

Perspective

When immune landscapes diverge: How immune cell heterogeneity shapes cancer immunotherapy response

Jessie L. Chiello ^{1,†}, Nijamuddin Shaikh ^{1,†}, AJ Robert McGray ^{1,2,*}

1. Department of Immunology, Roswell Park Comprehensive Cancer Center, Buffalo, NY 14263, USA; Emails: jessie.chiello@roswellpark.org (J.L.C.); Nijamuddin.Shaikh@RoswellPark.org (N.S.)
2. Department of Gynecologic Oncology, Roswell Park Comprehensive Cancer Center, Buffalo, NY 14263, USA

† These authors contributed equally to this work

* **Correspondence:** AJ Robert McGray; Email: ajrobert.mcgray@roswellpark.org

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Abstract

Amplifying the antitumor immune response using immunotherapy has significantly improved patient survival and transformed cancer care. Findings from preclinical studies as well as clinical observations have firmly established that the intratumoral accumulation of T cells often serves as a positive predictor of immunotherapy response. While this observation has led to the commonly used “cold or hot” classifiers to describe the T cell landscape within a tumor, this is increasingly being recognized as an oversimplification. Instead, there is a growing appreciation for the broader composition, spatial localization, and dynamic nature of the tumor immune landscape across cancer types. In this perspective, we describe the diverse and unique immune correlates that have been associated with response (or lack thereof) following immunotherapy. Beginning with our own published findings related to the heterogeneous immune landscapes associated with divergent responses to adoptive T cell therapy combined with immune checkpoint inhibition, we then overlay key observations from other recently published studies to highlight the impact of the broader immune landscape in determining treatment outcome. Finally, we recommend leveraging modern multi-omic analysis tools prior to and during immunotherapy treatment to define immune signatures associated with favorable response, those that can predict treatment outcome, or which can be leveraged to identify complementary therapeutic approaches.

Keywords: Tumor immune heterogeneity; Bispecific T cell engager; Adoptive T cell therapy; Multi-omics; Immune Checkpoint Blockade; Immunotherapy Response

1. The Immune Landscape of Cancer: Moving Beyond 'Cold' Versus 'Hot' Classifiers

Immunotherapies have revolutionized cancer treatment, leading to remarkable response durability and improved survival for many cancer patients. Despite this paradigm shift in cancer care, the benefit of immunotherapy is observed in only a subset of patients while others fail to respond [1,2]. Although various factors including age, cancer type and disease burden, number of metastatic sites, molecular alterations, and prior lines of therapy have been identified as potential determinants of immunotherapy response, the immune cell composition of the tumor microenvironment (TME) dramatically impacts therapeutic outcome. While earlier work focused on categorizing tumors into 'cold' or 'hot' phenotypes based on tumor infiltrating lymphocyte (TIL) abundance (**Figure 1A**), this is now considered to be an oversimplification of the nuanced immune niches and diverse cell subsets found in the broader tumor immune landscape [3]. As such, an improved understanding of the complex immune composition of the TME, how the immune landscape of cancer shifts over time or in response to therapy, as well as the spatial organization of intratumoral immune cells is needed to enhance our capacity to rationally select immunotherapies for cancer patients. In this perspective, we aim to explore how immune profiling of the TME at baseline and on treatment can provide crucial insights related to mechanisms of treatment response or failure, as well as how studying immune cell heterogeneity within and across cancers can be therapeutically leveraged. Focusing on recently published work from our group and others, we explore phenotypic, functional, and spatial determinants associated with immunotherapy response, which have the potential to identify improved predictive biomarkers and to better select tailored therapeutic options. Collectively, our goal is to provide an actionable framework for integrating baseline and on-treatment data that effectively captures both immune cell complexity and dynamic changes in the TME. Potential limitations and challenges in implementing these approaches, opportunities to use new knowledge to inform mechanistic hypotheses or novel therapeutic strategies, as well as how this information can improve patient outcomes will also be discussed.

2. Shifts in the Tumor Immune Landscape Arise During Divergent Therapeutic Responses

In our recent publication [4], we evaluated if adoptive transfer of T cells engineered to secrete folate receptor alpha (FR α)-targeted bispecific T cell engagers (FR-B T cells) could rationally combine with immune checkpoint blockade (anti-PD-1) to treat ovarian cancer (OC). We first tested FR-B T cells $\pm$ anti-PD-1 against primary OC patient specimens using an *in vitro* co-culture system. Here, 17/20 tested OC samples responded to FR-B T cell therapy (based on IFN- γ production), while only 8 of these 17 samples demonstrated an enhanced response upon anti-PD-1 addition. Categorizing these as either responders (R) or enhanced responders (R+), we interrogated potential phenotypic drivers of R versus R+. While no difference in OC FR α positivity, tumor/immune cell PD-L1 levels, or differences in the overall CD45+ immune cell abundance in the TME were observed between R and R+ specimens, R

specimens were found to have a >2.5-fold increase in CD206⁺ CD14⁺ myeloid cells (consistent with an immunosuppressive phenotype) compared to R⁺ specimens. As this finding was consistent with a role for the broader OC immune landscape in impacting the FR-B T cell + anti-PD-1 response, we next utilized an immunocompetent OC model to globally assess the cellular changes in the OC TME during FR-B T cells ± anti-PD-1 treatment. Similar to our observations in clinical OC samples, FR-B T cells + anti-PD-1 produced divergent treatment responses. Specifically, a subset of animals receiving combination therapy developed early progressive disease (PD), whereas approximately 50% of mice treated with FR-B T cells + anti-PD-1 achieved durable response (DR). Using single cell transcriptomics (scRNA-seq) during the acute phase of treatment response and again once PD and DR phenotypes had emerged, we observed that while FR-B T cells + anti-PD-1 led to rapid (and nearly complete) clearance of FRα⁺ OC cells, divergent immune landscapes developed between PD and DR. While PD mice showed limited accumulation of predominantly naïve T and B cells and had high frequencies of Arg1⁺ macrophages and increased neutrophils, DR mice were characterized by accumulation of activated B cells, increased effector memory CD4⁺ T cells, and Cxcl13-expressing macrophages. Of note, FR-B T cells were no longer readily detected in the OC TME at the time of PD/DR divergence, suggesting not only a shift towards endogenous antitumor responses over time, but also distinct immune trajectories impacting response durability.

3. Heterogeneous Immune Landscapes Impact Treatment Outcome Across Tumor Indications

Our observations in OC related to dynamic changes in the tumor immune composition following immunotherapy are not unique and multiple published studies have now demonstrated that the accumulation of distinct pro-inflammatory or immunosuppressive cell types correlates with treatment success or failure [5–7]. In order to contextualize these observations and begin to define the generalizable immune features or principles associated with improved therapeutic outcome across cancers, this section highlights other recently published studies identifying distinct immune features associated with immunotherapy response. Of note, recent advances in experimental models, exciting new developments in flow cytometry, multiplex imaging, and multi-omic analysis, and the emergence of next generation computational tools to integrate complex datasets have led to a deeper understanding of the cellular milieu underlying immunotherapy responses (**Figure 1B**). For example, Rosario & Long *et al.* [8] identified increased T cell and B cell infiltrates along with elevated levels of T and B cell activation, differentiation, and proliferation in OC patients that achieved durable clinical benefit (DCB) following combination immunotherapy. Additionally, an increased tertiary lymphoid structure (TLS) gene signature (Ccl19, Cxcl13, Ccl21) and enrichment for lactic acid-producing gut bacteria were also associated with improved therapeutic outcome. Indeed, mature TLS (mTLS) are associated with improved survival in many tumor types, including OC and non-small cell lung cancer (NSCLC), and are predictive of therapeutic response [9,10]. Regarding TLS, MacFawn *et al.* [11] have demonstrated that the immune cell activity in the case of OC is highly dependent on the level of TLS maturity, wherein less mature TLS niches have low immune cell activity, contrasting with increased immune cell function

within more-developed TLS. From a mechanistic standpoint, the presence of these more developed or mTLS provides a pro-inflammatory environment to support direct interaction between T cells, B cells, and antigen presenting cells (such as dendritic cells; DCs) to enhance antitumor responses, with the presence of mTLS associated with higher sensitivity to immunotherapies [12]. Importantly, these findings provide a potential framework to stratify patients for immunotherapy trials based on the presence of TLS.

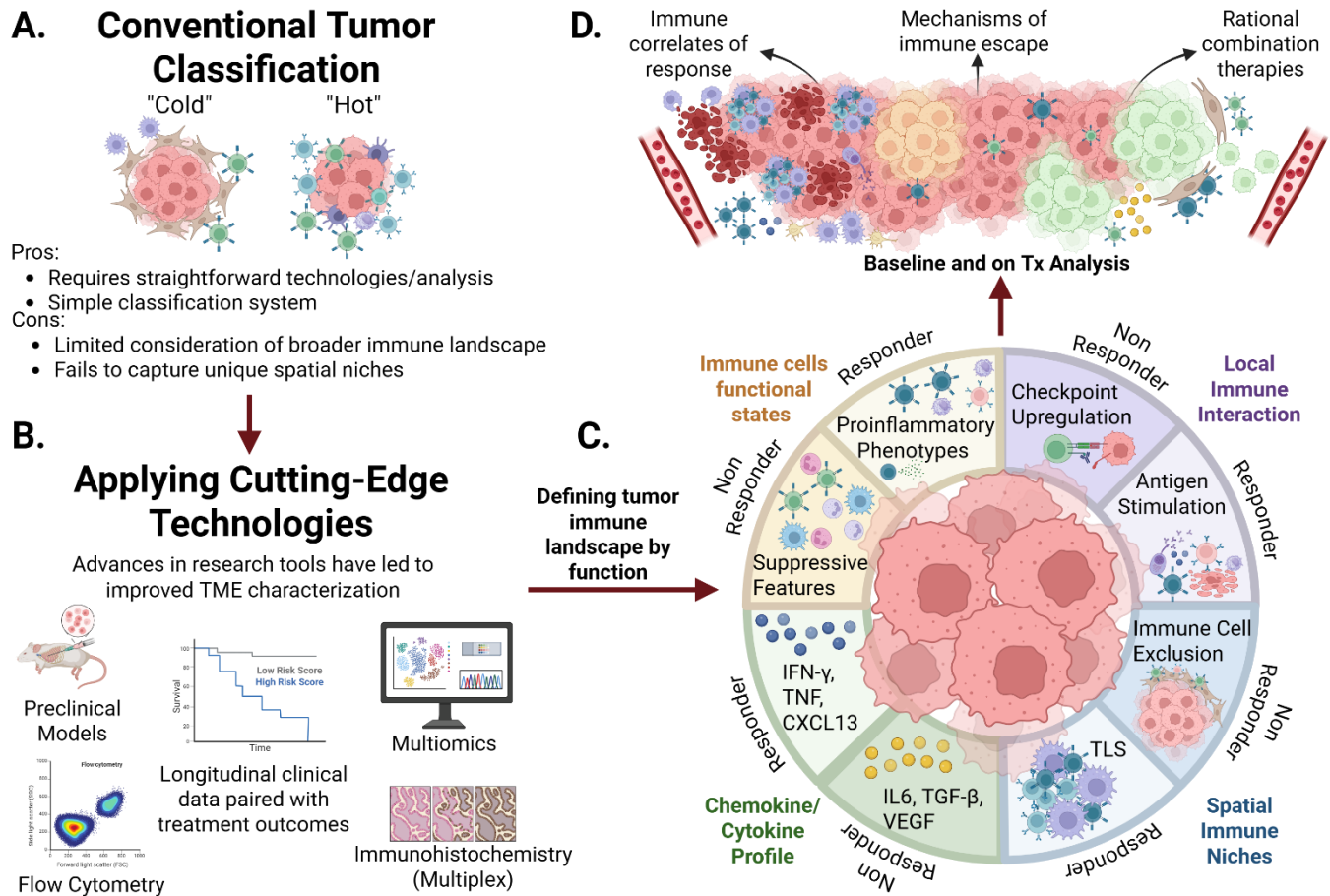


Figure 1. Reclassifying tumor immune landscapes through high resolution characterization. (A-D) Schematic overview of conventional and emerging approaches to improve the immune classification of the tumor microenvironment, as well as potential new knowledge that can be gained from defining immune heterogeneity with improved resolution. CXCL13: Chemokine (C-X-C Motif) Ligand 13; IFN- γ : Interferon Gamma; IL-6: Interleukin 6; TGF- β : Transforming Growth Factor Beta; TLS: Tertiary Lymphoid Structure; TME: Tumor Microenvironment; TNF: Tumor Necrosis Factor; Tx: Treatment; VEGF: Vascular Endothelial Growth Factor.

Beyond TLS formation and downstream functionality, multiple reports have identified unique immune cell subsets and/or spatially-defined characteristics that are associated with patient outcome and/or treatment response. Hammerl *et al.* [13] identified three discrete spatial immunophenotypes (inflamed, excluded, and ignored) in breast cancer, with the presence of specific immune cell subsets effectively predicting divergent anti-PD-1 responses. Responders exhibited enrichment of CLEC9A⁺ DCs, high T cell receptor (TCR) clonality, elevated expression of T cell co-inhibitory receptors, and necrosis markers, while non-responders demonstrated high CD163⁺ myeloid cell density, collagen-10 deposition, enhanced glycolysis, and activation of TGF- β /VEGF pathways. Another breast cancer study carried out longitudinal tumor

sampling during the course of immunotherapy, revealing the response to a PD-L1/CTLA-4 bispecific antibody in combination with a dual epitope blocking anti-HER2 bispecific antibody was associated with increased levels of CD8⁺ T cells, activated conventional type 1 and type 2 DCs, and reprogramming of macrophages towards an inflammatory state [14]. Looking more broadly at the impact of the tumor spatial microenvironment (TSME) across 12 different cancer types, Li *et al.* [15] identified multiple local cellular programs (LCP) and 13 recurrent cell-cell interacting niches, with each niche differentially impacting OS in patients. Stratifying patients across individual niches based on OS, the investigators found that Niche_4-like patients had the worst OS, whereas Niche_11-like patients had the longest OS, despite both niches being characterized by macrophage-related LCPs. Of note, Niche_4-associated macrophages were found in close proximity to tumor cells (M02 macrophages), whereas Niche_11 macrophages (M01 macrophages) were proximal to T cells. A secondary analysis compared proportions of M01 and M02, grouping macrophage states as G1 (M01^{hi}M02^{lo}), G2 (M01^{hi}M02^{hi}), G3 (M01^{lo}M02^{lo}), or G4 (M01^{lo}M02^{hi}) and overlaying these classifiers with survival outcomes. Across multiple indications (NSCLC, hepatocellular carcinoma, breast cancer), patients in G1 had better OS, whereas those categorized in G4 had reduced OS. Furthermore, analysis of pre-treatment samples from a cohort of melanoma patients treated with anti-PD-1 revealed that responders were enriched for M01 states (G1 and G2), whereas G4 trended towards increased abundance in non-responders, highlighting the distinct role of macrophages and their spatial distribution on prognosis and treatment outcomes.

Understanding cellular localization and tumor-host interactions can reveal key features related to the evolution of tumor metastasis, as well as mechanistic failure points of antitumor immune responses. Feng *et al.* [16] leveraged a multi-omic pipeline by combining paired whole genome and RNA sequencing samples, scRNA-seq, and high-resolution spatial transcriptomic data to interrogate tumor-host co-localization patterns in OC. Using the STARLETS framework (Spatiotemporal Tumor Clone Evolution Tracking System), they reported on bidirectional tumor-host interactions that can select for immune-evasive tumors, as well as the formation of tripartite structures containing SPP1⁺ macrophages, MMP11⁺ myofibroblastic cancer-associated fibroblasts (myCAFs), and epithelial cells, which formed at metastatic sites and in ascites. Targeting the SPP1-CD44 axis using a CD44 antagonist or a SPP1-neutralizing antibody reduced OC progression in preclinical studies and retrospective analysis of data from previously conducted clinical trials revealed that a higher abundance of SPP1⁺ macrophages was associated with responses to both oncolytic virotherapy and neoadjuvant poly(ADP-ribose) polymerase (PARP) inhibition, underscoring a potential for immune contexture to augment tumor sensitivity to treatment. In this regard, a recently published large-scale analysis of features associated with >10-year survival in OC patients highlighted that co-infiltration by diverse immune cell subsets including T cells, B cells, plasma cells, as well as CD68⁺PD-L1⁺ tumor-associated macrophages (TAMs) was increased in long-term survivors (LTS) when compared to short-term survivors (STS) [17]. Further, while immune infiltration was generally higher in epithelium-low compared to epithelium-high tumors, multiple immune cell subsets (including T cells, B cells, and plasma cells) were prognostically favorable in epithelium-high tumors and/or those with a C4/Differentiated molecular subtype,

suggesting that the epithelial content of tumors and not simply the overall immune cell abundance represents a key determinant of outcome.

Genetic alterations including tumor mutation burden (TMB) and mismatch repair (MMR) status significantly impact immune checkpoint inhibitor (ICI) responses, however, a study in colorectal cancer (CRC) patients suggests that the tumor immune composition is also a key hallmark of ICI response in CRC. Immune correlates associated with robust ICI response were cytotoxic T and NK cells, and antigen presenting CXCL10+ TAMs, contributing to induction of a local interferon-high immunophenotype [18]. The proximity to IFN-producing cells in turn stimulates expression of CD74 on antigen presenting cells, suggesting the presence of CD74 can potentially be used as a predictor of an ICI-responsive immune environment. In NSCLC, expression of the glucose transporter SLC2A1 on TAMs hindered CD8+ T cell infiltration and consequently conferred resistance towards anti-PD-L1 therapy [19], further highlighting the complexity of TAM functionality in the TME.

Collectively, emerging evidence from multiple studies highlights how distinct immune compositions (either present at baseline or resulting from treatment) can dramatically influence immunotherapy responses. To this point, Ma *et al.* [20] argue in their recent perspective article that understanding the global TME, described as cellular neighborhoods, not only can provide a more detailed and standardized approach for characterizing the TME, but also allows for development of actionable and spatially-targeted treatment approaches, based on spatial location, composition, and functional state of the cellular infiltrate, which aligns with our own views. While many of the mechanisms that differentiate responders from non-responders following immunotherapy may be (i) cancer-type specific, (ii) include multifaceted and complex phenotypic/functional cell types, (iii) differ in the availability of key cytokines and chemokines, or (iv) diverge in either the composition of immune niches or cellular interactions (all of which may change dynamically over the course of therapy; **Figure 1C**), an emerging consensus suggests a predominance of antitumor T cells, proinflammatory myeloid cells, localized structures harboring mature T and B cells (such as TLS), and a tumor-restraining chemokine and cytokine profile are associated with immunotherapy responsiveness. Importantly, while these immune features have been associated with improved outcomes and/or enhanced immunotherapy response, further validation across large patient cohorts will be required to distill these findings into robust and actionable biomarkers, particularly if they are to be implemented in real time to support clinical decision making. Furthermore, while beyond the scope of this immune landscape-focused perspective, non-immune components of the TME can also impact immunotherapy response. For example, two distinct subsets of cancer associated fibroblasts (CAFs), one found in early-stage (MYH11+ α SMA+ CAFs) and one in late-stage (FAP+ α SMA+ CAFs) tumors, were associated with ICI resistance in a significant subset of mTLS-positive NSCLC patients [21]. These CAF populations can restrict T cell extravasation, mediate immune exclusion, elicit T cell exhaustion, and increase the abundance of CD4+ T regulatory cells in the TME. As such, detailed analysis of the entire cellular landscape of tumors is required to uncover mechanisms of therapeutic success or failure.

For patients who fail to respond to current immunotherapies, it remains to be determined how best to leverage the local immune landscape and/or optimally reprogram infiltrating cells towards pro-inflammatory phenotypes. In our

recent publication, we explored magnifying the FR-B T cell + anti-PD-1 response through vaccine boosting, where improved tumor control was accompanied by increased accumulation of vaccine-boosted tumor-specific CD8⁺ T cells in the TME [4]. Alternatively, multiple groups have reported on 'armoring' approaches, wherein T cell therapies (eg. CAR T cells) are engineered to secrete proinflammatory cytokines to bolster the antitumor response [22–24].

4. Potential Opportunities to Exploit the Tumor Immune Landscape

There has been a concerted effort to better define predictive biomarkers of immunotherapy response, mechanistic drivers of immune escape, as well as strategies to rationally select combination immunotherapy approaches. Given inherent challenges related to intrinsic differences in the cellular composition of human and mouse TMEs [25] and (by extension) in effectively modeling clinical cancer treatments using preclinical models, analysis of serially collected patient samples at baseline and during immunotherapy treatment is likely to facilitate the development of improved 'reverse translational' models to effectively study clinical immunotherapy failure points using relevant lab-based assays. Importantly, such preclinical studies also provide an opportunity to carefully dissect and confirm the underlying mechanisms driving therapeutic response or resistance, strengthening the value of correlative observations linking unique tumor immune landscapes with response outcome, which should be interpreted with caution prior to definitive experimental evidence. Along with analysis of clinical samples using conventional assays, recent studies have demonstrated that incorporating advanced technologies to decipher spatial transcriptomic/proteomic signatures have the potential to uncover previously unappreciated immune subsets, novel immune cell contextures, as well as localized immune niches associated with productive antitumor responses [3,26,27]. Although the analysis of these large complex datasets can create fundamental challenges, multiple recent publications have successfully implemented the use of innovative AI and machine learning approaches to effectively integrate and analyze large single cell and spatial transcriptomic/proteomic datasets [28–32], with new analysis pipelines regularly emerging. While these new developments are likely to continue to provide novel insights related to the complex TME and inform previously unexplored therapeutic opportunities, such approaches require access to advanced technologies for generating the requisite input data, as well as the infrastructure and expertise needed to produce insightful conclusions. As such, these approaches may ultimately prove to be practical only in the setting of larger academically focused centers. Along with these technical limitations, patient welfare needs to be considered paramount, in addition to their willingness to consent to often invasive sample collection, particularly if done serially or if tumors are located in complex anatomical locations. This can in turn create additional challenges related to sampling bias, potential for heterogeneity in cellular composition or spatial organization within primary tumor lesions and when considering sampling from metastatic disease across anatomical locations, as well as variability in data generated across different platforms. Based on these current challenges, data collection and analysis pipelines may need to further mature before integration of larger 'omics' based data sets can be widely or practically applied to clinical cancer care,

although current rates of innovation will undoubtedly speed up this process. However, it is important to also carefully consider contexts where adding further complexity to ‘hot versus cold’ classifiers would be practical or necessary, particularly in instances where clinically actionable decisions will not be impacted by access to additional data.

Collectively, integrating in-depth TME analyses that decipher key immunological features (or lack thereof) will permit tailored design of immunotherapies for cancer patients, with on treatment analysis of the TME supporting further refinement to enhance response durability (**Figure 1D**). As current and emerging immunotherapies continue to advance clinically, refined approaches of defining actionable immune compositions, states, or topographies that better predict outcomes, can be therapeutically leveraged, or which serve as early identifiers of responder/non-responder phenotypes will serve as an important complement to improving the lives of patients diagnosed with cancer.

Abbreviations

The following abbreviations are used in this manuscript:

α SMA	Alpha Smooth Muscle Actin
Arg-1	Arginase 1
CAFs	Cancer-Associated Fibroblasts
CAR T cell	Chimeric Antigen Receptor T cell
CCL19	Chemokine (C-C Motif) Ligand 19
CCL21	Chemokine (C-C Motif) Ligand 21
CLEC9A	C-Type Lectin Domain Family 9 Member A
CRC	Colorectal Cancer
CTLA-4	Cytotoxic T-Lymphocyte Associated Protein 4
CXCL10	Chemokine (C-X-C Motif) Ligand 10
CXCL13	Chemokine (C-X-C Motif) Ligand 13
DCB	Durable Clinical Benefit
DR	Durable Response
FAP	Fibroblast Activation Protein
FR α	Folate Receptor Alpha
FR-B T cells	FR α -Targeted Bispecific T cell Engager-Secreting T cells
HER2	Human Epidermal Growth Factor Receptor 2
ICI	Immune Checkpoint Inhibitor
IFN- γ	Interferon Gamma
IL-6	Interleukin 6
LCP	Local Cellular Programs
LTS	Long-Term Survivors
MMR	Mismatch Repair
mTLS	Mature Tertiary Lymphoid Structure
myCAFs	Myofibroblastic Cancer-Associated Fibroblasts
MYH11	Myosin Heavy Chain 11
NSCLC	Non-Small Cell Lung Cancer
OC	Ovarian Cancer
PD	Progressive Disease
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Death Ligand 1

PARP	Poly(ADP-ribose) Polymerase
R	Responder
R+	Enhanced Responder
scRNA-seq	Single Cell RNA Sequencing
STS	Short-Term Survivors
STARLETS	Spatiotemporal Tumor Clone Evolution Tracking System
SLC2A1	Solute Carrier Family 2 Member 1
TAMs	Tumor Associated Macrophages
TCR	T Cell Receptor
TGF-β	Transforming Growth Factor Beta
TIL	Tumor Infiltrating Lymphocyte/T cell
TLS	Tertiary Lymphoid Structure
TMB	Tumor Mutational Burden
TME	Tumor Microenvironment
TNF	Tumor Necrosis Factor
TSME	Tumor Spatial Microenvironment
Tx	Treatment
VEGF	Vascular Endothelial Growth Factor.

Declarations

Ethics Statement

Not applicable.

Consent for Publication

Not applicable.

Availability of Data and Material

Not applicable.

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Competing Interests

JLC and AJRM are inventors on patents pertaining to the development and use of engineered CAR T cells, T cell engager-secreting T cells, and macrophages to treat cancer. AJRM is a scientific advisor for 9Bio Therapeutics. All authors disclose no additional conflicts of interest related to this manuscript.

Author Contributions

Conceptualization: JLC, NS, and AJRM.; Writing – Original Draft: JLC, NS, and AJRM.; Writing, Review, Editing, and Revision: JLC, NS, and AJRM.

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