Published in final edited form as:

Clin Cancer Res. 2020 July 01; 26(13): 3091–3099. doi:10.1158/1078-0432.CCR-19-3642.

Intratumoral immunotherapy for early-stage solid tumors

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Abstract

The unprecedented benefits of immunotherapy in advanced malignancies have resulted in increased interests in exploiting immune stimulatory agents in earlier stage solid tumors in the neoadjuvant setting. However, systemic delivery of immunotherapies may cause severe immune-related side-effects and hamper the development of combination treatments. Intratumoral delivery of neoadjuvant immunotherapy provides a promising strategy in harnessing the power of immunotherapy while minimizing off-target toxicities. The direct injection of immune stimulating agents into the tumor primes the local tumor-specific immunity to generate a systemic, durable clinical response. Intratumoral immunotherapy is a highly active area of investigation resulting in a plethora of agents, e.g. immune receptor agonists, non-oncolytic and oncolytic viral therapies, being tested in preclinical and clinical settings. Currently, more than 20 neoadjuvant clinical trials exploring distinct intratumoral immune stimulatory agents and their combinations are ongoing. Practical considerations including appropriate timing and optimal local delivery of immune stimulatory agents play an important role in safety and efficacy of this approach. Here we discuss promising approaches in drug delivery technologies and opportunity for combining intratumoral immunotherapy with other cancer treatments and summarize the recent preclinical and clinical evidences that highlighted its promise as a part of routine oncologic care.

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Conflict of Interest

The other authors report no conflicts of interest.

Keywords

cancer immunotherapy; intratumoral therapy; neoadjuvant; combination immunotherapy

Introduction

Significant advances in the field of immunotherapy over the past decade have provided an alternative to conventional treatments, which in many advanced solid tumors involve chemotherapy and/or radiation, and associated toxicities. Strong clinical benefits of immunotherapy have been observed for patients receiving immunotherapy in second line therapy or even in the adjuvant setting (defined as treatment after primary surgical resection or radiation)(1–3). This has generated interest in the adoption of cancer immunotherapies prior to local treatments as a neoadjuvant modality (4). Intratumoral immunotherapy, the direct inoculation of immune stimulating agents into the tumor itself, has a number of features that make it particularly useful in the neoadjuvant setting. In this approach immune stimulating agents are injected directly into the tumor site, thus avoiding off-target toxicities and adverse effects that can accompany global immune stimulation. Whereas toxicity of systemic immunotherapy has been shown to be dose related(5), local delivery of a high concentration immunotherapy agent generally translates to overall lower systemic dosages and lower systemic exposure due to limited diffusion of the agent(6). In addition, when compared to systemic administration, local administration requires a much lower dose of the agents to induce a local and systemic antitumor response. Intratumoral delivery can thus avoid problems with dose-limiting toxicity or allow for the use of combinations of agents that have poor systemic safety profiles(6).

Furthermore, direct injection at the tumor site ensures access to tumor infiltrating T cells already in the tumor microenvironment and potentially enriched for tumor antigen recognition. Recent studies have noted intratumor differences in T cell density and clonality, possibly due to differences in neoantigens in different tumor regions(7). As a result, local immunotherapy may elicit an immune response where systemic administration of immunotherapy is not efficacious by leveraging the rich pool of antigens within the tumor to provide better priming of polyclonal antitumor response(8).

In this review, we will address practical considerations for intratumoral immunotherapy and summarize recent preclinical and clinical studies utilizing neoadjuvant intratumoral immunotherapy. Finally, we will synthesize findings from clinical literature to provide suggestions for combining cancer surgery with intratumoral therapy to improve outcomes for patients with resectable solid tumors that have a high risk of distant recurrence.

Considerations for clinical utilization

The goal of intratumoral immunotherapy is to prime immune cells locally to generate a systemic antitumor effect. By using the tumor as its own vaccine, this approach allows for the generation of antitumor immunity against multiple cancer cell antigens without having to pre-identify those antigens. As such, intratumoral immunotherapy can potentially elicit a

polyclonal antitumor immune response against multiple concurrent targets and provide a broad attack against tumor heterogeneity (Figure 1).

Furthermore, intratumoral injections allow for the delivery of high concentrations of drugs at the tumor site while keeping total dose and systemic drug exposure low. However, there are several clinical factors that must be taken into consideration when using local immunotherapy. These include timing and scheduling of therapy, choice of agents utilized, and opportunity for combination with other therapies.

Timing of therapy: earlier the better?

Traditional chemotherapeutic or radiation therapy prior to surgery, termed neoadjuvant therapy, has demonstrated improved patient outcomes across a spectrum of solid tumors(9–11). The potential of neoadjuvant immunotherapy however remains under clinical evaluation and its utility in this setting is unclear (Figure 2).

Several groups have postulated that early immunotherapy in the neoadjuvant setting can potentially improve treatment options for a large number of patients with resectable solid tumors(4,12,13). There are several mechanisms by which this would be possible. First, upfront treatment can cause a local therapeutic effect to reduce primary tumor burden, minimizing the extent and morbidity of surgery. For some patients with locally advanced and borderline resectable tumors, neoadjuvant immunotherapy can shrink the primary tumor and even make an unresectable tumor resectable. Second, earlier treatment can reduce recurrence in patients by targeting systemic micro-metastatic disease at time of resection. Third, upfront immunotherapy allows for faster determination of initial therapeutic success through the evaluation of the resected tumor specimen to determine efficacy of treatment on primary tumor tissue and guide subsequent clinical decision-making. Lastly, neoadjuvant immunotherapy capitalizes on the presence of primary tumor as a rich source of antigens for T cell priming(14,15). The intact tumor can thereby act as an “*in situ*” vaccine, thereby inducing a broader and more potent anti-tumor immune response. This particular benefit can be magnified through the use of intratumoral immune stimulation to target tumor infiltrating lymphocytes. Therefore, by creating an earlier therapeutic window, decreasing risk of relapse, and providing an opportunity for tailored treatment planning, neoadjuvant treatment can improve the therapeutic power of immunotherapy. Indeed, a number of preclinical studies have recently demonstrated that administering immunotherapy prior to definitive surgical resection produces significant clinical benefits(15–18).

A direct comparison of neoadjuvant to adjuvant immunotherapy that included T regulatory cell (Treg) depletion, anti-CD25, anti-PD-1, and anti-CD137 in a murine model of metastatic triple-negative breast cancer found that neoadjuvant treatment was more efficacious than adjuvant treatment, and resulted in more long term survivors(15). A subsequent study utilizing a transgenic murine model of pancreatic adenocarcinoma found that neoadjuvant treatment with a PD-1 antagonist improved survival while adjuvant treatment was ineffective. Furthermore, the study determined that a combined maneuver utilizing neoadjuvant PD-1 blockade with gemcitabine along with adjuvant inhibition of CD96 and gemcitabine facilitated long term remission and long term survival, whereas other treatment groups not utilizing neoadjuvant therapy succumbed to recurrent disease(17). This study

highlights the increased therapeutic power of a neoadjuvant approach as well as the increased benefit from combining immunomodulating approaches with traditional chemotherapy.

In addition, using an orthotopic murine model of triple negative breast cancer, our lab has found that upfront intratumoral administration of a combination of CpG and agonistic antibody anti-OX40 (aOX40) together with resection offered the best local and distant disease control and survival compared to cohorts receiving immunotherapy or resection alone. When long term survivors from the neoadjuvant immunotherapy cohort were re-challenged with the same tumor, all cancer cells were rejected, while challenge of these survivors with an unrelated tumor was unimpeded, confirming the ability of neoadjuvant intratumoral CpG/aOX40 to confer specific immunological memory (unpublished results).

Intratumoral therapies under development

A number of high profile neoadjuvant immunotherapy trials are currently underway(14,19–22). At the time of this writing, there are 130 clinical studies listed on the [ClinicalTrials.gov](https://clinicaltrials.gov) website, studying a diverse array of immune modulating therapies in the neoadjuvant setting for treatment of solid tumors. However, clinical investigation into neoadjuvant intratumoral immunotherapy is still relatively new (Table 1).

Out of the 130 recently completed and ongoing neoadjuvant immunotherapy trials, only 24 utilize intratumoral immunotherapy (Figure 3). Of the completed trials, all utilize *ex situ* dendritic cell vaccines (autologous vaccines generated *ex vivo on a customized basis*) ([NCT01347034](https://clinicaltrials.gov/ct2/show/study/NCT01347034), [NCT00499083](https://clinicaltrials.gov/ct2/show/study/NCT00499083), [NCT00365872](https://clinicaltrials.gov/ct2/show/study/NCT00365872)). One of the three completed studies examined combination radiotherapy and intratumoral dendritic cell injection in patients with intermediate or high-grade soft tissue sarcomas and found enhanced T-lymphocyte response in 5/14 patients in the experimental arm versus 2/6 in the control arm ([NCT01347034](https://clinicaltrials.gov/ct2/show/study/NCT01347034)). Another study, also in patients with intermediate or high grade soft tissue sarcoma, recorded a T cell response in 10/18 individuals who received intratumoral dendritic cell vaccine with some correlation to clinical response(23).

While these studies demonstrate promising preliminary results, a cell-based vaccine is both labor and resource intensive. The most desirable intratumoral approach would be agnostic to tumor type, capable of eliciting an effective local and systemic antitumor against, and compatible with large scale production. An *in situ* immunization by which intratumoral administration of immune stimulating agents elicit an T cell response is most likely to meet the above criteria. This could include intratumoral gene therapy, antibodies or small molecule immune modulators.

Intratumoral gene therapy—Intratumoral electroporation of the IL-12 gene has been shown to be safe and effective in clinical trials in the metastatic disease setting, demonstrating systemic antitumor effects. As a monotherapy for melanoma, electroporation-mediated transfection of a plasmid encoding human IL-12 yielded a 33% overall response rate, with 50% of patients showing regression of untreated lesions(24,25). This therapeutic modality is currently under study as a monotherapy in patients with triple negative breast cancer ([NCT02531425](https://clinicaltrials.gov/ct2/show/study/NCT02531425)) and can be readily translated to the neoadjuvant setting.

Studies are also underway to examine the utility of intratumoral mRNA in solid tumors. Neoadjuvant intratumoral administration of mRNA encoding costimulatory molecule CD70, CD40 ligand, and Toll-like receptor 4 (TLR 4), collectively referred to as TriMix mRNA, is currently being investigated in patients in the neoadjuvant setting with early stage breast cancer ([NCT03788083](#)).

Immunostimulatory antibodies—There are a number of theoretical advantages to local administration of immunostimulatory antibodies. First, the most relevant target binding sites are on the surface of tumor infiltrating lymphocytes. Second, the route of administration circumvents any issues with tissue penetration of systemically administered antibodies, and allows targeting of lymphoid tissue downstream from the injected tumor. As such there is significant interest in investigating the utility of intratumoral antibodies in solid tumors, with several clinical trials looking at OX40 agonistic antibody ([NCT03831295](#)), bispecific antibody MDX-447 ([NCT00005813](#)) and anti-PD-1 and anti-CTLA-4 antibodies ([NCT03058289](#)) among a diverse array of solid tumors. However, at this current time, there are no clinical trials assessing neoadjuvant administration of immunostimulatory antibodies.

Small molecule immune modulators—Other candidate intratumoral therapies include small molecule immune modulators. The intratumorally administered STING agonist ADU-S100 has demonstrated antitumor activity in PD-1–naïve advanced triple negative breast cancer and PD-1–refractory melanoma when administered in conjunction with checkpoint inhibitor spartalizumab(26). It is also being studied in patients with head and neck cancer in conjunction with the checkpoint inhibitor pembrolizumab ([NCT03937141](#)).

Intratumoral administration of toll like receptor (TLR) agonists are also being studied in preclinical(8) and clinical settings(27,28). In a recently published phase II study utilizing perioperative local administration of CpG oligodeoxynucleotides, a TLR9 agonist, into the resection cavity in patients with newly diagnosed glioblastoma, followed by standard of care therapy following resection found no difference in survival between patients who received CpG and patients who did not, though the therapy was well tolerated(28). Intratumoral administration of TLR7/8 agonist NKTR-262 is currently being studied in patients with locally advanced or metastatic solid tumors ([NCT03435640](#)). Preliminary results from the phase I/II REVEAL trial, recently reported at ASCO 2019, noted that out of 11 patients with evaluable disease, 2 patients had partial response, 3 had stable disease and 6 had progressive disease, resulting in a disease control rate of 45.5%(29). Overall, these combinations have thus far been well-tolerated with no dose-limiting toxicities and could also be readily transferred to the neoadjuvant setting.

Combination strategies

As reflected in the growing number of clinical trials utilizing chemotherapy and radiation in conjunction with immunotherapy, combinations of immunotherapies with other therapies may be essential for achieving an effective anti-tumor response and improving patient outcomes(30–32). While it is not fully understood how immune modulating agents should best be combined synergistically, it is an actively growing field of preclinical and clinical investigation(33,34). And as previously mentioned, one of the benefits of local delivery of

immune-stimulatory agents is that by preventing significant systemic toxicity and off-target effects, it allows for safer administration of combinatory immunotherapy regimens. To date, most of the clinical trials combining intratumoral immunotherapy with other treatment modalities have been tested in patients with advanced disease. However, these combination strategies may be even more effective in the neoadjuvant setting.

Combination intratumoral immunotherapy with checkpoint inhibitors—Several high profile clinical trials have successfully utilized systemic immune checkpoint inhibitors in the neoadjuvant setting(14,19,22).Combining checkpoint therapy with local application of cytokines, oncolytic virus, or pathogen-associated molecular pattern to augment and maintain the local and systemic anti-tumor immune response is a rational next step and has demonstrated promise in preclinical and settings(35–37). For instance, in preclinical studies, intratumoral delivery of TLR 7 and TLR 9 in combination with PD-1 blockage promoted M1 polarization of tumor-associated macrophages and cytotoxic T cell and NK activity. (38–40). Furthermore, another preclinical study utilizing a triple-negative breast cancer model demonstrated that neoadjuvant oncolytic virotherapy sensitizes the tumor to immune checkpoint therapy(16). A phase II trial investigating the combination of local administration of HF10, an oncolytic virus, and ipilimumab demonstrated an overall response rate of 41% in patients with unresectable metastatic melanoma(41). Due to this encouraging results HF in combination with nivolumab is currently being tested in a neoadjuvant phase I trial in resectable melanoma patients ([NCT03259425](#)).

To date, clinical trials combining intratumoral agents with checkpoint inhibitors are preliminary and mainly in patients with advanced disease. However, clinical studies of intratumoral immunotherapy in conjunction with systemic checkpoint inhibitors in the neoadjuvant setting are ongoing and will shed light on the feasibility and efficacy of this approach in patients with earlier stage disease.

Combining intratumoral immunotherapy with radiotherapy—It is increasingly evident that radiotherapy, in addition to causing growth arrest and cell death, may also prime antitumor immunity and synergize with immunotherapy(42–45). This synergistic effect of immunotherapy and radiation is dependent on three variables: the individual radiation dose, the number, and the timing of radiotherapy treatments. These are critical determinants in successful generation of an antitumor immune response(46,47). For example, at certain dosages, radiation not only eliminates tumor cells via DNA-damage and programmed cell death, but also elicits tumor-specific immune responses by tumor antigen release and activation of effector cells (43,44,46,48).

So far, most ongoing clinical neoadjuvant trials combine local delivery of immune stimulatory agents with standard radiotherapy ([NCT00365872](#), [NCT01347034](#), [NCT02446093](#)). These conventional radiation regimens are primarily designed to eliminate tumor cells but might not be optimal for partnering with immunotherapy. Preclinical data has shown that a single dose of 20 Gy, in contrast to 3 fractions of 8 Gy, resulted in insufficient dendritic cell recruitment and lack of T cell activation. When combined with immunotherapy, this single dose of 20 Gy failed to elicit local and systemic antitumor response(47). In this instance, a lower dose radiation treatment, repeated over time, was

more effective in eliciting antitumor response than a more conventional, higher, single dose of radiation, illustrating the correlation between radiation dosage and its immune modulating effects.

In addition, studies have shown that optimization of radiotherapy dose-time fractionation can increase dendritic cell recruitment and enhance antitumor response(49). A neoadjuvant phase I/II trial combining localized fractionated radiotherapy geared towards stimulating antitumor immune response with intratumoral administration of dendritic cells demonstrated the feasibility and efficacy of this approach in patients with high-risk soft tissue sarcoma(23,50). While preclinical and clinical data from this combination approach are encouraging, optimal radiation regimens require further delineation and unanswered questions regarding dose, size and fraction of radiotherapy remain.

Combining intratumoral immunotherapy with chemotherapy—The main rationale for using neoadjuvant chemotherapy is its capacity to eliminate tumor cells, reduce tumor size and facilitate surgery(51–54). In addition, neoadjuvant chemotherapy can also target micro-metastatic disease and test chemo-responsiveness(15,55,56). While traditionally this modality has been considered to be immunosuppressive, this may be because cytotoxic chemotherapeutic agents were originally used in amounts that are close to the maximum-tolerated dose (MTD) in phase II and III clinical trials, which commonly causes myelo- and lymphopenia(57). Chemotherapy is now typically given at doses that are significantly lower than MTD, and have been shown to allow for the elicitation of normal immune responses by vaccines against the influenza virus, demonstrating that chemotherapy is compatible with initiation of an immune response(58,59). Moreover, accumulating evidence over the past several years suggest that certain chemotherapeutic agents can actually modulate tumor immunity and strengthen antitumor effects when combined with local delivery of immune stimulatory agents(60–62).

For instance, low-dose cyclophosphamide depletes T regulatory cells while increasing effector T cell function and gemcitabine enhances cross-priming of CD8 T cells and reduces MDSC infiltration(63–65). Furthermore, preclinical data shows that application of low-dose cyclophosphamide prior to local therapy with TLR 7 and radiation was able to enhance antitumor effect in a murine breast cancer model(66). And, another preclinical study found that intratumoral oncolytic peptide LTX-315 displayed a strong additive antitumoral effect when utilized in conjunction with standard of care doxorubicin(67).

Due to its ability to both eliminate tumor cells and trigger immune response, chemotherapy is a promising combination partner with immunotherapy. However, the optimal integration of these two therapeutic regimens should seek to minimize antagonistic interactions.

Challenges to intratumoral therapy

Existing clinical data utilizing intratumoral immunotherapy is preliminary and mainly in patients with advanced or refractory disease. To fully elucidate the potential of neoadjuvant intratumoral immunotherapy and make this therapeutic approach available to patients with early stage cancer, a number of practical considerations must first be addressed.

The ideal dose and schedule for intratumoral immunotherapy have yet to be established and is likely to vary according to safety profile of the immune stimulating agent and the combination of agents (68). While systemic immunotherapy is generally dosed by patient weight, intratumoral immunotherapy can be dosed according to size of a specific lesion (e.g. fixed dose/tumor volume), to overall tumor burden or to patient weight. Which dosing algorithm is most appropriate can also vary based on the agent or combination of agents utilized according to whether the treatment regimen is more likely to cause a local reaction or systemic toxicity. Thus the use of biomarkers and radiologic assessments is critical in Phase I clinical trials utilizing intratumoral immunotherapy for determining the optimal doses and schedules.

Accessibility of tumor lesions is another major challenge to intratumoral therapy, especially if repeated injections are needed to trigger an effective systemic immune response. Most intratumoral clinical studies have been performed in easily accessible lesions such as breast or skin cancer. However due to increased availability of interventional radiologic, endoscopic and laparoscopic procedures, most if not all lesions can now be accessed with or without the assistance of imaging modalities such as ultrasound, CT, etc⁵. At the European Society for Medical Oncology (ESMO)-sponsored meeting for human intratumoral immunotherapy (HIT-IT) in 2018, experts proposed that intralesional therapy be considered for any tumor where either the primary lesion or its metastases are accessible(68). Therefore, the challenge in intratumoral therapy now lies not in initial accessibility, but in optimization of drug delivery technologies to enhance intratumoral delivery and reduce repeat injections(6,69) Ways in which repeat dosing might be avoided include: development of better methodologies to confine therapeutics to target cells, block therapeutic diffusion and improve drug uptake by target cells(70–72).

Recent preclinical and clinical data demonstrate that intratumoral injection of immunostimulatory agents followed by electroporation is a safe and effective method to enhance drug uptake in tumor cells(73,74). Electroporation pulses, applied locally with electrodes, lead to permeabilization of the cell membrane and facilitate transduction of applied agents in the target cells. Clinical Phase I and II studies utilizing electroporation have shown an improved systemic therapeutic effect in patients with advanced melanoma and triple-negative breast cancer compared to cytokine delivery alone(74,75).

Another promising approach to promote tumor accumulation and reduce systemic effects is the utilization of nanoparticles(76–78). Nanoparticles serve as drug carriers through organ barriers or cell membranes. Since only a small portion of cells to be transduced to achieve an effective anti-tumor response, nanoparticles may be particularly effective when utilized in conjunction with intratumoral therapies(79–81). Reports of nanoparticle-based delivery, e.g. delivery of PD-L1 trap fusion protein in a colon cancer model, illustrated the feasibility and efficacy of this approach(82). In addition, nanoparticles may be utilized to deliver multiple pro-immune agents simultaneously. Preclinical data of co-delivery, e.g. IL-2 and TGF- β inhibitor or anti-CD137 and CpC, eliminated injected tumors and induced effective systemic anti-tumor responses(83,84). Lastly, nanoparticles can be designed to target a specific immune cell subpopulation, e.g. CD8⁺ T cells, to localize immunotherapeutic reagents and reduce off-target effects (85).

Conclusion

Intratumoral delivery of immunotherapy has multiple advantages that make it especially appealing in the neoadjuvant setting. However, to realize the full potential of neoadjuvant intratumoral immunotherapy, more clinical trials are needed to explore local administration in patients with early stage solid tumors. For this to happen, preclinical results first need to be translated into the clinical setting. As mentioned above, one of the main difficulties of local intratumoral administration is the requirement for invasive procedures for administering treatment to solid tumors that are not always readily accessible. However, new pharmaceutical formulations of immunotherapy agents incorporating advanced strategies of encapsulation and delivery are decreasing the procedural requirements for intratumoral immunotherapy and making it increasingly amenable to clinical translation(78,86,87).

Separately, a growing number of immunotherapies are being approved by the Food and Drug Administration and European Medicines Agency for clinical use. However, only a handful of immune modulating agents have been studied in the intratumoral setting even though such localized testing in most cases presents less risk than systemic applications and offer increased opportunity to explore immunotherapy in a combined clinical setting. Where clinical trials study the efficacy systemic administration of specific immune modulating agents, corresponding trials should be run in the intratumoral setting for comparison.

As increased options to incorporate immunotherapy in the clinic become available to clinicians, these studies would provide timely and clinically important information on how immunotherapy may optimally be combined with surgical resection. The results of such studies could then be utilized to inform establishment of neoadjuvant immunotherapy regimens for patients with early stage and locally advanced solid tumors.

Acknowledgement

This work was supported by grants from the National Institute of Health (5R35CA197353) (R.L.), Cancer Prevention and Research Institute of Texas (RR180017) (W.J.), The National Cancer Institute (K08CA241070) (W.J.), the Susan G. Komen Foundation (CCR19605871) (W.J.). Wan Xing Hong is supported by The National Institute of Health (5T32AI07290). Sarah Haebe is supported by The German Cancer Aid (Mildred-Scheel postdoctoral fellowship).

Dr. Ronald Levy serves on the advisory boards for Five Prime, Corvus, Quadriga, BeiGene, GigaGen, Teneobio, Sutro, Checkmate, Nurix, Dragonfly, Abpro, Apexigen, Spotlight, 47 Inc, XCella, Immunocore, Walking Fish.

Dr. Benedikt Westphalen is on the advisory boards for Celgene, Shire/Baxalta Rafael Pharmaceuticals, Redhill and Roche. He receives research support from Roche.

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Figure 1: Intratumoral immunotherapy initiates systemic antitumor response.

Intratumoral delivery of immunotherapy involves the direct injection of immune stimulating agents into the tumor. This primes tumor infiltrating T cells, which then circulate systemically to generate a global antitumor response. Compared to systemic immunotherapy, this approach avoids off target toxicities, requires a much lower dose of immune stimulating agents, utilizes the antigen rich tumor microenvironment to provide superior T cell priming and allows for the generation of a polyclonal T cell response.

Figure 2: Possible intervention timeline for neoadjuvant immunotherapy.

Neoadjuvant therapy is the therapy given before the primary cancer treatment, usually surgery, with the goal of enhancing the outcome of the primary treatment modality. Traditionally chemoradiation has been utilized but there is now increasing interest in incorporating immunotherapy into the neoadjuvant setting.

Figure 3: Neoadjuvant intratumoral immunotherapy trials.

There are twenty four recent and ongoing clinical trials utilizing neoadjuvant intratumoral immunotherapy across a diverse spectrum of solid tumors. The trial phase, immune stimulating agents used and solid tumor type for those clinical trials is summarized in the figure.

Table 1:

Recent and ongoing clinical trials utilizing neoadjuvant intratumoral immunotherapy.

	Intratumoral agent	Combination	Tumor Histotype	Clinical Phase	Trial ID	Status
PAMPs and analogs	Poly-ICLC (Hiltonol)		Prostate cancer	I	NCT03262103	Recruiting
	TLR7 agonist (Imiquimod)		Melanoma	III	NCT01720407	Active, not recruiting
	TLR9 agonist (CMP-001)	Anti-PD-1 (Nivolumab)	Melanoma Lymph node cancer	II	NCT03618641	Recruiting
	TLR8 agonist (VTX-2337)	Anti-PD-1 (Tislelizumab)	Head and neck cancer	I	NCT03906526	Not yet recruiting
Gene therapy	L19IL2/ L19TNF (Daromun)		Melanoma	III	NCT03567889	Recruiting
	L19IL2/L19TNF		Melanoma	III	NCT02938299	Unknown
	IL2 plasmid (Leuvectin)		Prostate Cancer	II	NCT00004050	Terminated
	CD70/CD40/OX40L mRNA (TriMix)		Breast Cancer	I	NCT03788083	Recruiting
Cell therapy	Dendritic cells	Chemotherapy Aromatase inhibitor Estrogen receptor modulator	Breast cancer	II	NCT00499083	Completed
	E7 TCR T cells		HPV-associated Head and neck cancer	II	NCT04044950	Not yet recruiting
	Dendritic cells	Radiotherapy	Soft Tissue Sarcoma	II	NCT00365872	Completed
	Dendritic cells	Radiotherapy	Soft Tissue Sarcoma	II	NCT01347034	Completed
Viro-therapy	JX-594 (Oncolytic virus)		Colorectal Carcinoma	II	NCT01329809	Terminated
	T-VEC (Oncolytic virus)		Melanoma	II	NCT02211131	Active, not recruiting
	MVA-BN-Brachyury	Anti-PD-L1 (Atezolizumab) Rilimogene galvacirepvec (PROSTVAC)	Prostate Adenocarcinoma	II	NCT04020094	Not yet recruiting
	GMCI (Adenovirus)	Radiotherapy Chemotherapy	Pancreatic Adenocarcinoma	II	NCT02446093	Recruiting
	T-VEC (Oncolytic virus)	Anti-PD-L1 (Atezolizumab)	Breast cancer	I	NCT03802604	Recruiting
	T-VEC (Oncolytic virus)	Chemotherapy	Breast cancer	I/II	NCT02779855	Recruiting
	T-VEC (Oncolytic virus)	Anti-PD-1 (Pembrolizumab)	Melanoma	II	NCT03842943	Not yet recruiting
	T-VEC (Oncolytic virus)	BRAF Inhibitor MEK Inhibitor	Melanoma	II	NCT03972046	Recruiting
	T-VEC (Oncolytic virus)	Radiotherapy	Soft Tissue Sarcoma	I/II	NCT02453191	Active, not recruiting
	T-VEC (Oncolytic virus)	Chemotherapy Radiotherapy	Rectal cancer	I	NCT03300544	Recruiting
	HF10 (Oncolytic virus)	Anti-PD-1 (Nivolumab)	Melanoma	II	NCT03259425	Active, not recruiting

Intratumoral agent	Combination	Tumor Histotype	Clinical Phase	Trial ID	Status
OrienX010 (Oncolytic virus)	Anti-PD-1 (Treprizumab)	Melanoma	I	NCT04197882	Recruiting

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