Journal for ImmunoTherapy of Cancer

Priorities for local immunotherapy research and drug development

James M Isaacs,[1] Jason Luke[2]

To cite: Isaacs JM, Luke J. Priorities for local immunotherapy research and drug development. *Journal for ImmunoTherapy of Cancer* 2026;**14**:e014222. doi:10.1136/jitc-2025-014222

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/jitc-2025-014222).

Accepted 31 January 2026

Check for updates

© Author(s) (or their employer(s)) 2026. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ Group.

[1]Department of Hematology and Medical Oncology, Cleveland Clinic, Cleveland, Ohio, USA
[2]Strand Therapeutics, Boston, Massachusetts, USA

Correspondence to
Dr James M Isaacs;
isaacsj3@ccf.org

ABSTRACT

Local immunotherapy comprises broad classes of therapeutics that aim to trigger a robust "in situ" immune response that can ultimately generate systemic antitumor immunity. These agents are appealing as resistance to standard immune checkpoint inhibitors has been linked to a lack of baseline immune activity or immune suppressive elements in the tumor microenvironment. By administering agents directly to the tumor microenvironment, local immune therapies can both stimulate immune response and attempt to "reprogram" or subvert the effects of immune suppressive cell populations. Proof of concept for the benefit of local immune therapy has been demonstrated by several Food and Drug Administration-approved therapies.

A "Summit on Intralesional Immunotherapy" was held in September 2024, which comprised lectures and discussion from an international panel of experts on local immune therapy. In this consensus paper, we will discuss unique considerations for local immunotherapy development across the continuum from pre-clinical and early-stage investigation through registration intent clinical trials.

Early phase trials offer an opportunity to gain understanding of the biologic activity of candidate therapies and determine optimal dosing schedules. For local immunotherapies, it is most informative to measure the direct effect of the therapy in the tumor microenvironment at both injected and non-injected tumor sites. Carefully planned pharmacodynamic endpoints using on-treatment biopsies and novel imaging strategies to track immune cell activity will maximize the insights from early phase trials. For promising local therapies, selecting the proper patient population and treatment setting are critical. In order to intervene before the tumor microenvironment has reached a fixed immune suppressive state, local immunotherapies may best be suited as part of neoadjuvant or frontline metastatic therapy regimens. We also highlight several specific classes of local immunotherapy under investigation including oncolytic viruses, radiation, messenger RNA, Toll-like receptor agonists, stimulator of interferon gene agonists, CD40 agonists and cytokines.

Novel local therapies currently being investigated are poised to expand the field and show promising activity in generating systemic antitumor immunity. Thoughtful trial design in both early stage as well as registration intent settings will accelerate the advancement of this field.

INTRODUCTION

Treatment with checkpoint inhibitors (ICIs) has substantially improved outcomes for multiple tumor types. Yet only a portion of patients will respond to standard immune therapies. Translational biology suggests that ICI are most effective when there is a pre-existing T cell-mediated immune response in the tumor microenvironment.[1] Many tumors lack immune infiltration or have immunosuppressive cell populations (myeloid-derived suppressor cells (MDSCs), fibroblasts) and soluble factors (TGFb, interleukin-6 (IL6)) that limit productive antitumor immunity.[2] Thus, a major focus of investigational therapeutics has been to "re-program" the tumor microenvironment to prime and activate antitumor responses. Local or intratumoral therapies offer several advantages by delivering sufficient local drug concentration while minimizing systemic toxicity. This approach has demonstrated clinical benefit in controlling unresectable or regionally advanced cancers and facilitated regulatory drug approval.[3] Recent enthusiasm centers around the use of potent local therapies to generate systemic antitumor responses, with the aim of controlling disseminated, metastatic cancers.[4] Additionally, local therapies are being explored in the neoadjuvant setting for high-risk resected tumors to reduce the risk of local and distant recurrences.[5]

Local immune therapies comprise diverse classes of therapeutics with multiple agents Food and Drug Administration (FDA)-approved and currently in clinical use. This includes intravesical agents for non-muscle invasive bladder cancer, imiquimod for basal cell carcinoma and the oncolytic virus talimogene laherparepvec (TVEC) for local-regionally advanced melanoma.[6] Novel investigational local therapies act at multiple phases of the cancer immune response cycle. For example, oncolytic viruses or radiation produce immunogenic cell death, leading to the release of damage-associated molecular patterns. Toll-like receptor (TLR) and stimulator of interferon gene (STING) agonists activate innate immune pathways by mimicking pathogens. Other local therapies include antibodies or cytokines that

can directly stimulate immune cells. Ultimately local therapies seek to induce a response that leads to tumor cell killing and ideally augments the presentation of tumor-associated antigens to T cells to generate adaptive immune control.

Advancements in the characterization of the cell types and pathways involved in a productive antitumor response have led to an era of numerous candidate intratumoral agents. Yet the translation of scientific insights into clinically effective therapies has proven challenging. Defining dose-response relationships in early phase trials is guided by pharmacokinetic (PK) and pharmacodynamic (PD) analysis. These endpoints are typically obtained from the peripheral blood and may not accurately reflect the relevant activity of a local therapy in the tumor microenvironment. For promising local therapies that advance out of the early phase trial setting, considerable debate still centers around which disease setting they are best used (ie, metastatic disease vs as neoadjuvant therapy).

HISTORICAL CONTEXT

Local therapies have been studied in multiple tumor types for several decades. For melanoma, local injection of BCG, granulocyte-macrophage colony-stimulating factor (GM-CSF) or IL2 was studied in several early phase trials, demonstrating clear biologic activity (infiltration and activation of immune cells in on-treatment biopsies) and clinical responses in injected lesions.[7–9] However, responses were limited in distant non-injected tumors, and these early therapies have not been shown to improve clinical outcomes in randomized trials.

An oncolytic virus, TVEC, emerged as the first FDA-approved intratumoral therapy for melanoma. When injected into the tumor, oncolytic viruses have preferential replication in cancer cells, leading to oncolysis and immunogenic cell death. This innate "antiviral" response aims to bridge to effective adaptive antitumoral T cell activity. Advances in bioengineering of oncolytic viruses have led to modifications that can increase the antitumor potency. TVEC is selected from a virulent clinical strain of Herpes virus and includes an ICP 34.5 gene deletion which limits the virus's ability to replicate in non-tumor cells. Additionally, GM-CSF is inserted into the viral vector to serve as an immune stimulatory payload. Preclinical murine models evaluating TVEC showed enhanced tumor cell killing and infiltration of T cells at the site of tumor injection, along with responses in non-injected tumors.[10] This was translated to early phase clinical trials showing biologic activity with viral replication, GM-CSF expression, and T cell infiltration in post-treatment tumor biopsies.[11] Importantly clinical activity was demonstrated in the early phase trials showing significant injected and non-injected treatment responses in melanoma.[12] In a phase III trial evaluating patients with unresectable melanoma, TVEC showed superior durable response (response lasting >6 months) compared with GM-CSF alone.[3] Based on this data, TVEC was FDA approved for treatment of unresectable melanoma with cutaneous, subcutaneous or nodal lesions.

TVEC was a landmark approval, demonstrating the clinical benefit of oncolytic viruses and local immune therapy. TVEC has a clear role in the treatment of regionally advanced melanoma, but development in more advanced melanoma disease settings highlighted that the use of intratumoral therapies can be context specific. Although generating responses in non-target lesions, these responses are mainly limited to subcutaneous and nodal metastasis, with limited activity for distant visceral disease sites (liver, lung, and brain).[13] As a newer standard of care emerged with anti-programmed cell death protein-1 (PD-1), the added benefit of TVEC for the treatment of metastatic melanoma with visceral sites of disease was not seen. This was despite an initial single-arm phase II trial suggesting that there may be synergistic activity when TVEC is combined with anti-PD-1.[14] A phase III trial did not show improvement with the combination of TVEC+pembrolizumab compared with pembrolizumab monotherapy in the frontline setting.[15] Additionally, TVEC did not provide clinical benefit for distant visceral metastasis in the anti-PD-1 refractory setting.[16]

Therapies under investigation offer promise of novel methods to locally target the tumor immune microenvironment. Mechanistic enhancements for some Intratumoral (IT) therapies may increase potency and allow for effectiveness in the metastatic disease setting. Other therapies may provide clinical value in specific patient populations or disease settings. Below we will highlight priorities in early phase drug development for local therapies and discuss considerations for the advancement of these therapies to regulatory approval(online supplemental file 1). We will also review recent examples of the development of multiple novel classes of local/intratumoral immunotherapies.

EARLY PHASE TRIALS: BIOLOGICAL ACTIVITY

First-in-human agents are typically developed in the metastatic, treatment-refractory setting to determine the initial safety profile and determine an optimal dose. For intratumoral therapies and immune therapy in general, the optimal dose may not be the maximum tolerated dose. In this setting PK and PD measurements are critical to the initial evaluation of a new therapy. Data from these measurements can inform biologic activity at each dose level, which ideally would correlate with more robust clinical outcomes in future trials (ie, response rate, progression-free survival (PFS), overall survival (OS)).

Pharmacokinetic measurements

PK assessment of local therapies is complex as PK is usually assessed through measurement of drug concentration in the peripheral blood. For local therapies, the aim is often to secure an optimal drug concentration in the tumor microenvironment or draining lymph node. Escalating peripheral PK values may miss this aim by reflecting a lack

of retention at the tumor site. Alternatively, agents that are truly staying in the tumor as intended may have limited peripheral PK concentrations as the dose is increased. Fine needle aspiration to detect local concentration of drug has been used in some trials, but even this simpler biopsy technique cannot be repeated at the frequency typical of peripheral blood PK analysis. Acknowledging these limitations, most early phase trials evaluating local therapies still have peripheral blood PK measurements as a key trial objective. These measurements and correlation with dose escalation are one of many considerations when determining an optimal dose.

Pharmacodynamic measurements

PD measurements assess the biologic activity of an investigational agent. They are an important method of determining if the drug has the intended target activation in the early phase setting. PD measurements can assess multiple components of the immune system and should be specific to the mechanism of action of the agent being studied. Common PD measurements can include direct target effect, that is, gene expression in the peripheral blood. They can also measure downstream aspects of immune activation including the presence of specific T or myeloid cell subsets in the tumor microenvironment or the presence of cytokines and chemokines in the peripheral blood. Identifying which PD marker is suggestive of biologic activity that will correlate with meaningful clinical outcomes is challenging. At a minimum, a promising treatment should show clear PD activation of the pathway of interest.

On-treatment biopsy

PD measurements commonly evaluate the peripheral blood due to the practical ease of assessment across multiple time periods. However, on treatment biopsy can provide a direct evaluation of the effect of a novel therapy on the tumor microenvironment. T cell-inflamed or "hot" tumors have shown superior outcomes for standard immune therapies compared with tumors devoid of T cells or "cold" tumors.[17] Thus, the demonstration of an increase in T cell infiltration post-treatment is often considered a key measure of biologic activity. While an increase in T cell activity may be a minimum standard to show immune activity, this may not be granular enough to describe meaningful antitumor activity. For example, with oncolytic virus therapy, reactive T cells recruited into the tumor may be related to the antiviral reaction and lack tumor specificity. Translational studies from standard checkpoint inhibitors have shown that non-specific "bystander" T cells are frequently activated.[18]

Although T cells are critical to the effector response, in many tumors myeloid cells comprise the most prevalent immune cell populations. Immunosuppressive myeloid cells can prohibit effective antitumor immunity. Thus, may novel therapies aim to "reprogram" or reset the non-lymphoid compartment. Common PD outputs for myeloid cells include the upregulation of antigen presentation (major histocompatibility complex) or costimulation (CD86) proteins. The subtypes and phenotypic states of myeloid cells are incredibly diverse, and translational studies continue to add to the understanding of the antitumor biology of these innate immune cells.[19]

Tumor biopsies are typically evaluated by standard immunohistochemistry (IHC) or bulk RNA signatures. There are many practical advantages to these strategies including technical feasibility and cost. Emerging techniques for spatial profiling can provide a nuanced understanding of productive antitumor immune responses. In particular the spatial arrangement of T cells with antigen-presenting niches (containing dendritic or B cells) or the development of tertiary lymphoid (TLS) structures is emerging biomarkers of a robust antitumor immune response.[20] Comprehensive profiling of on-treatment tumor biopsies is not typically feasible in large registration intent trials but may provide valuable information about drug effect in smaller early phase trials.

Non-injected lesion evaluation

A major aim of local therapy in most contexts is to generate a systemic immune response. A biopsy of non-injected tumors can be very informative, with demonstration of immune cell infiltration at distant sites serving as an early indicator of systemic biologic activity. Techniques such as T cell receptor sequencing and single-cell phenotyping of T cells can be used to determine if there are shared immune populations between the injected site, peripheral blood and distant tumors.[21] While providing valuable PD information, non-injected site biopsy adds complexity. For example, the time window to detect maximal immune response may differ between primary and metastatic sites. Repeating biopsies of multiple sites must also consider patient safety and quality of life as study schedule requirements in early phase trials can be intensive.

Imaging techniques offer a non-invasive method to evaluate systemic immune activation following administration of a novel therapy. Nuclear imaging studies can track the migration and infiltration of CD8 T cells,[22] and granzyme B positron emission tomography (PET) provides additional functional and phenotypic insights into these T cell populations.[23] In addition to following T cell activity (a PD endpoint), labeling of the candidate drug itself can allow imaging studies to follow the distribution and time course of the drug for a PK-like analysis.[24]

Conclusions from early phase

A combination of safety, PK and PD data is used to determine the optimal dose for further development of novel therapies. Often two or more doses may be explored in expansion phases to gather more data. Ideally some degree of clinical activity (reduction in tumor size of measurable lesions) should be seen with monotherapy dosing of a candidate drug. However, in selected cases with compelling PD data, a drug may be considered for advancement with combination immune therapies such as with anti-PD-1.

CLINICAL VALIDATION

Agents that show promising biologic activity in early phase trials are advanced to larger trials with clinical efficacy endpoints. Some local agents may be evaluated in randomized trials in the metastatic treatment refractory setting. However, there is a general concern that the advanced setting may be a challenging place to demonstrate clinical activity. Preclinical murine models often evaluate treatment response in tumors that are 5–10 days old. The tumor microenvironment in the metastatic, treatment-refractory state may be in a much more fixed state and impacted by prior therapies.[25] Given this consideration, novel local therapies are also investigated at earlier time periods (such as frontline metastatic settings), and often in combination with additional agents (anti-PD-1). For combination therapy, it is particularly important that the treatment effect of the local agent is isolated from the components of the regimen, necessitating randomized trials.

Neoadjuvant therapy, or treatment prior to surgical resection of locally advanced tumors has shown substantial benefit across multiple cancer types.[26] There is compelling mechanistic rationale to develop intratumoral therapies in this setting. Injection of the primary tumor may allow a robust immune response that includes the draining lymph nodes. Additionally, early-stage tumors have less heterogeneity than metastatic settings and the tumor burden is lower. These factors may allow intratumoral therapies to trigger a systemic immune response and eliminate micrometastatic disease, a more feasible aim than treating established distant tumors in the metastatic setting. Finally, neoadjuvant therapy allows a "window of opportunity" with resection specimens allowing translational studies to dissect mechanisms of activity and further refine treatment regimens. However, with the emergence of standard of care neoadjuvant regimens for many cancer types, there will be fewer situations where local therapy can be given as a monotherapy. Local therapies can be added to standard of care regimens in the neoadjuvant setting. However, as discussed above, it is not possible to isolate the treatment effect of the local therapy when given as part of a combination regimen in single-arm trials.

Key outcome measures for clinical trials

In a registration intent trial, standard outcome measures are needed to show long-term benefits of a novel therapy in comparison to the standard of care. In the metastatic setting the treatment should demonstrate PFS or OS benefit. In the neoadjuvant setting the primary outcome is often event-free survival/recurrence-free survival and OS. Surrogate outcomes have been used to prioritize promising therapies as they advance through earlier phases prior to a randomized registration trial. The surrogate outcome measures such as response rate or pathologic response rate should ideally correlate with long-term outcomes of PFS and OS.

For the metastatic disease setting, a key outcome measure is the radiographic response by Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Here index lesions are chosen from each organ site, and a treatment response is classified by a radiographic tumor reduction of >30%.[27] For local or intratumoral therapies there are several unique aspects because response patterns may differ between injected and non-injected lesions. Injected lesions should be excluded from formal RECIST measurements, and response rates reported as an aggregation of non-injected tumors. Additionally, response patterns for immune therapy in general differ from conventional chemotherapy or targeted cancer therapies. Activation of the immune system and infiltration of immune cells into the tumor can cause lesions to "flare" or become larger before regressing in the setting of a response. A revised RECIST for immune-based therapeutics or "iRECIST" was developed as a new response assessment tool which differs from standard RECIST by allowing a confirmatory scan 4–8 weeks after an initial scan that is concerning for progression.[28] In cases of a delayed response or "pseudoprogression", patients can stay on therapy and are reclassified as having a response by iRECIST criteria. Building on this, for intratumoral therapies, a new framework has been developed termed itRECIST. This captures responses in both injected and non-injected lesions as a composite response outcome,[29] and also accounts for the potential of pseudoprogression. Although cumbersome to perform, this system allows standardized reporting of response patterns. In addition to data on non-injected lesion responses, it is also valuable to report if responses are occurring in distant visceral organs (rather than limited to subcutaneous or nodal metastasis). Finally, the duration of treatment response is also a key outcome measure to suggest if the novel therapy has generated true adaptive immune response. Further data are needed to determine the correlation between itRECIST measurements and long-term clinical outcomes (PFS, OS).

In the neoadjuvant setting, pathologic response can be evaluated on the tumor resection specimen.[30] Pathologic response rates have correlated with disease-free survival outcomes for therapies such as neoadjuvant chemotherapy in breast cancer or neoadjuvant checkpoint inhibitors in breast, lung and melanoma.[31] However, the correlation between pathologic response rate and long-term outcomes is context-specific and should be evaluated for each therapy class.[32]

Novel agents that show promising itRECIST responses (including non-injected tumors) in the metastatic setting or high pathologic response rates in the neoadjuvant setting may be prioritized for registration intent studies. In most cases, a randomized trial comparing the novel therapy or

combination regimen to the available standard of care is required.

Professional considerations

The administration of intratumoral therapies requires a large multidisciplinary team including medical oncologists, surgeons, radiation oncologists and interventional radiologists. Some tumors present on the skin or palpable lymph nodes are safe for injection in the office. Deeper lesions or lesions near sensitive anatomical locations require the use of ultrasound guidance. Finally, as promising new intratumoral therapies emerge there is a growing interest in injection of visceral sites including liver lesions.[33] These efforts require strong collaboration and coordination across the treatment team.

NOVEL LOCAL IMMUNOTHERAPIES IN DEVELOPMENT

There are many novel local therapies under investigation across multiple therapy classes. The discussion below reviews the development pathway for selected agents, highlighting the importance of disease setting, outcome measurements and the need for definitive randomized trials.

Viral therapies

Local immune therapies have shown clinical benefit in earlier stages of cancer therapy. Non-muscle invasive bladder cancer can be resected with transurethral resection of the bladder tumor, but many cases are at high risk of future recurrence. Infusion of BCG (BCG, an inactivated bacteria) into the bladder is an FDA-approved standard of care treatment to reduce recurrences and prevent the need for cystectomy. In 2022 a novel adenovirus, nadofargene firadenovec was approved as an additional local therapy for non-muscle invasive bladder cancer that was not responsive or recurred after BCG. Nadofargene is a non-oncolytic adenovirus that delivers an interferon (IFN) alpha payload to the bladder epithelium. Prior attempts at IFNa instillation directly into the bladder were not as successful, believed to be in part due to limited duration of IFNa exposure. Nafadofargene showed sustained IFNa expression in the urine in a phase 1 trial.[34] Subsequently a phase 3 trial in BCG-refractory non-muscle invasive bladder cancer found that 46% of patients were free of high-grade recurrence at 1 year, leading to FDA approval.[35]

Next-generation oncolytic viruses have shown promising activity even in metastatic cancer settings. Vusolimogene oderparepvec (RP1) is an HSV-1 oncolytic virus that is engineered to secrete a fusogenic glycoprotein leading to cell-cell fusion in the tumor microenvironment. Preclinical models demonstrated that this enhancement increased immunogenic cell death of tumor cells, leading to systemic antitumor immunity.[36] A phase 1 trial showed single-agent activity with PD outcomes demonstrating enhanced T cell infiltration in tumor biopsies.[37] When advanced to a phase II trial enrolling 140 patients with PD-1 refractory melanoma, the response rate was 32.9%. Importantly, among responding patients, 79% of non-injected lesions also had a clinical response. This included visceral lesions, with an overall median duration of response of 33.7 months.[4] This detailed reporting of non-injected lesions is critical to characterizing the systemic efficacy potential. RP is now being evaluated in a randomized trial for anti-PD-1 refractory melanoma, compared with the physician's choice of standard of care therapies. The primary outcome measure is OS.[38]

Multiple other oncolytic viruses are in development, with many centering around the ability to insert payload genes into the viral vector which can further augment the immune priming effect. JNJ-87704916 is an oncolytic virus with four payload genes (FLT3L, CD40 agonist, anti-cytotoxic T-lymphocyte-associated protein 4 and IL12). A phase 1 trial for this agent involved injection of visceral lesions and demonstrated responses in anti-PD-1 refractory melanoma.[39]

Radiation

Radiation can induce immunogenic cell death of tumors, priming an "in-situ" vaccine effect and potentially contributing to systemic antitumor immunity. It is hypothesized that lower dose radiation regimens may be more efficient in priming this response, by generating a degree of tumor cell death without ablating immune cell activity in the tumor microenvironment.[40] A phase II trial in metastatic non-small cell lung cancer randomized patients to low dose radiation at one tumor lesion followed by pembrolizumab compared with pembrolizumab alone. The study arm with radiation had a numerically higher response rate and PFS compared with pembrolizumab alone.[41] This benefit appeared to be enriched in the population that was PD-L1 negative, suggesting the potential for radiation to provoke immune responses in tumors with limited baseline immune infiltration. Subsequent analysis of blood and post-treatment tumor biopsies showed enhanced antigen presentation gene expression, and IFN response among patients who had received radiation.[42] Additional studies have shown that hypofractionated radiation regimens can generate systemic responses (in non-radiated tumors) in anti-PD-1 refractory melanoma.[43]

Toll-like receptors

Local therapies also aim to directly activate innate immune pathways in the tumor microenvironment. TLRs are present in myeloid cells and are activated by DNA and RNA from viruses and bacteria. Signaling through TLR can induce the activation of myeloid cells, leading to the secretion of cytokines and upregulation of costimulatory and antigen presentation molecules on the cell surface.[44] TLR agonists in the context of cancer therapeutics can provide local antitumor properties but also aim to activate a downstream adaptive immune response. Imiquimod is an FDA-approved TLR 7/8 agonist that is applied for local application to treat basal cell carcinoma of the skin. Translational studies have shown that imiquimod leads to

the infiltration of macrophages and T cells in the microenvironment with increased expression of IFN response and tumor control.[45]

New synthetic DNA-like molecules are designed to specifically activate TLR. Tilsotolimod is a TLR 9 agonist that was studied in anti-PD-1 refractory melanoma in combination with ipilimumab and showed a promising response rate of 22.4%.[46] Biomarker analysis showed on-target treatment effects including induction of IFNa gene expression, dendritic cell activation and antigen presentation genes. However, when advanced to a phase III trial in PD-1 refractory melanoma, the combination of tilsotolimod+ipilimumab did not improve durable response rate in comparison to ipilimumab alone.[47] Despite well-designed PD evaluations in early phase trials and suggestions of clinical activity, it is difficult to separate the treatment effect of novel therapies when given in combination as part of a single-arm trial.

Vidutolimod is another CpG-A TLR9 that is hypothesized to have several potency advantages.[48] A phase 1 trial evaluating vidutolomid+pembrolizumab in patients with melanoma who were refractory or non-responsive to anti-PD-1 therapy showed favorable responses including at visceral sites of disease.[49] Vidutolimod was also studied in locally advanced melanoma in a phase II trial given as a neoadjuvant therapy in combination with nivolumab. Tumor resection specimens allowed in-depth analysis with responding patients having increased Ki67+T cells, plasmacytoid dendritic cells, and gene signatures of myeloid activation. Patients who had a major pathologic response had baseline gene signatures suggestive of myeloid cell activity in the tumor microenvironment.[50] A larger randomized trial in the neoadjuvant setting would be needed to establish the role of vidutolimod in clinical practice. Identifying the proper treatment context, such as patients with a baseline high myeloid gene signature may be needed to maximize the benefit of this therapy.

STING agonists

Another highly investigated immune activating target is the STING pathway. STING recognizes cytosolic DNA to activate interferon signaling and has been shown in preclinical models to generate an antitumor immune response.[51] Several synthetic or small molecule activators of STING have been evaluated in early phase trials as intratumoral therapies. These trials showed clear PD activity with elevation of STING pathway gene expression and increases in chemokines and IFN gamma in the peripheral blood.[52–54] Despite activation of the intended target pathway, the STING agents have shown limited clinical activity to date. The pathways leading to innate immune activation downstream from STING agonism are complex with several counter-regulatory processes also occurring. Recent studies have suggested that IL6, and NFkB pathway activation triggered by STING may have tumor-promoting roles,[55] and the STING pathway may activate immunosuppressive cell populations that limit antitumor immunity.[56] These results highlight that despite activating the pathway of interest, the totality of PD data and early clinical response information from phase 1 trials are required to determine which therapies to advance to larger trials. In the case of STING agonists future investigations will need to determine which specific cell types (immune cells vs tumor cells themselves) are most activated by STING and determine precision targeting strategies to prevent the activation of counter-regulatory immunosuppressive pathways.

Nucleic acid therapies

TLR and STING agonists target specific pathways to activate the antitumor immune response. Recent data have suggested that messenger RNA (mRNA) lipid nanoparticle therapeutics broadly can induce innate immune pathways, although precise mechanisms are still being uncovered. In a retrospective analysis, patients who received a COVID-19 mRNA vaccine prior to starting frontline immune therapy for non-small cell lung cancer or melanoma had superior survival outcomes.[57] This effect was shown in preclinical models to be mediated by activation of myeloid cells and secretion of IFN alpha. In the murine models the antitumor and immune-activating effects were more pronounced with the mRNA-lipid nanoparticle than IFN alpha treatment alone.[57] There are many mRNA products in development, including tumor antigen-specific vaccine targets[58] and mRNA lipid nanoparticles that deliver an intratumoral payload such as IL12.[59] Whether these therapies are most effective when administered locally near the tumor or have systemic effects regardless of physical injection site requires further investigation.

Antibodies

There are advantages to direct tumor injection of monoclonal antibodies particularly if the intended target has a narrow therapeutic window. CD40 is an activating receptor on antigen-presenting cells such as dendritic cells, B cells and macrophages. Clinical trials of systemic CD40 agonist antibodies have led to systemic dose-limiting effects including cytokine release syndrome, thrombocytopenia and hepatotoxicity. 2141-V11 is FC-enhanced CD40 that was studied as a single agent intratumoral therapy in a phase 1 trial.[60] Responses were seen in injected as well as non-injected lesions and on treatment biopsies showed the formation of mature TLSs in responding patients. This agent is now being studied as a local therapy in earlier treatment settings for non-muscle invasive bladder cancer, prostate cancer prior to resection, and glioblastoma.[60]

Cytokines

Prior studies evaluating intratumoral IL2 or DNA plasmids expressing IL12 showed promising responses in initial early phase trials,[9 61] but have failed to meet clinical endpoints in definitive trials.[62] One concern is that injected cytokines may rapidly egress from the tumor. Local concentration and spatial orientation of cytokines

within the tumor microenvironment are hypothesized to be critical components of priming an immune response,[63] whereas systemic exposure to cytokines has led to dose-limiting toxicity.[64] Based on this rationale, strategies to retain cytokines in the tumor microenvironment have emerged.[63] Daromun is a protein containing IL2 and tumor necrosis factor fused to a fibronectin domain that allows retention near vasculature in the tumor microenvironment.[65] In a randomized phase III trial, neoadjuvant daromun showed improvement in recurrence-free survival compared with surgery alone for locally advanced melanoma.[5] However, there was inconsistent use of immune checkpoint inhibitors, now a standard of care as (neo)adjuvant therapy for stage III melanoma.[66] This highlights that the rapidly changing standard of care landscape can affect the clinical impact of well-designed definitive trials which take several years to design and complete. There are several cytokine agents in clinical trials studying additional methods of anchoring cytokines to tumor microenvironment.[67 68]

CONCLUSIONS

Local immunotherapies have shown clinical benefit in several tumor settings, and numerous agents are currently being investigated in clinical trials. They represent diverse classes of therapeutics, with local administration priming systemic antitumor immunity. In some cases, this may be limited to local or regional control of tumors. However, newer agents have shown promise as neoadjuvant therapies to prevent systemic recurrence or even as treatment for refractory metastatic tumors.

Advancing our understanding of the basic science underlying an optimal "in situ" immune response will aid development of local therapies. While classical murine models are effective starting points, there are significant limitations in comparing the tumor microenvironment in these models to highly immune-suppressive environments in advanced human tumors. Translational analysis from patient samples will continue to shed light on the nuanced function of the multiple cell types and immune pathways involved in a productive local antitumor response. Early phase clinical trials allow an opportunity to further refine the insights from animal models by using PD endpoints. This can verify activation of the intended target, and gain insight into unanticipated biologic activity that may be induced by any candidate therapy.

The main goal of early phase clinical trials is to assess safety and determine an optimal dosing schedule based on early readouts of biologic activity. Established pathways to monitor dose-response relationships using PK and PD endpoints from the peripheral blood can prove challenging to interpret for local therapies. In many instances local therapy is most effective if the drug is retained in the tumor or draining lymph node. In this case, analyzing changes in the tumor microenvironment in on-treatment biopsies is the most accurate way of assessing biologic activity. As most agents aim to have systemic activity beyond just the injected tumor, this also may require obtaining non-injected tumor biopsies. Novel techniques such as PET imaging of immune cell populations may allow less invasive methods to inform optimal dosing concentrations and treatment schedules. Local therapies aim to trigger a productive immune response in tumors that are devoid of immune cells or have immunosuppressive populations at baseline. Thus, biomarkers that define the tumor microenvironment for each patient (IHC or RNA seq profiles) may be particularly suited to optimize patient selection for local therapies and can be developed during the course of early phase trials.

In addition to characterizing biological effects, clinical outcomes from early phase trials (ie, RECIST response rates) can inform which agents show enough promise to continue developing. Detecting a signal of meaningful clinical activity is challenging as early phase investigation starts in the treatment-refractory metastatic disease setting. Local therapies may better be suited as part of combination regimens in earlier settings such as neoadjuvant therapy or as frontline treatment for metastatic tumors. However, clinical responses reported as part of a combination regimen in single-arm trials can be misleading, as it is difficult to isolate the effect of the novel local therapy. Thus, in most instances some degree of single-agent clinical activity should be demonstrated. New methods to characterize clinical activity such as itRECIST allow organized reporting of the full picture of injected and non-injected lesions. Agents that have demonstrated both biological and clinical activity are advanced to randomized trials for registration intent.

Local immunotherapy is rapidly expanding with several investigational agents now spanning the landscape of drug development from preclinical development to reaching registration intent randomized trials. These therapies are a promising avenue to overcome standard immune checkpoint inhibitor resistance and expand the scope of patients who benefit from immunotherapy. As this new era of immunotherapy develops it is an exciting opportunity for continued multidisciplinary partnerships between translational researchers and multiple medical subspecialists.

Contributors JI: Initial conceptualization and drafting of article, editing, figure/table. JL: Content/conceptualization input, editing, revision. JI is the Guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests JI: Funding to institution—Merck, BMS, Iovance, TSCAN, Bayer, Strand Therapeutics. JL: Strand Therapeutics.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Commissioned; externally peer reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines,

terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See https://creativecommons.org/licenses/by-nc/4.0/.

REFERENCES

1 Ayers M, Lunceford J, Nebozhyn M, *et al*. IFN-γ-related mRNA profile predicts clinical response to PD-1 blockade. *J Clin Invest* 2017;127:91190:2930–40:.
2 Bagaev A, Kotlov N, Nomie K, *et al*. Conserved pan-cancer microenvironment subtypes predict response to immunotherapy. *Cancer Cell* 2021;39:845–65.
3 Andtbacka RHI, Kaufman HL, Collichio F, *et al*. Talimogene Laherparepvec Improves Durable Response Rate in Patients With Advanced Melanoma. *J Clin Oncol* 2015;33:2780–8.
4 Wong MK, Milhem MM, Sacco JJ, *et al*. RP1 Combined With Nivolumab in Advanced Anti–PD-1–Failed Melanoma (IGNYTE). *J Clin Oncol* 2025;43:3589–99.
5 Kähler KC, Hassel JC, Ziemer M, *et al*. Neoadjuvant intralesional targeted immunocytokines (daromun) in stage III melanoma. *Ann Oncol* 2025;36:1166–77.
6 Luke JJ, Davar D, Andtbacka RH, *et al*. Society for Immunotherapy of Cancer (SITC) recommendations on intratumoral immunotherapy clinical trials (IICT): from premalignant to metastatic disease. *J Immunother Cancer* 2024;12:e008378.
7 Morton DL, Eilber FR, Holmes EC, *et al*. BCG immunotherapy of malignant melanoma: summary of a seven-year experience. *Ann Surg* 1974;180:635–43.
8 Hoeller C, Jansen B, Heere-Ress E, *et al*. Perilesional injection of r-GM-CSF in patients with cutaneous melanoma metastases. *J Invest Dermatol* 2001;117:371–4.
9 Weide B, Eigentler TK, Pflugfelder A, *et al*. Survival after intratumoral interleukin-2 treatment of 72 melanoma patients and response upon the first chemotherapy during follow-up. *Cancer Immunol Immunother* 2011;60:487–93.
10 Liu BL, Robinson M, Han Z-Q, *et al*. ICP34.5 deleted herpes simplex virus with enhanced oncolytic, immune stimulating, and anti-tumour properties. *Gene Ther* 2003;10:292–303.
11 Hu JCC, Coffin RS, Davis CJ, *et al*. A phase I study of OncoVEXGM-CSF, a second-generation oncolytic herpes simplex virus expressing granulocyte macrophage colony-stimulating factor. *Clin Cancer Res* 2006;12:6737–47.
12 Senzer NN, Kaufman HL, Amatruda T, *et al*. Phase II clinical trial of a granulocyte-macrophage colony-stimulating factor-encoding, second-generation oncolytic herpesvirus in patients with unresectable metastatic melanoma. *J Clin Oncol* 2009;27:5763–71.
13 Kaufman HL, Amatruda T, Reid T, *et al*. Systemic versus local responses in melanoma patients treated with talimogene laherparepvec from a multi-institutional phase II study. *J Immunother Cancer* 2016;4:12.
14 Ribas A, Dummer R, Puzanov I, *et al*. Oncolytic Virotherapy Promotes Intratumoral T Cell Infiltration and Improves Anti-PD-1 Immunotherapy. *Cell* 2017;170:1109–19.
15 Chesney JA, Ribas A, Long GV, *et al*. Randomized, Double-Blind, Placebo-Controlled, Global Phase III Trial of Talimogene Laherparepvec Combined With Pembrolizumab for Advanced Melanoma. *J Clin Oncol* 2023;41:528–40.
16 Robert C, Gastman B, Gogas H, *et al*. Open-label, phase II study of talimogene laherparepvec plus pembrolizumab for the treatment of advanced melanoma that progressed on prior anti-PD-1 therapy: MASTERKEY-115. *Eur J Cancer* 2024;207:114120.
17 Cristescu R, Mogg R, Ayers M, *et al*. Pan-tumor genomic biomarkers for PD-1 checkpoint blockade-based immunotherapy. *Science* 2018;362:eaar3593.
18 Oliveira G, Stromhaug K, Klaeger S, *et al*. Phenotype, specificity and avidity of antitumour CD8$^+$ T cells in melanoma. *Nature New Biol* 2021;596:119–25.
19 Cheng S, Li Z, Gao R, *et al*. A pan-cancer single-cell transcriptional atlas of tumor infiltrating myeloid cells. *Cell* 2021;184:792–809.
20 Teillaud J-L, Houel A, Panouillot M, *et al*. Tertiary lymphoid structures in anticancer immunity. *Nat Rev Cancer* 2024;24:629–46.
21 Luoma AM, Suo S, Wang Y, *et al*. Tissue-resident memory and circulating T cells are early responders to pre-surgical cancer immunotherapy. *Cell* 2022;185:2918–35.
22 Kist de Ruijter L, van de Donk PP, Hooiveld-Noeken JS, *et al*. Whole-body CD8$^+$ T cell visualization before and during cancer immunotherapy: a phase 1/2 trial. *Nat Med* 2022;28:2601–10.
23 LaSalle T, Austin EE, Rigney G, *et al*. Granzyme B PET imaging of immune-mediated tumor killing as a tool for understanding immunotherapy response. *J Immunother Cancer* 2020;8:e000291.
24 Meyblum L, Chevaleyre C, Susini S, *et al*. Local and distant response to intratumoral immunotherapy assessed by immunoPET in mice. *J Immunother Cancer* 2023;11:e007433.
25 Olson B, Li Y, Lin Y, *et al*. Mouse Models for Cancer Immunotherapy Research. *Cancer Discov* 2018;8:1358–65.
26 Awada G, Cascone T, van der Heijden MS, *et al*. The rapidly evolving paradigm of neoadjuvant immunotherapy across cancer types. *Nat Cancer* 2025;6:967–87.
27 Eisenhauer EA, Therasse P, Bogaerts J, *et al*. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228–47.
28 Seymour L, Bogaerts J, Perrone A, *et al*. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet Oncol* 2017;18:e143–52.
29 Goldmacher GV, Khilnani AD, Andtbacka RHI, *et al*. Response Criteria for Intratumoral Immunotherapy in Solid Tumors: itRECIST. *J Clin Oncol* 2020;38:2667–76.
30 Stein JE, Lipson EJ, Cottrell TR, *et al*. Pan-Tumor Pathologic Scoring of Response to PD-(L)1 Blockade. *Clin Cancer Res* 2020;26:545–51.
31 Deutsch JS, Cimino-Mathews A, Thompson E, *et al*. Association between pathologic response and survival after neoadjuvant therapy in lung cancer. *Nat Med* 2024;30:218–28.
32 Menzies AM, Amaria RN, Rozeman EA, *et al*. Pathological response and survival with neoadjuvant therapy in melanoma: a pooled analysis from the International Neoadjuvant Melanoma Consortium (INMC). *Nat Med* 2021;27:301–9.
33 Sheth RA, Murthy R, Hong DS, *et al*. Assessment of Image-Guided Intratumoral Delivery of Immunotherapeutics in Patients With Cancer. *JAMA Netw Open* 2020;3:e207911.
34 Dinney CPN, Fisher MB, Navai N, *et al*. Phase I trial of intravesical recombinant adenovirus mediated interferon-α2b formulated in Syn3 for Bacillus Calmette-Guérin failures in nonmuscle invasive bladder cancer. *J Urol* 2013;190:850–6.
35 Boorjian SA, Alemozaffar M, Konety BR, *et al*. Intravesical nadofaragene firadenovec gene therapy for BCG-unresponsive non-muscle-invasive bladder cancer: a single-arm, open-label, repeat-dose clinical trial. *Lancet Oncol* 2021;22:107–17.
36 Thomas S, Kuncheria L, Roulstone V, *et al*. Development of a new fusion-enhanced oncolytic immunotherapy platform based on herpes simplex virus type 1. *J Immunother Cancer* 2019;7:214.
37 34th Annual Meeting & Pre-Conference Programs of the Society for Immunotherapy of Cancer (SITC 2019): part 1. *J Immunother Cancer* 2019;7:282.
38 Luke JJ, Davarifar A, Najjar YG, *et al*. A randomized, controlled, multicenter, phase 3 study of vusolimogene oderparepvec combined with nivolumab vs treatment of physician's choice in patients with advanced melanoma that has progressed on anti–PD-1 and anti–CTLA-4 therapy (IGNYTE-3). *JCO* 2025;43.
39 Moreno Garcia V, Calvo E, Villaruz L, *et al*. 1566P Phase I study of intratumoral administration of JNJ-87704916, an oncolytic virus, as monotherapy and in combination with cetrelimab in advanced solid tumors. *Ann Oncol* 2025;36:S871.
40 Galluzzi L, Aryankalayil MJ, Coleman CN, *et al*. Emerging evidence for adapting radiotherapy to immunotherapy. *Nat Rev Clin Oncol* 2023;20:543–57.
41 Theelen WSME, Peulen HMU, Lalezari F, *et al*. Effect of Pembrolizumab After Stereotactic Body Radiotherapy vs Pembrolizumab Alone on Tumor Response in Patients With Advanced Non-Small Cell Lung Cancer: Results of the PEMBRO-RT Phase 2 Randomized Clinical Trial. *JAMA Oncol* 2019;5:1276–82.
42 Huang J, Theelen WSME, Belcaid Z, *et al*. Combination of pembrolizumab and radiotherapy induces systemic antitumor immune responses in immunologically cold non-small cell lung cancer. *Nat Cancer* 2025;6:1676–92.
43 Lukens JN, Huang AC, Minn AJ III, *et al*. Immune Profiling of "Radvax" Abscopal Responses in Metastatic Melanoma Patients Progressing on Anti-PD1 Therapy Treated with Hypofractionated Radiotherapy (HFRT) to One Lesion Combined with Pembrolizumab. *International Journal of Radiation Oncology*Biology*Physics* 2024;120:S89–90.
44 Rolfo C, Giovannetti E, Martinez P, *et al*. Applications and clinical trial landscape using Toll-like receptor agonists to reduce the toll of cancer. *NPJ Precis Oncol* 2023;7:26.

45 Urosevic M, Maier T, Benninghoff B, *et al*. Mechanisms underlying imiquimod-induced regression of basal cell carcinoma in vivo. *Arch Dermatol* 2003;139:1325–32.
46 Haymaker C, Johnson DH, Murthy R, *et al*. Tilsotolimod with Ipilimumab Drives Tumor Responses in Anti-PD-1 Refractory Melanoma. *Cancer Discov* 2021;11:1996–2013.
47 Diab A, Ascierto PA, Maio M, *et al*. Randomized, Open-Label, Phase III Study of Tilsotolimod in Combination With Ipilimumab Versus Ipilimumab Alone in Patients With Advanced Refractory Melanoma (ILLUMINATE-301). *J Clin Oncol* 2025;43:1800–9.
48 Sullivan RJ. For Whom the Bell Tolls? A Toll-Like Receptor 9 Agonist's Journey from Vaccine Adjuvant to Promising Agent in Anti-PD-1-Resistant Melanoma. *Cancer Discov* 2021;11:2960.
49 Ribas A, Medina T, Kirkwood JM, *et al*. Overcoming PD-1 Blockade Resistance with CpG-A Toll-Like Receptor 9 Agonist Vidutolimod in Patients with Metastatic Melanoma. *Cancer Discov* 2021;11:2998–3007.
50 Davar D, Morrison RM, Dzutsev AK, *et al*. Neoadjuvant vidutolimod and nivolumab in high-risk resectable melanoma: A prospective phase II trial. *Cancer Cell* 2024;42:1898–918.
51 Fu J, Kanne DB, Leong M, *et al*. STING agonist formulated cancer vaccines can cure established tumors resistant to PD-1 blockade. *Sci Transl Med* 2015;7:283ra52.
52 Luke JJ, Sweis RF, Hecht JR, *et al*. Intratumoral or Subcutaneous MK-2118, a Noncyclic Dinucleotide STING Agonist, with or without Pembrolizumab, for Advanced or Metastatic Solid Tumors or Lymphomas. *Clin Cancer Res* 2025;31:1233–42.
53 Harrington KJ, Champiat S, Brody JD, *et al*. Phase I and II Clinical Studies of the STING Agonist Ulevostinag with and without Pembrolizumab in Participants with Advanced or Metastatic Solid Tumors or Lymphomas. *Clin Cancer Res* 2025;31:3400–11.
54 Jacoby J, Mahalingam D, Alistar A, *et al*. Phase 1 first-in-human dose-escalation study of IMSA101, a novel cyclic di-nucleotide STING agonist, for patients with advanced solid tumor malignancies. *J Immunother Cancer* 2025;13:e011572.
55 Hong C, Schubert M, Tijhuis AE, *et al*. cGAS-STING drives the IL-6-dependent survival of chromosomally instable cancers. *Nature New Biol* 2022;607:366–73.
56 Li S, Mirlekar B, Johnson BM, *et al*. STING-induced regulatory B cells compromise NK function in cancer immunity. *Nature New Biol* 2022;610:373–80.
57 Grippin AJ, Marconi C, Copling S, *et al*. SARS-CoV-2 mRNA vaccines sensitize tumours to immune checkpoint blockade. *Nature New Biol* 2025;488–97.
58 Weber JS, Luke JJ, Carlino MS, *et al*. INTerpath-001: Pembrolizumab with V940 (mRNA-4157) versus pembrolizumab with placebo for adjuvant treatment of high-risk stage II-IV melanoma. *JCO* 2024;42:TPS9616.
59 Piha-Paul SA, Sankhala KK, Menzies AM, *et al*. Phase I dose escalation trial of STX-001, an LNP-encapsulated self-replicating mRNA expressing IL-12, in patients (pts) with advanced solid tumors. *JCO* 2025;43:9556.
60 Osorio JC, Knorr DA, Weitzenfeld P, *et al*. Fc-optimized CD40 agonistic antibody elicits tertiary lymphoid structure formation and systemic antitumor immunity in metastatic cancer. *Cancer Cell* 2025;43:1902–16.
61 Algazi A, Bhatia S, Agarwala S, *et al*. Intratumoral delivery of tavokinogene telseplasmid yields systemic immune responses in metastatic melanoma patients. *Ann Oncol* 2020;31:532–40.
62 A multicenter phase 2, open label study of intratumoral tavokinogene telseplasmid (Tavo, pIL-12) + electroporation with pembrolizumab in patients with stage 3/4 melanoma who are progressing on either pembrolizumab or nivolumab treatment. 2017. Available: https://clinicaltrials.gov/study/NCT03132675
63 Agarwal Y, Milling LE, Chang JYH, *et al*. Intratumourally injected alum-tethered cytokines elicit potent and safer local and systemic anticancer immunity. *Nat Biomed Eng* 2022;6:129–43.
64 Atkins MB, Lotze MT, Dutcher JP, *et al*. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. *J Clin Oncol* 1999;17:2105–16.
65 Danielli R, Patuzzo R, Di Giacomo AM, *et al*. Intralesional administration of L19-IL2/L19-TNF in stage III or stage IVM1a melanoma patients: results of a phase II study. *Cancer Immunol Immunother* 2015;64:999–1009.
66 Fallarino F, Blank CU. Lessons from neoadjuvant immunotherapy in melanoma: understanding antitumour immunity and tumour escape. *Nat Rev Immunol* 2026;26:152–62.
67 Park JC, Curti B, Butler MO, *et al*. Abstract CT039: Results of a first-in-human phase 1 trial of anchored IL-12 drug conjugate (ANK-101). *Cancer Res* 2025;85:CT039.
68 Mehta NK, Rakhra K, Meetze KA, *et al*. CLN-617 Retains IL2 and IL12 in Injected Tumors to Drive Robust and Systemic Immune-Mediated Antitumor Activity. *Cancer Immunol Res* 2024;12:1022–38.