agent with Cytokines	Nab-paclitaxel, GM-CSF
Vassilaros et al., 2013 [27]	31	III	Breast Cancer	Vaccine	Oxidized Mannan–MUC1 Vaccine
Ma et al., 2022 [28]	36	Ib	Esophageal Cancer	Combination Checkpoint Inhibitor with Treatment	Chemoradiotherapy, Camrelizumab
Bota et al., 2018 [29]	9	II	Glioblastoma	Combination Cytokines with Monoclonal Antibodies and Vaccine	ERC1671, GM-CSF, Cyclophosphamide, Bevacizumab
Palma et al., 2018 [30]	10	II	Chronic Lymphocytic Leukemia	Combination Cytokines with Chemotherapeutic Agents and Immunomodulatory Drugs and Vaccine	Apo-DC, Lenalidomide, GM-CSF, Cyclophosphamide
Mittendorf et al., 2016 [31]	301	II	Breast Cancer	Combination Cytokines with Vaccine	AE37 Peptide Vaccine, GM-CSF
Garcia et al., 2014 [32]	32	I-/I	Castration-resistant prostate cancer (CRPC)	Combination Cytokines with Immunomodulatory Drugs	GM-CSF, Lenalidomide
Talleur et al. 2017 [33]	34	II	Neuroblastoma	Combination Cell Transplant with Chemotherapeutic agents and Cytokines and Monoclonal antibody	Busulfan, Melphalan, Autologous Hematopoietic Cell Transplant, GM-CSF, IL-2, Haploidentical NK Cells, Anti-GD2 Antibody (hu14.18K322A)
Heo et al., 2013 [34]	30	II	Advanced HCC	Oncolytic Viruses	JX-594 or Pexa-Vec
Mittendorf et al., 2014 [35]	195	I/II	Breast cancer	Combination Cytokines with Vaccine	Nelipepimut-S, GM-CSF
Chen et al., 2014 [36]	20	I	Breast cancer	Combination Chemotherapeutic agents with Checkpoint Inhibitor and Vaccine	Cyclophosphamide, Trastuzumab, GM-CSF-Secreting Tumor Vaccine
Poiré et al., 2010 [37]	46	II	non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL)	Combination Cell Transplant with Cytokines and Monoclonal antibody	GM-CSF, IL-2, Rituximab
Smith et al, 2010 [38]	19	II	Chronic myelogenous leukemia (CML)	Combination Immunomodulatory Drugs with Multi-Kinase Inhibitor and Vaccine	Imatinib Mesylate, GM-CSF-Secreting Vaccine
Rapoport et al., 2014 [39]	27	II	Multiple myeloma	Combination Cell Transplant Immunomodulatory Drugs and Vaccine	MAGE-A3 Trojan Peptide Vaccine, GM-CSF, Poly-ICLC, Autologous Stem Cell Transplant
Segal et al., 2016 [40]	18	II	Metastatic colorectal cancer (CRC)	Combination Monoclonal Antibody with Immunomodulatory Drugs	Imprime PGG, Cetuximab
Cheung et al., 2014 [41]	79	II	Neuroblastoma	Combination Cytokines with Monoclonal Antibodies	3F8, GM-CSF
Gunturu et al, 2010 [42]	18	I/II	Metastatic Melanoma	Combination Cytokines	Lymphodepleting Chemotherapy, IL-2, GM-CSF
Gomez-Roca et al., 2022 [43]	221	Ib	Various advanced solid tumors	Combination Checkpoint Inhibitor with Monoclonal Antibodies	Emactuzumab, Atezolizumab

Results

The systematic review initially identified 15,681 studies, which were filtered based on publication date, peer-reviewed status, and relevance to TAM-targeted cancer immunotherapy, as depicted in Figure 1. This process narrowed the selection to 259 studies, and following detailed screening, 37 clinical trials were included in the final analysis. These trials explored a diverse range of TAM-targeting strategies across 25 cancer types, highlighting the growing interest in the TME as a therapeutic target. The included studies investigated both solid tumors and hematological malignancies, with the latter being the most frequently studied group (24%) [3]. Among solid tumors, breast cancer, prostate cancer, and melanoma were the most represented, each accounting for 10–14% of studies [8-10]. Cancers of the digestive, reproductive, and urinary systems were less commonly investigated, contributing between 3% and 8% of trials [6, 11, 12]. Most studies focused on advanced or metastatic cancers, addressing unmet needs in treatment-refractory settings [3, 8]. Only three trials specifically targeted early-stage, resectable disease, underscoring the limited research on TAM-targeting in earlier cancer stages [3].

Patient enrollment varied widely, ranging from six participants in early-phase trials to 815 in larger Phase III studies [5, 13, 10]. The diverse trial designs, ranging from Phase I safety studies to later-stage efficacy trials, highlight the exploratory nature of TAM-targeted therapies. Early-phase trials focused on safety, dosing, and pharmacodynamics, while larger studies assessed clinical endpoints like progression-free survival (PFS) and overall survival (OS) [8, 13, 14]. In addition to these clinical parameters, the distribution of macrophage immunotherapy techniques is an important factor, as illustrated in Figure 2, which depicts the relative prevalence of cytokines, checkpoint inhibitors, monoclonal antibodies, vaccines, and OVs.

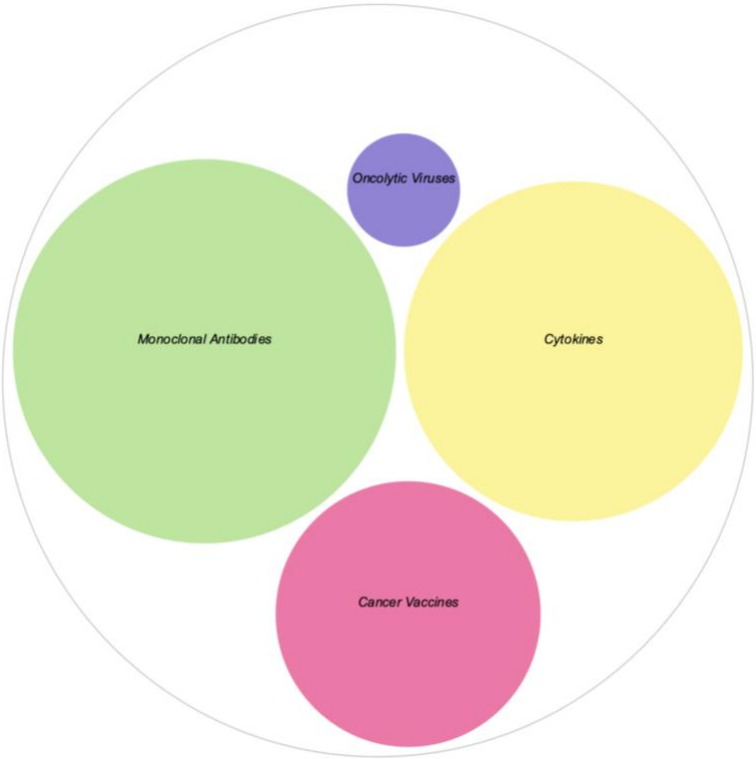

Figure 2. Circular Packing Chart of the Prevalence of Macrophage Immunotherapy Techniques, including Cytokines, Checkpoint Inhibitors, Monoclonal Antibodies, Vaccines, and Oncolytic Viruses. This figure was created using RAWgraphs.

Monoclonal Antibodies

Monoclonal antibodies have been widely explored in TAM-targeted immunotherapy, with numerous clinical trials evaluating their role in macrophage modulation and tumor control. Among these, CSF-1R inhibitors have received significant attention due to their impact on TAM survival and differentiation. Blocking CSF-1R led to a 50% reduction in M2-like TAMs and a 35–45% increase in $CD8^+$ T-cell infiltration, correlating with improved tumor control in glioblastoma and other solid malignancies [8, 14-16]. While these inhibitors showed promise, clinical efficacy varied, with breast and pancreatic cancers responding poorly, likely due to compensatory immunosuppressive mechanisms such as VEGF and TGF-β signaling [8, 16].

The safety profile of CSF-1R inhibitors was generally favorable, with patients experiencing mild-to-moderate fatigue (30–40%), nausea (20–30%), and transient liver enzyme elevations (15%) [8, 14-16]. Some trials, however, reported dose-limiting toxicities, including reversible hepatic transaminase elevations and neutropenia, emphasizing the need for optimized dosing in combination therapies [8, 14].

Another promising target is TREM2, a receptor involved in TAM regulation. TREM2-targeting mAbs reduced immunosuppressive TAM subsets by 40%, while simultaneously enhancing $CD8^+$ T-cell activation and cytokine production in preclinical models [17]. Despite these encouraging preclinical findings, early clinical trials demonstrated only modest improvements in PFS in renal cell carcinoma, suggesting the need for combination strategies with ICIs or other TAM-modulating therapies [17].

ICIs, particularly those targeting the PD-1/PD-L1 axis, serve a dual role by reinvigorating T-cell function while reducing TAM-mediated immunosuppression. In melanoma and non-small cell lung cancer (NSCLC), ICIs have led to durable responses exceeding 36 months in some patients, with OS benefits ranging from 8 to 15 months [13, 18]. Response rates, however, were lower in TAM-rich "cold" tumors, reinforcing the need for combination approaches [13]. Pairing PD-1 inhibitors with lymphocyte activation gene-3 (LAG-3) inhibitors further improved outcomes, achieving response rates of up to 57% in advanced cancers [13]. Additionally, Tislelizumab, designed to minimize Fcγ receptor binding and macrophage-induced immunosuppression, produced a 24% objective response rate in PD-L1-positive urothelial carcinoma [12].

Cytokines

Cytokine-based therapies alter the TME by converting TAMs from an M2-like immunosuppressive state into an M1-like phenotype, promoting T-cell engagement and stronger anti-tumor responses [19]. Among these, GM-CSF is the most extensively studied due to its role in recruiting dendritic cells and boosting antigen presentation [19].

In metastatic renal cell carcinoma (mRCC), a combination of GM-CSF and interleukin-2 (IL-2) resulted in a 20% overall response rate (ORR), with a median PFS of 6.0 months and OS of 23.4 months [19]. Treatment adjustments were necessary for 34% of patients, mainly due to IL-2-induced toxicities, including vascular leak syndrome in 35% of cases [20].

GM-CSF therapy also showed potential in melanoma, where it increased median OS by 10.3 months, though the difference was not statistically significant [10]. In castration-resistant prostate cancer (CRPC), GM-CSF led to PSA declines in 81% of patients, yet only 18% met objective response criteria, reflecting differences in response across tumor types [21].

The route of administration significantly influenced treatment outcomes. Subcutaneous GM-CSF was better tolerated than intravenous administration, as it sustained immune activation while minimizing systemic toxicity [19]. In melanoma trials, intratumoral GM-CSF resulted in a median OS of 8.2 months, demonstrating its potential for localized immune enhancement [22]. Despite these benefits, grade 3–4 toxicities such as thrombocytopenia (9%) and neutropenia (19%) remained a concern [23].

Although not classified as a cytokine, MTL-CEBPA mimics cytokine-driven immune activation by reprogramming tumor-associated myeloid cells. As a small activating RNA (saRNA), it upregulates C/EBPα, reducing M2-like TAMs and myeloid-derived suppressor cells (MDSCs). In hepatocellular carcinoma (HCC), MTL-CEBPA combined with sorafenib achieved a 26.7% ORR, largely by reshaping the TME [4]. While it does not engage cytokine receptors, its immune-modulating effects complement cytokine-based therapies.

Cancer Vaccines and Oncolytic Viruses

Cancer vaccines and OVs offer innovative methods to reshape the immune landscape by reprogramming TAM activity and enhancing tumor recognition. Peptide-based vaccines, in particular, have demonstrated potential in enhancing adaptive immunity and altering the TME. In clinical trials, AE37 combined with GM-CSF improved disease-free survival (DFS) from 85% to 93%, highlighting its role in prolonging immune surveillance [24]. Dendritic cell-based vaccines further amplified tumor-specific immunity by promoting a shift in TAMs toward a pro-inflammatory phenotype. Notably, dendritic cell fusion vaccines triggered a 6.76-fold increase in myeloma-specific $CD8^+$ T cells (95% CI, 3.02–15.49), peaking at an 11.48-fold increase post-vaccination (95% CI, 4.17–32.36), demonstrating their ability to sustain long-term immune activation [25].

OVs, such as JX-594 (Pexa-Vec) and T-VEC, leverage tumor-selective viral replication and immune system activation to enhance anti-tumor effects. JX-594, a genetically engineered vaccinia virus expressing GM-CSF, promotes immune infiltration, disrupts tumor vasculature, and elicits systemic anti-tumor responses. High-dose administration extended median OSs to 14.1 months, nearly doubling survival compared to low-dose recipients (6.7 months) [15].

Similarly, T-VEC, a modified herpes simplex virus, boosts $CD8^+$ T-cell recruitment and cytokine-driven immune activation, increasing tumor immunogenicity. In melanoma clinical trials, T-VEC achieved an objective response rate of up to 24%, proving effective in immunologically "cold" tumors [5]. Unlike systemically delivered agents, T-VEC's intratumoral administration localizes immune activation, reducing systemic toxicity while ensuring robust anti-tumor responses [5].

Biomarkers in TAM-Targeted Therapies

Biomarkers play a crucial role in identifying patients most likely to respond to TAM-targeted therapies and monitoring therapeutic outcomes. Among the most studied is PD-L1 expression, which frequently correlates with TAM-enriched TMEs and improved responses to ICIs. In NSCLC and melanoma, higher PD-L1 levels were associated with increased T-cell infiltration and a 20–30% improvement in PFS and OS, making it a valuable marker for patient stratification [13]. However, responses remain variable due to additional immunosuppressive mechanisms within the TME [13].

TAM density has also emerged as a significant prognostic marker, with elevated M2-like populations correlating with poorer outcomes in glioblastoma and pancreatic cancer [1]. Studies on CSF-1R inhibitors demonstrated that blocking this pathway could reduce M2-like TAM populations by 35–50%, leading to greater $CD8^+$ T-cell infiltration and improved tumor control [8]. Yet, some tumors remained resistant, as alternative immunosuppressive pathways allowed TAMs to sustain their tumor-supportive role [8].

CD40 expression serves as both a biomarker and a therapeutic target. Its activation drives TAM polarization toward an M1-like state, improving T-cell infiltration and mitigating fibrosis. In pancreatic ductal adenocarcinoma (PDAC), combining CD40 agonists with chemotherapy improved TAM functionality and led to tumor regression, establishing CD40 as a marker of therapeutic response [23].

Heat shock proteins (HSPs) have been investigated for their potential role in TAM modulation and immune activation. Higher HSP expression correlated with stronger anti-tumor immune responses, though its clinical applicability remains under investigation [22].

Emerging technologies, including single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics, have begun to provide deeper insights into TAM heterogeneity and immune profiling. In NSCLC, scRNA-seq helped categorize distinct TAM subpopulations, though its predictive value in clinical settings is still being explored [26]. Spatial transcriptomics has shown potential for mapping TAM-enriched regions and immune-exclusion zones, which could inform localized therapeutic interventions, but further validation is needed [27].

Discussion

Tumor-associated macrophages play a pivotal role in shaping the TME, influencing immune suppression, tumor progression, and therapeutic resistance [2, 3]. This review highlights the complexity of TAM-targeted therapies and the need for context-specific strategies. Among evaluated approaches, TAM reprogramming—converting M2-like macrophages into tumor-suppressive M1-like phenotypes—shows promise, especially in immunologically "cold" tumors [4, 19]. Agents such as GM-CSF and MTL-CEBPA have demonstrated the ability to enhance immune cell infiltration and reshape the TME across multiple malignancies. However, their efficacy remains highly dependent on tumor context, reinforcing the need for precise patient stratification and combination strategies to maximize response rates.

Conversely, TAM depletion strategies, particularly CSF-1R inhibitors, have yielded mixed results. While glioblastoma, a TAM-dense malignancy, has shown responsiveness to CSF-1R blockade, cancers such as breast and pancreatic tumors—where VEGF and TGF-β signaling sustain immunosuppression—exhibited limited benefit [8]. This discrepancy highlights the importance of combination regimens that simultaneously target multiple immune evasion pathways. Preclinical and early clinical studies suggest that CSF-1R inhibition combined with ICIs enhances responses in pancreatic and ovarian cancers, offering a synergistic approach to overcoming TAM-driven immune exclusion [8, 16]. Similarly, TREM2-targeting antibodies, though still in early development, represent an emerging direction for selectively modulating specific TAM subpopulations rather than indiscriminately depleting macrophages [17].

Beyond therapeutic agents, drug delivery plays a crucial role in determining treatment success. Subcutaneous GM-CSF administration has enabled sustained immune activation while reducing systemic toxicity, whereas intertumoral delivery, exemplified by T-VEC, has proven effective in enhancing localized immune responses in tumors with dense stromal barriers [5, 9, 10]. In contrast, intravenous monoclonal antibodies often struggle to adequately penetrate immune-suppressive tumor niches, limiting their efficacy [1]. Future research should prioritize novel delivery systems, such as nanoparticle-based TAM reprogramming or biodegradable scaffolds, to optimize drug stability and local retention while minimizing off-target effects [6].

A promising frontier is Chimeric Antigen Receptor Macrophages (CAR-Ms), which harness macrophages' tumor-homing abilities while enhancing direct cytotoxicity [28]. Unlike T cell-based therapies, CAR-Ms infiltrate solid tumors more efficiently, recruiting effector immune cells and remodeling the TME. Preclinical models indicate potential efficacy in treatment-resistant ovarian and pancreatic cancers, though challenges remain regarding macrophage persistence, antigen escape, and possible pro-tumorigenic effects [28]. Integrating CAR-Ms with ICIs or metabolic inhibitors could help overcome immune resistance, but rigorous clinical trials are needed to confirm long-term safety and efficacy.

Biomarkers are integral to optimizing TAM-targeted therapies, yet their inconsistent application across clinical trials limits reproducibility. PD-L1 expression remains one of the most widely studied biomarkers, correlating with improved outcomes in melanoma and NSCLC when treated

with ICIs [13]. However, its predictive value varies across tumor types, underscoring the necessity of multi-marker panels rather than reliance on single biomarkers. CD40 expression has gained attention as a predictor of TAM reprogramming success, particularly in pancreatic ductal adenocarcinoma, where CD40 agonists enhance T-cell recruitment and TAM polarization [23].

Despite advancements in biomarker research, many clinical trials lack standardized assessment protocols, creating challenges in cross-study comparisons and data integration. Emerging technologies such as scRNA-seq and spatial transcriptomics offer unprecedented insights into TAM heterogeneity, revealing distinct macrophage subsets and immune-exclusion zones [26, 27]. However, their high cost and limited accessibility hinder routine clinical implementation. Future research must prioritize the development of cost-effective, clinically actionable biomarker panels to refine patient selection and guide precision medicine approaches.

While TAM-targeted therapies offer a promising avenue in cancer immunotherapy, several challenges must be addressed for widespread clinical translation. TAM plasticity, the ability of macrophages to dynamically switch phenotypes in response to environmental cues, raises concerns about the durability of therapeutic effects [2]. Additionally, tumor heterogeneity complicates treatment standardization, requiring cancer-specific rather than one-size-fits-all approaches. Future research should focus on synergistic combination regimens, integrating metabolic inhibitors, epigenetic modulators, and next-generation ICIs to overcome resistance mechanisms and enhance therapeutic efficacy [6, 8]. Expanding clinical trials to underrepresented cancer types and patient populations will be critical for improving generalizability. Furthermore, regulatory considerations, such as FDA approval processes, manufacturing scalability, and cost-effectiveness, must be actively addressed to ensure real-world accessibility of TAM-targeted interventions.

Conclusion

TAM-targeted therapies offer significant potential for reshaping the tumor microenvironment and enhancing cancer immunotherapy, but their success depends on tumor-specific factors. This review examined the determinants of efficacy in TAM-targeted therapies, emphasizing how monoclonal antibodies, immune checkpoint inhibitors, and cytokine-based treatments influence immune modulation. While promising outcomes have been achieved, variability in clinical responses underscores the need for biomarker-driven patient selection and optimized combination regimens.

Bridging the gap between preclinical promise and clinical reality requires deeper insights into tumor heterogeneity, immune evasion mechanisms, and TAM interactions with other immune cells. Advances in scRNA-seq, spatial transcriptomics, and novel drug delivery systems offer promising avenues for refining treatment strategies and predicting patient responses. Expanding clinical trials to diverse cancer types and integrating these strategies into personalized medicine will be critical for maximizing therapeutic success. By addressing these challenges, TAM-targeted therapies can transition from experimental interventions to established immunotherapies, offering new hope for patients with treatment-resistant cancers.

List of Abbreviations

APCs: antigen-presenting cells
CAF: cancer-associated fibroblasts
CAR-M: chimeric antigen receptor-macrophages
CD8+ T cells: cytotoxic T cells
CRPC: castration-resistant prostate cancer
CSF-1R: colony-stimulating factor 1 receptor
FAO: fatty acid oxidation
GM-CSF: granulocyte-macrophage colony-stimulating factor
HCC: hepatocellular carcinoma
HSPs: heat shock proteins
ICIs: immune checkpoint inhibitors
IFN-α: interferon alpha
IFN-γ: interferon gamma
IL: interleukin
JAK: Janus kinase
JX-594: pexa-vec
LAG-3: lymphocyte-activation gene 3
mAbs: monoclonal antibodies
mDCs: myeloid dendritic cells
MDSCs: myeloid-derived suppressor cells
MHC: major histocompatibility complex
NK: natural killer cells
NSCLC: non-small cell lung cancer
ORR: objective response rate
OS: overall survival
PD-1: programmed cell death protein 1
PD-L1: programmed death-ligand 1
PFS: progression-free survival
PI3K/Akt: phosphatidylinositol 3-kinase/protein kinase B pathway
RNA-seq: RNA sequencing
scRNA-seq: single-cell RNA sequencing
TAAs: tumor-associated antigens
TAMs: tumor-associated macrophages
TEAEs: treatment-emergent adverse events
TGF-β: transforming growth factor beta
TILs: tumor-infiltrating lymphocytes
TME: tumor microenvironment
TNF-α: tumor necrosis factor alpha
Tregs: regulatory T cells
TREM2: triggering receptor expressed on myeloid cells 2
T-VEC: talimogene laherparepvec
VEGF: vascular endothelial growth factor

Conflicts of Interest
The author declares no conflicts of interest.

Ethics Approval and/or Participant Consent
The study did not require any ethics approval and/or participant consent because this was a scoping review.

Authors' Contributions
CR: made substantial contributions to the conception and design of the study, the acquisition, analysis, and interpretation of data, drafted the manuscript, revised it critically for important intellectual content, and gave final approval of the version to be published.

Acknowledgements
The author expresses deepest gratitude to Zi Yan Chen, who was their mentor throughout this project, providing invaluable guidance and support. The author also thanks Professor Roland Müller for introducing them to this opportunity. Additionally, the author thanks their partner, Lukas, for his love, support and comforting meals that sustained them throughout this journey.

Funding
This paper was not funded.

References
[1] Beckermann KE, Patnaik A, Winer I, Tan W, Bashir B, Kyriakopoulos C, et al. A phase 1b open-label study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of py314 in combination with pembrolizumab in patients with advanced renal cell carcinoma. Investigational New Drugs. 2024;42:179–84. https://doi.org/10.1007/s10637-024-01419-1
[2] Qian Y, Yin Y, Zheng X, Liu Z, Wang X. Metabolic regulation of tumor-associated macrophage heterogeneity: Insights into the tumor microenvironment and immunotherapeutic opportunities. Biomark Res. 2024;12(1):1-28. https://doi.org/10.1186/s40364-023-00549-7
[3] Mantovani A, Allavena P, Marchesi F, Garlanda C. Macrophages as tools and targets in cancer therapy. Nat Rev Drug Discov. 2022 Nov;21(11):799–812. https://doi.org/10.1038/s41573-022-00520-5
[4] Hashimoto A, Sarker D, Reebye V, Jarvis S, Sodergren M, Kossenkov A, et al. Upregulation of C/EBPα inhibits suppressive activity of myeloid cells and potentiates antitumor response in mice and patients with cancer. Clin Cancer Res. 2021 Nov 1;27(21):5961–78. https://doi.org/10.1158/1078-0432.CCR-21-0986
[5] Andtbacka RHI, Kaufman HL, Collichio F, Amatruda T, Senzer N, Chesney J, et al. Talimogene laherparepvec improves durable response rate in patients with advanced melanoma. J Clin Oncol. 2015;33:2780–8. https://doi.org/10.1200/JCO.2014.58.3377
[6] Zheng J, Jiang J, Pu Y, Xu T, Sun J, Zhang Q, et al. Tumor-associated macrophages in nanomaterial-based anti-tumor therapy: As target spots or delivery platforms. Front Bioeng Biotechnol. 2023;11:1248421. https://doi.org/10.3389/fbioe.2023.1248421
[7] Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med. 2009;6(7):e1000097. https://doi.org/10.1371/journal.pmed.1000097
[8] Autio KA, Klebanoff CA, Schaer D, Kauh JSW, Slovin SF, Adamow M, et al. Immunomodulatory activity of a colony-stimulating factor-1 receptor inhibitor in patients with advanced refractory breast or prostate cancer: A phase I study. Clin Cancer Res. 2020 Nov 1;26(21):5609–20. https://doi.org/10.1158/1078-0432.CCR-20-0855
[9] Borazanci E, Schram AM, Garralda E, Brana I, Vieito Villar M, Spreafico A, et al. Phase I, first-in-human study of MSC-1 (AZD0171), a humanized anti-leukemia inhibitory factor monoclonal antibody, for advanced solid tumors. ESMO Open. 2022;7(4):100530. https://doi.org/10.1016/j.esmoop.2022.100530
[10] Yarchoan M, Huang CY, Zhu Q, Ferguson AK, Durham JN, Anders RA, et al. A phase 2 study of GVAX colon vaccine with cyclophosphamide and pembrolizumab in patients with mismatch repair proficient advanced colorectal cancer. Cancer Med. 2020 Feb;9(4):1485–94. https://doi.org/10.1002/cam4.2763
[11] Amaria RN, Postow M, Burton EM, Tetzlaff MT, Ross MI, Torres-Cabala C, et al. Neoadjuvant relatlimab and nivolumab in resectable melanoma. Nature. 2022 Nov;611(7934):155–163. https://doi.org/10.1038/s41586-022-05368-8
[12] Song Y, Gao Q, Zhang H, Fan L, Zhou J, Zou D, et al. Tislelizumab for relapsed/refractory classical Hodgkin lymphoma: 3-year follow-up and correlative biomarker analysis. Clin Cancer Res. 2022;28(6):1147–56. https://doi.org/10.1158/1078-0432.CCR-21-2023
[13] Ye D, Liu J, Zhou A, Zou Q, Li H, Fu C, et al. Tislelizumab in Asian patients with previously treated locally advanced or metastatic urothelial carcinoma. Cancer Sci. 2021 Jan;112(1):305–13. https://doi.org/10.1111/cas.14681

[14] Barqawi AB, Pessoa RR, Crawford ED, Al-Musawi M, MacDermott T, O'Donell C, et al. Boosting immune response with GM-CSF optimizes primary cryotherapy outcomes in the treatment of prostate cancer: A prospective randomized clinical trial. Prostate Cancer and Proszatic Dis. 2021;24:750–7. https://doi.org/10.1038/s41391-021-00321-8

[15] Lawson DH, Lee S, Zhao F, Tarhini AA, Margolin KA, Ernstoff MS, et al. Randomized, placebo-controlled, phase III trial of yeast-derived GM-CSF versus peptide vaccination versus GM-CSF plus peptide vaccination versus placebo in patients with no evidence of disease after complete surgical resection of locally advanced and/or stage IV melanoma. J Clin Oncol. 2015 Dec 1;33(34):4066–76. https://doi.org/10.1200/JCO.2015.62.0500

[16] Garcia JA, Mekhail T, Elson P, Wood L, Bukowski RM, Dreicer R, et al. Phase I/II trial of subcutaneous interleukin-2, granulocyte-macrophage colony-stimulating factor and interferon-α in patients with metastatic renal cell carcinoma. BJU Int. 2012 Jan; 109(1):63–9. https://doi.org/10.1111/j.1464-410X.2010.10011.x

[17] Rosenblatt J, Avivi I, Vasir B, Uhl L, Munshi NC, Katz T, et al. Vaccination with dendritic cell/tumor fusions following autologous stem cell transplant induces immunologic and clinical responses in multiple myeloma patients. Clin Cancer Res. 2013 Jul 1;19(13): 3640–8. https://doi.org/10.1158/1078-0432.CCR-13-0282

[18] Yu AL, Gilman AL, Ozkaynak MF, London WB, Kreissman SG, Chen HX, et al. Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. N Engl J Med. 2010 Sep 30;363(14): 1324–34. https://doi.org/10.1056/NEJMoa0911123

[19] Rodrigues M, Vanoni G, Loap P, Dubot C, Timperi E, Minsat M, et al. Nivolumab plus chemoradiotherapy in locally-advanced cervical cancer: The NICOL phase 1 trial. Nat Commun. 2023;14:3698. https://doi.org/10.1038/s41467-023-39383-9

[20] Byrne KT, Betts CB, Mick R, Sivagnanam S, Bajor DL, Laheru DA, et al. Neoadjuvant selicrelumab, an agonist CD40 antibody, induces changes in the tumor microenvironment in patients with resectable pancreatic cancer. Clin Cancer Res. 2021 Aug 15;27 (16):4574–86. https://doi.org/10.1158/1078-0432.CCR-21-1047

[21] Domingo-Musibay E, Heun JM, Nevala WK, Callstrom M, Atwell T, Galanis E, et al. Endogenous heat-shock protein induction with or without radiofrequency ablation or cryoablation in patients with stage IV melanoma. Oncologist. 2017 Sep;22(9): 1026–e93. https://doi.org/10.1634/theoncologist.2017-0060

[22] Kolstad A, Kumari S, Walczak M, Madsbu U, Hagtvedt T, Bogsrud TV, et al. Sequential intranodal immunotherapy induces antitumor immunity and correlated regression of disseminated follicular lymphoma. Blood. 2015 Jan 1;125(1):82–9. https://doi.org/10.1182/blood-2014-07-592162

[23] Chu X, Tian Y, Lv C. Decoding the spatiotemporal heterogeneity of tumor-associated macrophages. Mol Cancer. 2024;23(150):1-24. https://doi.org/10.1186/s12943-024-02064-1

[24] Huang T, Bei C, Hu Z, Li Y. CAR-macrophage: Breaking new ground in cellular immunotherapy. Front Cell Dev Biol. 2024 Oct;12:1464218. https://doi.org/10.3389/fcell.2024.1464218

[25] LaMarche NM, Hegde S, Park MD, Maier BB, Troncoso L, Le Berichel J, et al. An IL-4 signalling axis in bone marrow drives pro-tumorigenic myelopoiesis. Nature. 2024 Jan;625(7993):166–74. https://doi.org/10.1038/s41586-023-06797-9

[26] Liao JB, Swensen RE, Ovenell KJ, Hitchcock-Bernhardt KM, Reichow JL, Apodaca MC, et al. Phase II trial of albumin-bound paclitaxel and granulocyte macrophage colony-stimulating factor as an immune modulator in recurrent platinum-resistant ovarian cancer. Gynecol Oncol. 2017 Mar;144(3):480–5. https://doi.org/10.1016/j.ygyno.2017.01.008

[27] Vassilaros S, Tsibanis A, Tsikkinis A, Pietersz GA, McKenzie IFC, Apostolopoulos V. Up to 15-year clinical follow-up of a pilot phase III immunotherapy study in stage II breast cancer patients using oxidized mannan–MUC1. Immunotherapy. 2013 Nov;5(11): 1177–1182. https://doi.org/10.2217/imt.13.126

[28] Ma X, Guo Z, Wei X, Zhao G, Han D, Zhang T, et al. Spatial distribution and predictive significance of dendritic cells and macrophages in esophageal cancer treated with combined chemoradiotherapy and PD-1 blockade. Front Immunol. 2022;12:786429. https://doi.org/10.3389/fimmu.2021.786429

[29] Bota DA, Chung J, Dandekar M, Carrillo JA, Kong XT, Fu BD, et al. Phase II study of ERC1671 plus bevacizumab versus bevacizumab plus placebo in recurrent glioblastoma: interim results and correlations with CD4+ T-lymphocyte counts. CNS Oncol. 2018;7(3). https://doi.org/10.2217/cns-2018-0009

[30] Palma M, Hansson L, Mulder TA, Adamson L, Näsman-Glaser B, Eriksson I, et al. Lenalidomide as immune adjuvant to a dendritic cell vaccine in chronic lymphocytic leukemia patients. Eur J Haematol. 2018 Jul;101(1):68–77. https://doi.org/10.1111/ejh.13065

[31] Mittendorf EA, Ardavanis A, Symanowski J, Murray JL, Shumway NM, Litton JK, et al. Primary analysis of a prospective, randomized, single-blinded phase II trial evaluating the HER2 peptide AE37 vaccine in breast cancer patients to prevent recurrence. Ann Oncol. 2016 Jul;27(7):1241–8. https://doi.org/10.1093/annonc/mdw150

[32] Garcia JA, Elson P, Tyler A, Triozzi P, Dreicer R. Sargramostim (GM-CSF) and lenalidomide in castration-resistant prostate cancer (CRPC): Results from a phase I-II clinical trial. Urol Oncol. 2014 Jan;32(1):33.e11–7. https://doi.org/10.1016/j.urolonc.2012.12.004

[33] Talleur AC, Triplett BM, Federico S, Mamcarz E, Janssen W, Shook D, et al. Consolidation therapy for newly diagnosed pediatric patients with high-risk neuroblastoma using busulfan/melphalan, autologous hematopoietic cell transplantation, anti-GD2 antibody, granulocyte-macrophage colony-stimulating factor, interleukin-2, and haploidentical natural killer cells. Biol Blood Marrow Transplant. 2017 Nov;23(11):1910–7. https://doi.org/10.1016/j.bbmt.2017.07.011

[34] Heo J, Reid T, Ruo L, Breitbach CJ, Rose S, Bloomston M, et al. Randomized dose-finding clinical trial of oncolytic immunotherapeutic vaccinia JX-594 in liver cancer. Nat Med. 2013 Mar;19(3):329–336. https://doi.org/10.1038/nm.3089

[35] Mittendorf EA, Clifton GT, Holmes JP, Schneble E, van Echo D, Ponniah S, et al. Final report of the phase I/II clinical trial of the E75 (nelipepimut-S) vaccine with booster inoculations to prevent disease recurrence in high-risk breast cancer patients. Ann Oncol. 2014 Sep;25(9):1735–42. https://doi.org/10.1093/annonc/mdu211

[36] Chen G, Gupta R, Petrik S, Laiko M, Leatherman JM, Asquith JM, et al. A feasibility study of cyclophosphamide, trastuzumab, and an allogeneic GM-CSF-secreting breast tumor vaccine for HER-2+ metastatic breast cancer. Cancer Immunol Res. 2014 Oct;2(10):949–61. https://doi.org/10.1158/2326-6066.CIR-14-0058

[37] Poiré X, Kline J, Grinblatt D, Zimmerman T, Conner K, Muhs C, et al. Phase II study of immunomodulation with granulocyte-macrophage colony-stimulating factor, interleukin-2, and rituximab following autologous stem cell transplant in patients with relapsed or refractory lymphomas. Leuk Lymphoma. 2010 Jul;51(7):1241–50. https://doi.org/10.3109/10428194.2010.486876

[38] Smith BD, Kasamon YL, Kowalski J, Gocke C, Murphy K, Miller CB, et al. K562/GM-CSF immunotherapy reduces tumor burden in chronic myeloid leukemia patients with residual disease on imatinib mesylate. Clin Cancer Res. 2010 Jan 1;16(1):338–47. https://doi.org/10.1158/1078-0432.CCR-09-2046

[39] Rapoport AP, Aqui NA, Stadtmauer EA, Vogl DT, Xu YY, Kalos M, et al. Combination immunotherapy after ASCT for multiple myeloma using MAGE-A3/Poly-ICLC immunizations followed by adoptive transfer of vaccine-primed and costimulated autologous T cells. Clin Cancer Res. 2014 Mar 1;20(5):1355–65. https://doi.org/10.1158/1078-0432.CCR-13-2817

[40] Segal NH, Gada P, Senzer N, Gargano MA, Patchen ML, Saltz LB, et al. A phase 2 efficacy and safety, open-label, multicenter study of Imprime PGG injection in combination with cetuximab in patients with stage IV KRAS-mutant colorectal cancer. Clin Colorectal Cancer. 2016 Sep;15(3):222–7. https://doi.org/10.1016/j.clcc.2016.02.013

[41] Cheung NK, Cheung IY, Kramer K, Modak S, Kuk D, Pandit-Taskar N, et al. Key role for myeloid cells: Phase II results of anti-GD2 antibody 3F8 plus granulocyte-macrophage colony-stimulating factor for chemoresistant osteomedullary neuroblastoma. Int J Cancer. 2014 Nov 1;135(9):2199–205. https://doi.org/10.1002/ijc.28851

[42] Gunturu KS, Meehan KR, Mackenzie TA, Crocenzi TS, McDermott D, Usherwood EJ, et al. Cytokine working group study of lymphodepleting chemotherapy, interleukin-2, and granulocyte-macrophage colony-stimulating factor in patients with metastatic melanoma: Clinical outcomes and peripheral-blood cell recovery. J Clin Oncol. 2010 Mar 1;28(7):1196–202. https://doi.org/10.1200/JCO.2009.24.8153

[43] Gomez-Roca C, Cassier P, Zamarin D, Machiels JP, Perez Gracia JL, Hodi FS, et al. Anti-CSF-1R emactuzumab in combination with anti-PD-L1 atezolizumab in advanced solid tumor patients naïve or experienced for immune checkpoint blockade. J Immunother Cancer. 2022 May;10(5):e004076. https://doi.org/10.1136/jitc-2021-004076

[44] Xiao L, Wang Q, Peng H. Tumor-associated macrophages: New insights on their metabolic regulation and their influence in cancer immunotherapy. Front Immunol. 2023;14:1157291. https://doi.org/10.3389/fimmu.2023.1157291

[45] Li M, He L, Zhu J, Zhang P, Liang S. Targeting tumor-associated macrophages for cancer treatment. Cell Biosci. 2022 Dec 21;12(85):1-13. https://doi.org/10.1186/s13578-022-00823-5

Article Information
Managing Editor: Jeremy Y. Ng
Peer Reviewers: Zi Yan Chen, Kimberly Seaman
Article Dates: Received Jul 26 24; Accepted Feb 02 25; Published Feb 12 25

Citation
Please cite this article as follows:
Rohner C. Targeting the tumor microenvironment: A review of macrophage immunotherapies across cancer types. URNCST Journal. 2025 Feb 12: 9(2). https://urncst.com/index.php/urncst/article/view/700
DOI Link: https://doi.org/10.26685/urncst.700

URNCST Journal
"Research in Earnest"

Funded by the Government of Canada | Canada