

# Expanding the role of interventional oncology for advancing precision immunotherapy of solid tumors

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**Adoptive cell therapy with chimeric antigen receptors (CAR) T cells has proven effective for hematologic malignancies, but success in solid tumors has been impeded by poor intratumoral infiltration, exhaustion of effector cells from antigen burden, and an immunosuppressive tumor microenvironment. Results from recent clinical trials and preclinical studies lend promising evidence of locoregional approaches for CAR T cell delivery, priming the tumor microenvironment, and performing adjuvant therapies that sustain T cell activity. Interventional oncology is a subspecialty of interventional radiology where imaging guidance is used to perform percutaneous and catheter-directed procedures for localized, non-surgical therapy or interrogation of solid tumors. Interventional oncology provides unique synergies with immunotherapy, which has been well-studied to improve treatment efficacy while reducing toxicities associated with systemic treatment. Besides aiding in CAR T cell delivery, priming, or the stimulation of the tumor microenvironment to promote effector survival and function, interventional oncology can also aid in the monitoring of treatment response through selective, multiplex tumor sampling and catheter-based venous sampling. This review presents an overview of interventional oncology, its various procedures, and its potential for advancing CAR T cell immunotherapy of solid tumors.**

## INTRODUCTION

T lymphocytes (T cells) play a central role in cancer immunotherapy. T cells are capable of long-term antigen-specific cytotoxicity after activation by antigen-presenting cells. However, cancer cells develop multiple pathways to evade, modify, and suppress the immune system despite ongoing immunosurveillance and anti-tumor activity.<sup>1–3</sup> The development of immune checkpoint inhibitors (ICIs) has enabled efficacious immunotherapy of several types of cancer,<sup>4,5</sup> yet clinical evidence suggests that only a fraction of patients demonstrate a durable or complete response to treatment, presenting an opportunity for improvement in both treatment efficacy and the patient population who can benefit from this therapy.<sup>6</sup> Tumor-infiltrating lymphocytes

(TILs) are a major determinant of ICI efficacy.<sup>7,8</sup> Tumors with TILs (“hot tumors”) correlate with the expression of the PD-1/PD-L1 and are predictive of response to ICIs, while tumors without TILs (“cold tumors”) have a muted response.<sup>9–11</sup> Recent research has led to the stratification of the tumor microenvironment (TME) into three major subtypes: immune-inflamed, immune-excluded, and immune-desert phenotypes.<sup>12</sup> There is growing evidence that altering the TME by increasing TIL presence and function can improve cancer immunotherapy independent of disease characteristics or stage, with an increased emphasis on approaches that can yield this outcome.<sup>11,13</sup>

## ADOPTIVE CELL THERAPY

Adoptive cell therapy (ACT) is an innovative approach used to increase the number of TILs wherein the patients’ own immune cells are collected, cultured *ex vivo* with or without additional genetic manipulation or biological modification, expanded, and reinfused into the patient. Immune cells introduced into the patient through this technique exhibit high tumor-antigen specificity and anti-cancer potency. However, three challenges emerged that limited the broader utility of ACT using TILs: TILs must be extracted from tumor samples, the proliferation and function of TILs is heavily dependent on age and gender;<sup>14</sup> and the time between TIL extraction and administration often takes several weeks, all of which can be detrimental to patients with rapidly progressing cancers. These hurdles have impeded to the use of TILs in the broader clinical setting despite strong preliminary data in patients with several different cancers.<sup>15–17</sup>

## Engineered T cell-based therapies

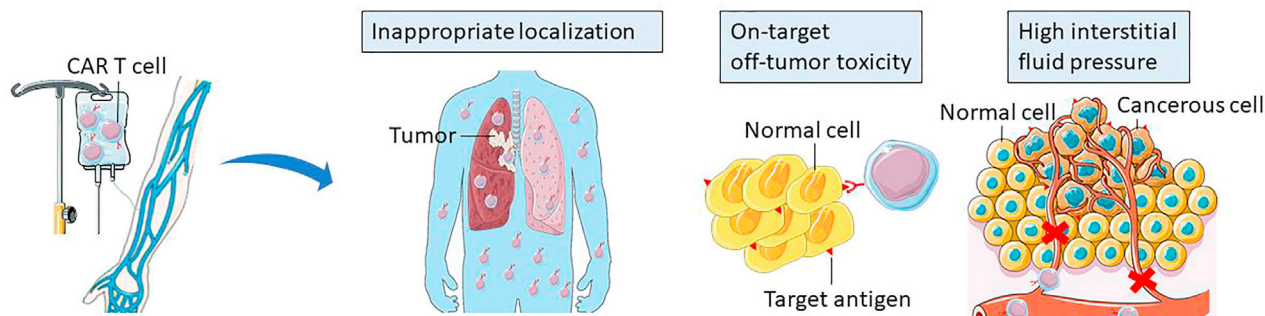
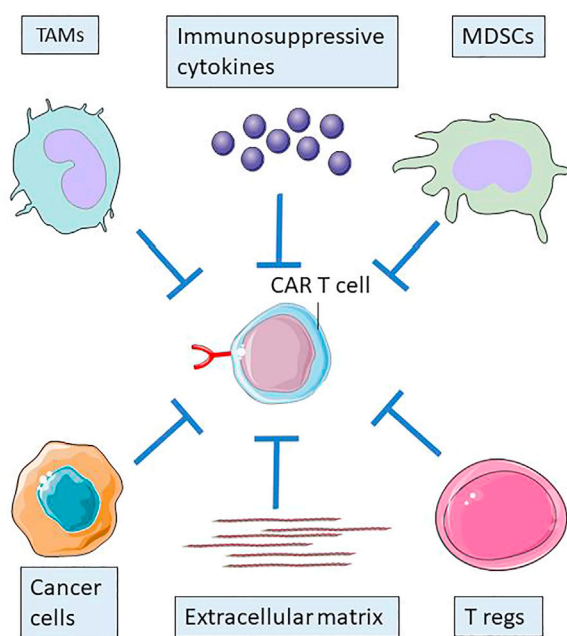
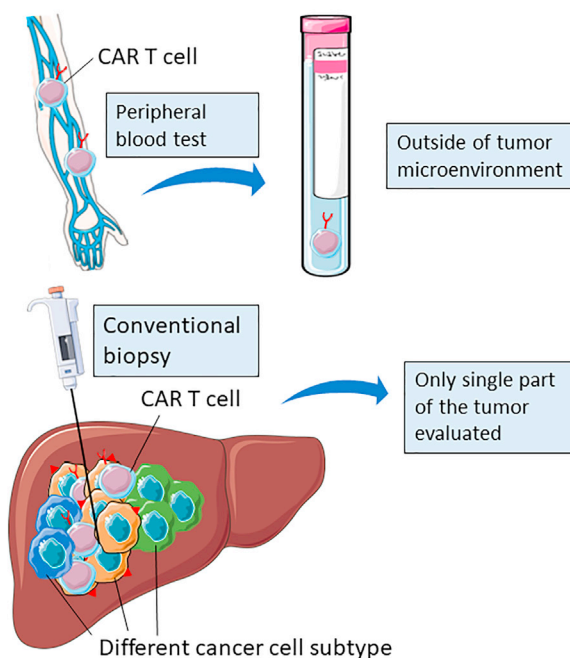
To overcome the drawbacks of ACT with TILs, two different approaches have been proposed using autologous genetically engineered immune cells, namely T cell receptor (TCR) and chimeric antigen receptor (CAR) T cell therapies. During TCR therapy, circulating T cells

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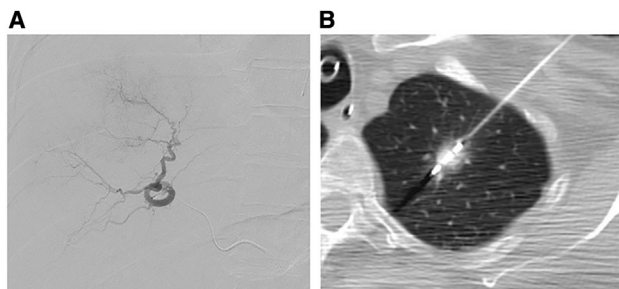


**A Systemic administration****B Immunosuppressive tumor microenvironment****C Monitoring CAR T-cell activity****Figure 1. Obstacles for CAR T cell application in solid tumors**

are collected and undergo TCR gene manipulation to augment recognition of the tumor antigen on the major histocompatibility complex (MHC).<sup>18</sup> TCR has the potential limitation of treatment failure due to both antigen loss or MHC expression loss, whereas only antigen loss can affect the CAR T cells.<sup>19,20</sup> CAR T cells represent an alternate non-MHC-dependent approach to cellular immunotherapy. The CAR comprises three sections, including an extracellular antigen recognition domain derived from monoclonal antibodies, the transmembrane domain, and the intracellular T cell activation domain.<sup>21</sup> This approach has demonstrated success in the treatment of several hematologic malignancies in patients, such as acute lymphocytic leukemia (ALL) and diffuse large B cell lymphoma.<sup>22,23</sup> CAR T cells targeting CD19 expressed in B cells have demonstrated very high objective response rates in patients with refractory ALL, with sustained responses in the majority of patients.

**Current barriers to the effective CAR T treatment of solid tumors**

While research to extend the application of CAR T cells to solid tumors is currently ongoing, there are challenges that have limited its efficacy when compared with hematologic malignancies. Obstacles include T cell localization, infiltration, systemic toxicity, insufficient activation due to immunosuppressive TME, and the lack of suitable tools for monitoring CAR T cell activity. Tumor-specific localization and infiltration have been identified as major impediments for the application of CAR T cell therapy in solid tumors (Figure 1A). Compared with hematological malignancies, CAR T cells need to home in to the tumor site and penetrate the tumor mass. Solid tumors secrete chemokines that can interfere with T cell localization and infiltration,<sup>24</sup> which are further exacerbated by the TME having a disorganized extracellular matrix (ECM), immature or dysfunctional blood vessels, and high interstitial fluid pressure (IFP).<sup>25,26</sup>



**Figure 2. Examples of minimally invasive, image-guided interventional oncology procedures performed with catheter-directed and percutaneous approaches**

(A) Arteriogram showing selective injection of Y90 microspheres in the anterior branch of the right hepatic artery. (B) Axial non-enhanced CT showing a microwave ablation of an apical left upper lobe nodule.

Patients undergoing ICI and CAR T cell therapies can experience systemic toxicities due to intravenous treatment delivery.<sup>27,28</sup> Clinical benefits and systemic toxicity are usually in conflict and may limit the maximum therapeutic dose a patient can receive. Immunosuppressive TME can impede CAR T cell activity in solid tumors (Figure 1B). The presence of other immune cells such as myeloid-derived suppressor cells, regulatory T cells (T regs), and tumor-associated macrophages (TAMs) can blunt CAR T cell effectiveness through multifactorial pathways.<sup>29</sup> Monitoring the persistent activity of CAR T cells is also essential for evaluation of treatment response and making adjustments to the dosing regimen. Flow cytometry and local tumor biopsies have been used as tools for tracking CAR T cells.<sup>30</sup> However, these approaches may provide skewed results, as blood samples from systemic circulation or tumor samples from a central core may not represent actual CAR T cell levels or the activity within heterogeneous solid tumors (Figure 1C).<sup>31</sup>

Combination or adjuvant strategies that can alleviate these hurdles to augment efficacy of CAR T cells are therefore considered to be crucial for the success of solid tumor immunotherapy. Preclinical studies using CAR T cell therapy with adjuvant chemotherapy have demonstrated potential synergies through increased calreticulin and chemokine expression, augmented tumor antigen exposure,<sup>32,33</sup> improved dendritic cell maturation and activation,<sup>34</sup> and reduced autoimmunity to CAR T cells.<sup>35</sup> Radiotherapy in combination with CAR T cells has also shown promise in preclinical studies. Radiotherapy is known to enhance MHC expression on tumor cells,<sup>36</sup> induce chemokine release to help trafficking,<sup>37</sup> and help dendritic cell maturation,<sup>38</sup> factors that can aid CAR T cell infiltration and function. However, radiation can cause the death of T cells due to the inherent radiation sensitivity of lymphocytes.<sup>39,40</sup> Finally, adjuvant use of ICIs can also improve CAR T cell therapy in solid tumors. Both preclinical studies and phase I clinical trials revealed that ICIs can improve CAR T cell activity.<sup>41–46</sup> While these combination therapy approaches are promising, barriers to effective treatment such as tumor heterogeneity, limited life span of functional CAR

T cells, morbidity from multiple therapeutic agents, and on-target/off-tumor toxicity remain major challenges. We propose that interventional oncology provides a novel procedural approach to tackle several of these challenges.

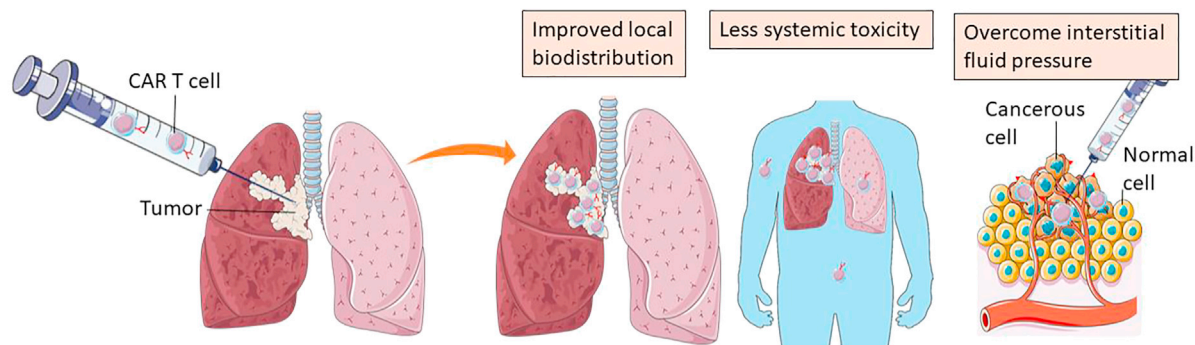
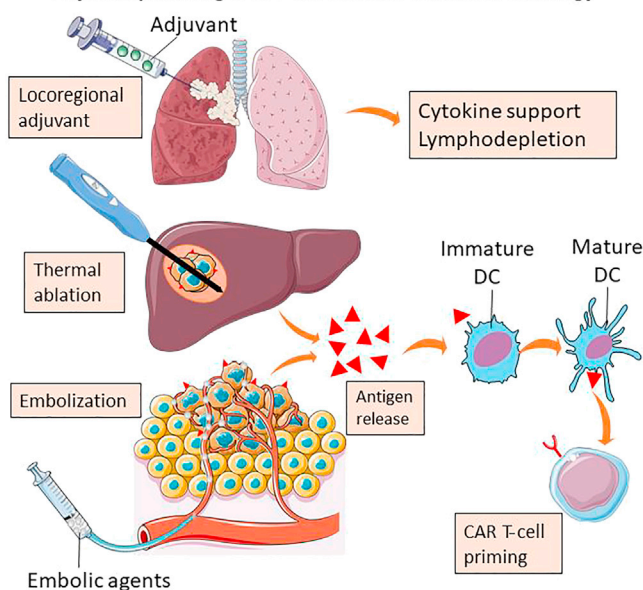
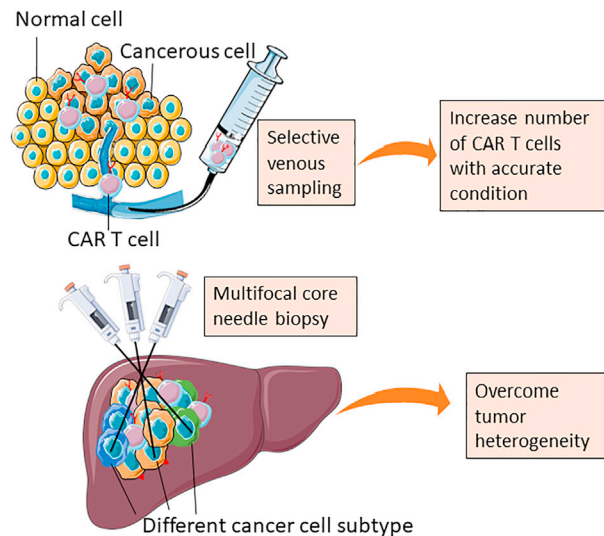
## INTERVENTIONAL ONCOLOGY

Interventional oncology is a sub-discipline of interventional radiology (IR) that utilizes imaging guidance to perform minimally invasive, non-surgical procedures to treat patients with cancer.<sup>47–49</sup> The interventions are performed using imaging modalities such as X-ray fluoroscopy, ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI), which support intraprocedural imaging and prognostication of outcomes. Interventional oncology procedures can be broadly classified into two categories based on the approach used to gain access to the anatomical location of interest: (1) vascular procedures (V-IO - Vascular Interventional Oncology), where blood vessels or lymph ducts are used to navigate catheters to the tumor, and (2) percutaneous procedures (P-IO - Percutaneous Interventional Oncology), where cross-sectional imaging is used to guide percutaneous needle placement into the tumor.

## DELIVERY APPROACHES WITH INTERVENTIONAL ONCOLOGY

### Vascular interventional oncology

During V-IO, a catheter is advanced under fluoroscopy to the primary artery feeding tumors, allowing for the selective and high-dose delivery of therapeutic material. Intraarterial injection of a cytotoxic drug or selective internal radiation therapy are image-guided approaches for the local delivery of chemotherapy/radiotherapy with the capacity to achieve very high local dosages.<sup>50–52</sup> Embolization is a method of deliberately occluding a blood vessel with embolic materials. Several embolic materials are available for V-IO, such as gelatin sponges, microspheres, metallic coils, and liquid agents.<sup>53</sup> The embolic materials can be classified as temporary (such as gelatin sponges) or permanent (such as metallic coils), and the choice of embolic material depends on the target vessel, location, and clinical objective. As for tumors, occluding the feeding arteries causes the tumor to become ischemic, infarcted, or necrotic, resulting in tumor shrinkage or a reduction of tumor growth.<sup>54–59</sup> In addition, embolization can be effective for tumors with active bleeding<sup>60–62</sup> or a reduction of intraoperative blood loss.<sup>63–66</sup> The combined transcatheter delivery of both chemotherapy and embolization to hypervascular tumors is called transarterial chemoembolization (TACE). TACE has been the first-line treatment for hepatocellular carcinoma (HCC) patients with an intermediate stage (Barcelona Clinic Liver Cancer Stage B).<sup>51,55,67</sup> As another type of V-IO treatment, selective internal radiation therapy (SIRT) is a developing modality for the treatment of patients with unresectable liver tumors such as HCC, colorectal liver metastasis, and neuroendocrine liver metastases (Figure 2A).<sup>68–70</sup> The procedure consists of a transcatheter injection of radioactive particles through the hepatic artery. Moreover, the V-IO technique can also assist in diagnosis; liquid biopsy with selective venous sampling using a catheter-based approach has been reported in patients.<sup>71</sup>

**A Locoregional administration by Interventional Oncology****B Adjuvant/Priming CAR T cell via Interventional Oncology****C Monitoring CAR T cell by Interventional Oncology**

**Figure 3. Interventional oncology solutions for challenges in solid tumor immunotherapy**

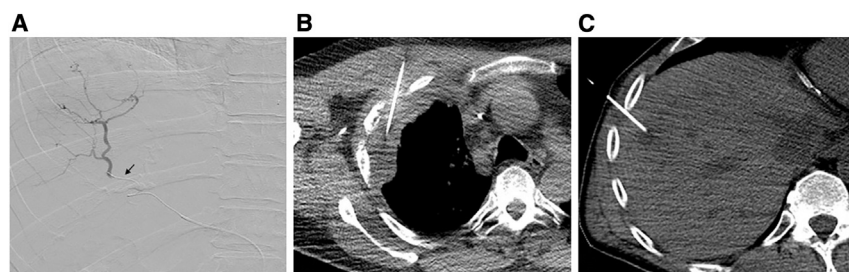
**Percutaneous interventional oncology**

Under image guidance, physicians can accurately place a needle into a tumor to perform diagnostic and therapeutic interventions. Percutaneous biopsy is an example of a diagnostic intervention that is used to collect specimens from the tumor for pathology and molecular interrogation.<sup>72</sup> Ablation is an example of a therapeutic interventional procedure (Figure 2B) where percutaneous probes are used to deliver non-ionizing energy or other therapeutic agents to destroy the tumor *in situ* without surgical resection. Ablation is widely used for the treatment of malignancies in liver, kidney, bone, and lung.<sup>73–78</sup> Ablation techniques can be divided into two categories based on biophysical principles mediating the injury to the tumor, including chemical (ethanol or acetic acid) and non-ionizing energy-based ablation (thermal ablation and non-thermal ablation).<sup>79</sup> This review will focus on the latter technique, which includes radiofrequency ablation (RFA), micro-

wave ablation (MWA), cryotherapy (Cryo), and irreversible electroporation (IRE).

**Locoregional CAR T therapy**

Delivering immunotherapy directly into the tumor at the highest concentration may overcome problems with localization, infiltration, and systemic toxicity (Figure 3A). Over the past few decades, intraarterial chemotherapy has transformed the care of cancer patients using a minimally invasive image-guided approach. For example, intraarterial chemotherapy via the hepatic artery for liver colorectal metastasis has been shown to significantly improve the survival rate of patients compared with systemic therapy.<sup>80–82</sup> This approach overcomes the disadvantages of intravenous systemic infusions, including systemic toxicity, first-pass metabolism, and non-targeted delivery. Interventional oncology procedures can therefore aid the efficacy of CAR T cell therapy by leveraging direct local delivery of the therapeutic



**Figure 4. Image-guided locoregional infusion of CAR T cells**

(A) Arteriogram showing selective intraarterial infusion of CAR T cells through a 2.4 Fr microcatheter (black arrow) placed in the posterior branch of the right hepatic artery. (B) Axial non-enhanced CT showing intratumoral infusion of CAR T cells through a percutaneously placed 18 G needle in a right upper lobe pleural mesothelioma. (C) Direct infusion of CAR T cells in a 12 mm liver metastasis in segment VIII, shown here on non-enhanced axial CT.

(Figures 4A–4C). Locoregional delivery can have two specific advantages, namely (1) increasing delivery for greater local expansion and overcoming the issue of limited trafficking and (2) reducing the potential for on-target/off-tumor toxicity. Locoregional infusion of CAR T cells may also reduce on-target/off-tumor off-target toxicities. While severe colitis was observed via systemic infusion of CAR T cells targeting carcinoembryonic antigen (CEA), intraarterial infusion of TCR-modified T cells expressing anti-CEA TCR eliminated the incidence of grade 4 or 5 adverse events.<sup>83,84</sup> Locoregional infusion potentially helps T cell trafficking. Direct infusion as well as transarterial infusion have been applied to metastatic liver tumors and metastatic breast cancer with evidence of intratumoral CAR T cells.<sup>84–86</sup> Katz et al. showed an intratumoral presence of CAR T cells in patients 12 weeks after completing treatment for colorectal liver metastases.<sup>84</sup> In addition, locoregional-infused CAR-T cells may expand locally and traffic safely to other tumor sites to promote further immune responses.<sup>87,88</sup> Locoregional infusion presents several advantages, including increased hydrodynamic forces, improved T cell trafficking, and limited CAR T cell toxicity, by lowering the infused volume.<sup>87</sup> Hydrodynamic force via transarterial infusion can overcome an elevated IFP that can inhibit CAR T cell migration through dense tumor stroma.<sup>26</sup> Systemic infusion, however, theoretically cannot exceed intravascular pressure, which is typically lower than intratumoral IFP. Locoregional approaches for CAR T cell delivery have shown promising initial results.<sup>89–92</sup> Vitanza et al. recently reported a clinical study with locoregional infusion of HER2-specific CAR T cells for a central nervous system (CNS) tumor.<sup>93</sup> They reported that administration of CAR T cells through a CNS catheter was feasible and tolerable. Therefore, randomized trials that compare systemic and locoregional infusion have to be performed to understand underlying mechanisms and identify comparative efficacy.

#### PRIMING THE TME FOR CAR T CELL ENTRY

Interventional oncology can deliver agents that can increase the infiltration or efficacy of systemically delivered CAR T cell in tumors. CAR T cell infiltration into solid tumors can be impeded from the lack of appropriate chemokines and other biological mediators. Therefore, priming the TME prior to infusion of CAR T cells can be another strategy to improve treatment outcomes (Figure 3B). Tumor ablation, regardless of the specific technique used, induces robust chemokine release and stimulates the localized inflammatory response and immune cell activation.<sup>94–102</sup> Tumor ablation has also been shown to exhibit synergistic effects when combined with ICIs. Waitz et al. reported that combining Cryo with anti-CTLA-4 therapy

induces anti-tumor immunity.<sup>94</sup> Also, Zhao et al. reported that IRE has the potential to reverse resistance to immune checkpoint blockades.<sup>101</sup> Likewise, TACE has been shown to promote immunogenic cell death and induce tumor-antigen-specific responses.<sup>103,104</sup> As another V-IO treatment, SIRT may induce more immune cell infiltration when compared with TACE or surgery.<sup>105</sup>

The combination of these interventional oncology procedures, neoadjuvant to CAR T cell, has not been investigated but presents several interesting synergies. Oncolytic virus (OV) is one of the other options for priming CAR T cell therapy. While systemic delivery of OV has demonstrated limited success,<sup>106</sup> intratumoral delivery has advantages regarding lower systemic toxicity, less probability of inactivation by immune cells, and reduction of the administered viral load.<sup>107</sup> Similar to ablation, the role of interventional oncology in OV delivery is not just injecting but also appropriate targeting with image modalities before and during the procedure.<sup>108</sup> Another advantage of image-guided needle delivery is the possibility of monitoring targeted lesions and the ability to profile tumors by taking pretreatment samples. As for a larger tumor, a multipronged injection needle is available to reduce the number of injections in clinical studies.<sup>109–111</sup> While injection procedures through needles have been the most investigated,<sup>112</sup> several studies have provided the rationale for intraarterial regional delivery of OV.<sup>113–115</sup> Combination of OV with CAR T cells showed promising results in preclinical studies,<sup>116–118</sup> and one clinical trial is ongoing (ClinicalTrials.gov: NCT03740256). Similar to OV, interventional oncology can help prime TME for CAR T cells in many ways. Studies for combinational interventional oncology procedures with CAR T cells should be proposed.

#### ADJUVANT STRATEGIES FOR CAR T CELLS VIA INTERVENTIONAL ONCOLOGY TECHNIQUES

The efficacy of CAR T cells is often limited by immunosuppressive TMEs from the upregulation of PD-L1 and the presence of T regs, as well as other factors.<sup>24,119</sup> This highlights the need for additional adjuvant strategies to support CAR T cells (Figure 3B). In fact, inadequate activation of tumor-specific CAR T cells has been reported in several clinical trials in solid tumors.<sup>42,120</sup> Cytokine support is important for the proper activation of CAR T cells, as both interleukin (IL)-12 and IL-18 have been shown to enhance anti-tumor responses in preclinical models of solid tumors.<sup>121–123</sup> However, the systemic infusion of cytokines has the potential to result in severe adverse events, as IL-12 systemic infusion resulted in severe toxicity.<sup>124</sup> Historically, transarterial immunotherapy with interferon-gamma (IFN $\gamma$ ) and

IL-2 followed by transarterial chemotherapy has been reported for HCC and unresectable colorectal liver metastasis in the 1990s.<sup>125,126</sup> More recently, granulocyte macrophage colony-stimulating factor (GM-CSF) injection via a hepatic artery followed by chemoembolization was performed for patients with liver metastases of colorectal cancer and uveal melanoma.<sup>127-129</sup> In these studies, GM-CSF was administered intraarterially to enhance local anti-tumor immune responses and reduce systemic side effects. Therefore, locoregional cytokine injections using interventional oncology techniques may be better tolerated in patients and may enhance anti-tumor responses during CAR T cell therapy.

Lymphodepletion was used prior to adoptive TIL transfer for the treatment of metastatic melanoma, leading to enhanced TIL homing and anti-tumor effects.<sup>130</sup> The use of a regimen containing fludarabine and cyclophosphamide improved the overall response rate compared with patients without preconditioning, and this regimen has been subsequently adopted as part of the therapeutic strategy.<sup>131</sup> Lymphodepletion prior to CAR T cell therapy also increased CAR T cell expansion and persistence, resulting in improved clinical outcomes.<sup>132-134</sup> However, fludarabine is still potentially toxic for patients with renal failure or who are highly pretreated.<sup>135</sup> Intraarterial chemotherapy, however, can increase the exposure time and the local concentrations of chemo-agents while reducing systemic toxicity.<sup>136-140</sup> Therefore, locoregional chemotherapy theoretically provides locoregional lymphodepletion with less toxicity, resulting in good CAR T cell response with patients, especially those who are sensitive to fludarabine. Regional adjuvant cytokine delivery and lymphodepletion potentially activate CAR T cells and inactivate immunosuppressive cells. However, it is unclear whether it would recapitulate the homeostatic cytokine production or the innate immune activation due to damage to the gut epithelium. The comparison studies against systemic infusion also have not been performed yet. In addition, optimization of local drug delivery (dose, sustained release formulation, etc.) will be needed.

#### MONITORING T CELL ACTIVITY

CAR T cells are designed to recognize the target antigen, become activated, proliferate, and attack tumors after infusion into patients.<sup>141</sup> Monitoring these steps is important for understanding the biological mechanisms that determine or influence *in vivo* efficacy.<sup>141,142</sup> In some clinical trials, the sustained activity of the CAR T cell population is also considered an important predictor of anti-tumor efficacy.<sup>143,144</sup> CAR T cell activity is currently monitored by detecting CAR T cells in peripheral venous blood sampled from upper limbs and in biopsy samples from local tumor sites.<sup>145</sup> These clinical samples can be processed and analyzed with cytokine profile, flow cytometry, qPCR, or RNA sequencing (RNA-seq).<sup>22,30,145</sup> These assays have potential limitations, as blood samples from systemic circulation or tumor cores may not properly represent the CAR T cell presence or activity in heterogeneous solid tumors. In addition to molecular biological assays, immunohistochemistry of tissue samples is commonly performed to understand the status of CAR T cells within the TME.<sup>86,146</sup> The immunohistochemistry (IHC) method is commonly used to prove

actual infiltration into solid tumors, but tumor tissue with heterogeneity does not provide accurate information about the temporal and spatial distribution of immune cells.<sup>147</sup> Interventional oncology techniques could solve these limitations. Using V-IO, a catheter can be advanced close to the tumor site through the vessels. Selective venous sampling has the possibility of improving the diagnostic accuracy of liquid biopsy, as recently reported.<sup>71</sup> Likewise, this method could be applied to collect samples to analyze CAR T cell activity with more CAR T cells and a more accurate condition than peripheral blood sampling. Using P-IO, physicians can perform multiple targeted biopsies. Conventional biopsies from the tumor core are affected by not only tumor heterogeneity but also necrotic avascular tumor tissue, which is unlikely to contain active immune cells. Biological hot spots in the tumor, however, can be peripheral, so multiple sampling at different sites should be appropriate.<sup>49</sup> Multiple biopsies potentially increase the risk of complication, but interventional oncology physicians are experienced in evaluating anatomical accessibility, understanding the surrounding structure, and avoiding complications.<sup>148</sup> Therefore, tumor biopsies can improve diagnostic accuracy with high information content and ease the negative effect of intertumoral heterogeneity. Together, V-IO and P-IO have the potential to provide more accurate and precise information in a minimally invasive manner.

#### CONCLUSIONS

Immunotherapy has grown to play a central role in oncology. Interventional oncology is an emerging modality for treating patients with cancer in a minimally invasive manner with unique features that can advance the utility and success of adoptive cell immunotherapy in solid tumors. This concept provides intriguing research opportunities with potential beneficial impacts on patients with what were historically considered to be incurable cancers. While preclinical data for combinational therapy using these two approaches appear promising, rigorous assessment of effectiveness with well-designed clinical trials must be performed to validate interventional oncology to advance CAR T cell immunotherapy of solid tumors.

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#### AUTHOR CONTRIBUTIONS

Conceptualization, G.S., P.S.A., and S.B.S; investigation, Y.K. and M.G.; resources, Y.K., M.G., and W.C.; data curation, Y.K. and M.G.; writing – original draft preparation, G.S. and Y.K.; writing – review & editing, G.S., P.S.A., W.C., M.G., and S.B.S; supervision, G.S.; project administration, G.S.; funding acquisition, G.S., P.S.A., and S.B.S. All authors have read and agreed to the published version of the manuscript.

#### DECLARATION OF INTERESTS

P.S.A. has received research funding from ATARA Biotherapeutics, has served on the Scientific Advisory Board or as consultant to ATARA Biotherapeutics, Bayer, Carisma Therapeutics, Imugene, ImmPACT Bio, and Takeda Therapeutics, and has patents, royalties, and intellectual property on mesothelin-targeted CARs and T cell therapies, which have been licensed to ATARA Biotherapeutics, as well as methods for the detection of cancer cells using virus, and pending patent applications on T cell therapies. S.B.S. is a consultant to BTG, Johnson & Johnson, XACT, Adeqro, and Medtronic. S.B.S. has funding support from GE Healthcare and Angiodynamics and holds stock in Aperture Medical. G.S. has received consulting fees from Farapulse and Intuitive Surgical and holds stock options in Aperture Medical. All other authors declare no competing interests. Memorial Sloan Kettering Cancer Center (MSK) has licensed intellectual property related to mesothelin-targeted CARs and T cell therapies to ATARA Biotherapeutics and has associated financial interests.

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