HHS Public Access

Author manuscript

Surg Oncol Clin N Am. Author manuscript; available in PMC 2021 July 01.

Published in final edited form as:

Surg Oncol Clin N Am. 2020 July ; 29(3): 433–444. doi:10.1016/j.soc.2020.02.008.

Injectable Therapies for Regional Melanoma

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Keywords

In transit melanoma; Intralesional therapies; Injectable therapies; Melanoma vaccines; Immunotherapy; Oncolytic viral therapy

Introduction

While early stage, localized melanoma is curable with surgical resection, a significant proportion of patients go on to develop recurrence. Approximately 4–12% of all patients develop recurrence in the form of in-transit (IT) disease, with involvement of dermal or subdermal lymphatics between the primary tumor site and the draining lymph nodes.[1,2] Patients with recurrent or metastatic disease, including IT disease, have significantly decreased survival compared to those with localized disease.[1,3] While patients with isolated locoregional disease may benefit from metastasectomies when it is possible to resect for curative intent, many of these patients develop multiple IT lesions that are unresectable and require alternative approaches. Patients with regional IT disease are classified by the American Joint Committee on Cancer (AJCC) 8th edition as having stage IIIB-IIID disease depending on the absence, presence and extent of concurrent regional nodal involvement. Similar to in transit locoregional disease, patients with stage IV M1a disease have one or

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Conflict of Interest/Disclosure: Authors have no disclosures related to this work.

Statement of Originality: To the best of our knowledge this review contains no material previously published or written by another person except where due references are made.

more subcutaneous or dermal metastasis beyond the regional lymph node basin, and other patients with stage IV disease can also have concurrent subcutaneous disease.[4]

These cutaneous and subcutaneous tumor deposits pose a unique challenge for patients and providers, as they commonly become a source of discomfort, bleeding and infection, and can be prohibitively morbid or impractical to resect. However, the superficial and accessible nature of these lesions provides the unique opportunity for treatment with intralesional therapy using injectable therapies which are easy to deliver and generally have low toxicity profiles. Intralesional therapies are thought to ideally work via both local anti-tumor effects as well as the induction of tumor infiltrates and engagement of a systemic anti-tumor immune response. They have shown promise in select patients, leading to localized responses in the injected tumors and sometimes systemic or abscopal responses in distant lesions.[5–6]

Patients with IT or dermal metastases are not only eligible for injectable therapy, but also for regional chemotherapy (limb only) and systemic therapy. Regional infusion therapies, indicated in a subset of patients with unresectable disease limited to an extremity, require general anesthesia and are limited by potentially severe limb toxicities.[7] Available systemic treatments now include multiple effective systemic therapies including immune checkpoint blockade (ICB) and targeted therapy with BRAF/MEK inhibitors. While these systemic therapies have shown remarkable gains in patient outcomes in recent years, they are limited by significant toxicity profiles and high costs of delivery, as well as resistance to therapy and the development of recurrence.[8,10] Given the variety of treatment options currently available, the treatment strategy for advanced melanoma should be personalized and consider the number, location and size of tumor deposits, as well the patient's condition and wishes. Additionally, therapy should be multidisciplinary and is often multifactorial, employing local, regional and systemic therapies, as well as surgical resection.

Numerous clinical trials are currently evaluating a variety of injectable therapies for advanced melanoma, including immune modulators, gene therapies, peptide vaccines and oncolytic viruses, and the number of ongoing clinical trials investigating injectable therapies in melanoma has quickly surpassed the number of trials investigating limb infusion for locally advanced melanoma. (Table 1) Intralesional therapy can be directly cytotoxic to tumors as well as promote tumor infiltration with immune cells, which has emerged as an important component of developing an anti-tumor response. Their role in the current landscape of treatment is evolving, and includes the potential for therapeutic strategies combining injectable and systemic therapies such as ICB to convert and augment responses, as well as use in the neoadjuvant or adjuvant settings.[11–14] This review will cover the intralesional injectable therapies of historical importance, talimogene laherparevec (T-VEC) which is the only currently FDA approved injectable therapy in wide clinical use, and promising therapies in development.

Historical Agents

Bacille-Calmette-Guerin—Bacille-Calmette-Guerin or BCG is a live attenuated strain of *Mycobacterium bovis*, which has historically been used in treatment of metastatic melanoma and other malignancies.[15,16] Intralesional injection of BCG produces a non-specific

inflammatory response and showed promise with reports of treatment responses in both injected and noninjected lesions, particularly cutaneous lesions (compared to subcutaneous lesions) and improvement in survival.[17] However, its use was associated with significant and sometimes severe side effect profile including malaise, flu-like symptoms, hepatic dysfunction and anaphylaxis.[18,19] Despite initial reports of high response rates, BCG failed to show a difference in disease-free or overall survival in stage I-III melanoma in a phase III randomized controlled trial and is now rarely used clinically.[20]

Interferon-alpha—Interferon alpha (IFN-a) was used via systemic administration for patients with metastatic melanoma or in the adjuvant setting for many years, but was associated with significant toxicity and has now been largely replaced by newer therapies such as ICB and targeted therapies.[21] It has also been used as an intralesional injection, though the evidence supporting its use is minimal and it is no longer used clinically.[22]

IL-2—Another therapy used historically is IL-2, an endogenous immunomodulatory cytokine normally produced by activated T cells which is important for T cell survival and proliferation as well as augmentation of natural killer cell cytotoxicity.[23] IL-2 was initially used as intravenous systemic therapy, which showed a modest 10–15% response but was limited by high rates of toxicities.[24] Intralesional IL-2 was introduced in the 1980s and is generally well tolerated with common grade 1–2 adverse effects including flu-like symptoms and erythema but rare grade 3–4 toxicities, as well as promising response rate.[11,25] Though studies have not definitively shown an associated improvement in overall survival or noninjected lesions, a few studies have shown durable responses in a proportion of patients, with improvement in survival among complete responders.[11,26] More recent studies investigating IL-2 have explored recombinant forms of the cytokine, as well as its use in conjunction with other systemic or local therapies.[13,27,28] One technique actively being investigated to improve the clinical benefit of intralesional IL-2 is through the combination of IL-2 with other cytokines and antibody fragments to promote delivery to and retention in the tumor. Daromun (L19-IL-2 + L19-TNF) is a combination of the cytokines IL-2 and TNF each fused with the antibody fragment L19, which targets fibronectin expressed selectively in tumors.[13] Daromun has showed promise in a phase II trial and a phase III trial is ongoing that will evaluate the added benefit of Daromun as neoadjuvant therapy in patients with stage IIIB/C melanoma undergoing surgery (NCT03567889). Outside of clinical trials, the use of IL-2 has decreased as more effective systemic therapies have been developed in recent years. Additionally, its use remains limited due to the frequency of injections required as well as significant associated cost. However, like IFN and BCG, it remains an option for patients with unresectable disease when T-VEC is not available.[29]

Current and Developing Treatment Options

Oncolytic Viral Therapy

Talimogene Laherparepvec: Another treatment strategy in advanced melanoma is oncolytic viral therapy, or the use of viruses delivered directly to the tumor intralesionally, leading to direct cytotoxicity of tumor cells and the creation of an inflammatory response.[30] Talimogene laherparepvec (T-VEC, Imlygic™) is an FDA-approved genetically modified type 1 herpes simplex viral immunotherapy developed to selectively infect and replicate in

tumor cells. T-VEC causes direct cytolysis of tumor cells, recruits and activates immune cells and drives production of granulocyte macrophage colony stimulating factor (GM-CSF), which stimulates the differentiation of progenitor cells into dendritic cells, maximizing the systemic immune response to the tumor.[31]

T-VEC was initially evaluated in a phase I trial in the early 2000's, in which thirty patients with cutaneous or subcutaneous tumor deposits of breast, head and neck, gastrointestinal or refractory melanoma tumors received intratumoral injection of the virus.[32] The injections were generally well tolerated with the most common side effects being local inflammation, erythema, and febrile responses.[32] A subsequent phase II trial evaluating T-VEC in fifty patients with stage IIIC to IV melanoma patients revealed a 26% overall response rate by Response Evaluation Criteria in Solid Tumors (RECIST) criteria, which showed responses not only in injected lesions, but also in noninjected lesions, including visceral lesions.[33] This study found that adverse effects were limited primarily to transient flu-like symptoms which was consistent with the phase I trial.[33]

The OPTiM study was a phase III multi-center trial that enrolled 436 patients at 64 international sites with AJCC 7th edition stage IIIB, IIIC, and IV unresectable melanoma with at least one injectable lesion and without bone metastases, active cerebral metastases or visceral metastases >3 cm or >3 in number between 2009–2011. The majority of patients in each arm had stage IV disease, and about 47% of all patients had not yet had systemic therapy for melanoma. Patients were randomized in a 2:1 ratio to receive repeat intralesional injection with T-VEC or subcutaneous recombinant GM-CSF for a planned 6 months.[34] At a median treatment duration of 23 weeks in the T-VEC arm and 10 weeks in the GM-CSF arm, the study met its primary endpoint of durable response rate (DRR), defined as the rate of complete response (CR) or partial response (PR) lasting at least 6 months, noting a significantly higher DRR rate in the T-VEC arm of 16.3% versus the GM-CSF arm of 2.1% ($P<0.001$). The overall response rate (ORR) was also higher in the T-VEC arm (26.4% versus 5.7%) consistent with the phase II trial findings.[34] Median overall survival (OS) was 23.3 months in the T-VEC arm and 18.9 months in the GM-CSF arm ($P=0.051$). The benefits of T-VEC were found to be more pronounced in patients with stage IIIB-IVM1a disease compared to those with later-stage IV disease, with the improved DRR more pronounced in patients with stage IIIB or IIIC disease (33% vs 0%) and IVM1a disease (16% vs 2%) compared to patients with IVM1b (3% vs 4%). The results of the OPTiM trial ultimately lead to FDA approval of T-VEC in 2015 as first-in-its class oncolytic viral therapy, approved for intralesional (cutaneous, subcutaneous and nodal lesions) treatment of unresectable stage III and stage IV melanoma.

In a recently published update, the OPTiM group presented an updated final analysis of the trial with a median follow-up of 49 months.[35] This updated analysis reports an improved DRR of 19.3% with T-VEC compared to 1.4% with GM-CSF, an ORR of 31.5% with T-VEC compared to 6.4% with GM-CSF.[35] Overall, 16.9% of patients in the T-VEC arm achieved a CR, with a median time to CR of 8.6 months, and achieving a CR was associated with improvement in OS. However, at this time, T-VEC has not been shown to improve survival when used as single therapy.[34,35] Similar to the primary OPTiM analysis, achieving a CR was significantly associated with earlier stage metastatic disease (stage IIIB-IVM1a),

as was DRR, ORR and disease control rate. The T-VEC arm had an 11.3% grade 3 or 4 adverse event rate, including cellulitis (2.1%), fatigue, vomiting, dehydration, deep vein thrombosis and tumor pain (each 1.7%). While the most common adverse events seen with administration of T-VEC include fatigue, chills, pyrexia, nausea and influenza-like illness, it is generally well tolerated and is currently in wide clinical use.

Oncolytic viruses, such as T-VEC, are thought to cause both specific and nonspecific inflammatory responses, leading to increased tumor immune infiltrates and creating an engaged immune microenvironment that may be better able to respond to systemic immune therapies such as ICB or BRAF/MEK inhibitors.[30,36] Injectable therapies therefore have the potential to convert tumors that are devoid of immune cells ("cold" tumors) into tumors with immunologically engaged, T cell infiltrated microenvironments ("hot tumors") that may be more responsive to systemic immune therapies. To this end, a number of recent and ongoing clinical trials (NCT02965716, NCT03972046) are investigating combinations of systemic therapies and T-VEC to enhance responses to systemic therapy.[36–39] In a phase II study of 198 patients with stage IIIB-IV unresectable melanoma comparing ipilimumab alone to combined ipilimumab with T-VEC, the combination therapy resulted in a significantly higher objective response rate (39% vs 18%, odds ratio, 2.9; 95% CI, 1.5–5.5, P=0.002), with responses in injected and noninjected lesions, including visceral lesions.[37] Adverse events grade 3 or higher were noted in 45% of patients in the combination group and 35% of the ipilimumab alone group. Based on these results, this combination of intralesional T-VEC and ipilimumab is now considered a treatment option for certain patients with progression of metastatic or unresectable disease on first line therapies by NCCN guidelines.[29]

Oncolytic Viral Therapies in Development—A number of other promising oncolytic viruses are currently being evaluated.[40–43] The engineered serotype 5 adenovirus ONCOS-102 has been well tolerated in a phase I study and is currently being evaluated in clinical trials in combination with pembrolizumab for unresectable melanoma (NCT03003676).[42,44] Similar to T-VEC, ONCOS-102 has been genetically modified to express GM-CSF to enhance antitumor immunity.[42] Correlative immune studies during the phase I trial in refractory solid tumors (though melanoma was not included) found that intralesional treatment with the virus was associated with an increase in systemic pro-inflammatory cytokines, as well as infiltration of immune cells, particularly CD8+ T cells, into the tumors.[44]

Another promising oncolytic virus is the genetically unaltered coxsackie virus A21 (CVA21, CAVATAK™), which preferentially infects tumor cells and causes cell lysis and an enhanced anti-tumor response.[45] In the phase II CALM trial 57 patients with stage IIIC-IVM1c melanoma received injections of CVA21 on days 1, 3, 5, 8 and 22, and then every three weeks for 6 additional injections. Results showed an overall response rate of 28.1% with a median time to response of 2.8 months, and the study met its primary endpoint of immune-related progression free survival of 38.6% at 6 months.[45] There were no grade 3 or 4 events, and the most common grade 1 events were fatigue, chills, local injection site reactions and fever. Ongoing trials are currently investigating CVA21 combinations with pembrolizumab as well as ipilimumab (NCT02565992, NCT02307149). In preliminary data from the initial 23 patients enrolled in the phase Ib MITCI trial combining CVA21 with ipilimumab, there

were no dose limiting toxicities and the overall response rate in evaluable patients was 50%.[46]

PVSRIPO is a live attenuated, recombinant poliovirus type 1 (Sabin) that contains the internal ribosome entry site of human rhinovirus type 2, thus eliminating neurovirulence of the virus.[41] It exhibits tropism for multiple tumor types including melanoma due to upregulation of the poliovirus receptor (CD155) on tumor cells and has shown promise in preclinical models by eliciting an interferon-dominant immune response in the tumor microenvironment leading to dendritic and T cell infiltration.[41,47]Intratumoral injection of PVSRIPO has shown promising results in glioblastoma multiforme trials, and a phase I trial in refractory melanoma is currently ongoing (NCT03712358).[48] Other ongoing clinical trials include evaluation of a vesicular stomatitis virus (VSV) modified to contain human IFN-beta and TYRP1, an antigen expressed in melanocytes (NCT03865212), and HF10 and RP1, both genetically modified herpes viruses (NCT03259425, NCT03767348).

Melanoma Vaccines—Melanoma vaccines aim to overcome tumor immune evasion mechanisms and stimulate an antitumor immune response via delivery of a target antigen or antigens and an adjuvant designed to enhanced immune responses to the vaccine.[49] Vaccines in development have been used as monotherapy or in conjunction with other immunotherapies such as ICB to provide synergistic immune activation and improved antitumor efficacy, with the goal of producing a durable, targeted immunologic memory against the tumor to prevent metastasis or recurrence. Melanoma vaccines differ based on the adjuvant provided as well as the type and number of antigens involved, which can be whole cells including tumor or dendritic cells, tumor lysates, peptides or peptide fragments, RNA or DNA. Many previously explored vaccine antigens are commonly shared across many melanomas, such as the tumor-associated antigens MAGE-1, MAGE-3, MART-1, glycoprotein100 (gp100) and tyrosinase.[49] A vaccine incorporating a modified gp100 peptide designed to increase affinity to HLA-A2 has been extensively studied and was evaluated in a phase III trial in combination with high-dose IL-2 versus IL-2 alone, and showed an improvement in overall clinical response in the vaccine group (16% vs 6%, P=0.03) as well as a trend towards longer OS (17.8 vs 11.1 months, P=0.06).[50] However, a subsequent trial combining the vaccine with ipilimumab failed to show that adding the vaccine potentiated the clinical benefits of ipilimumab alone.[51] Another melanoma vaccine is 6-MHP (6 melanoma helper peptides), which combines multiple melanoma peptides derived from cancer-testis antigens and melanocytic differentiation proteins.[52,53] Delivery of the vaccine leads to T cell and antibody responses in patients with stage III and IV melanoma, which when present were associated with improved survival.[53] Ongoing trials are currently evaluating 6-MHP and other peptide vaccines (NCT03617328, NCT02382549, NCT02515227, NCT02126579).

Recent advances in tumor sequencing technologies have led to significant breakthroughs in the development of neoantigen vaccines designed to target personal tumor-specific mutations.[54,55] Two recent landmark studies developed neoantigen vaccines based on algorithms to select personalized immunopeptides predicted to generate immunologic responses from individual melanoma genome mutations.[54,55] Both were able to show that these personalized neoantigen vaccines were able to create robust immune responses to the

neoantigens, and showed encouraging clinical results in small cohorts of patients. Numerous trials are now ongoing to evaluate these vaccines. While promising, disadvantages to this approach are the high costs associated, labor intensive development and the lag time required to synthesize these vaccines.

Rose Bengal (PV-10)—PV-10 is a 10% solution of rose bengal disodium dye, a fluorescein derivative that has been studied extensively and accumulates in lysosomes of tumor cells, leading to autolysis.[56] A phase I trial and subsequent phase II trial have shown that intralesional injection of PV-10 is well tolerated and can lead to treatment responses in more than 50% of injected lesions as well as a bystander effect with response in non-injected lesions and significant delays in disease progression.[56,57] An international, multicenter phase II trial is currently ongoing to evaluate the combination of PV-10 with pembrolizumab (NCT02557321).

Proinflammatory Cytokines

Similar to IL-2 and IFN, which are FDA-approved for use in melanoma but rarely used in current clinical practice due to the advent of more effective treatments as well as significant side effects when delivered systemically, other inflammatory cytokines have been explored for their ability to stimulate an inflammatory tumor microenvironment. IL-12 is a proinflammatory cytokine produced by dendritic cells, macrophages and neutrophils that has a variety of proinflammatory immunologic functions including promotion of a Th1 response.[58] Early studies evaluating intratumoral injection of IL-12 plasmid DNA in melanoma showed that the local treatment was well tolerated and leads to reduction of size in a proportion of injected lesions, but did not have an effect on nontreated lesions.[59] Electroporation is being evaluated as a way to improve clinical benefit of IL-12, by permeabilizing cell membranes and increasing transfection of IL-12 DNA plasmids to increase localized IL-12 expression (NCT03132675).[58]

Toll-Like Receptor (TLR) Agonists—Finally, another encouraging opportunity in injectable therapies for melanoma is administration of toll-like receptor (TLR) agonists, either as vaccine adjuvants or by direct intratumoral injection. TLR agonists stimulate the innate immune system, leading to production of local cytokines and a proinflammatory response that may lead to more effective antitumor responses. SD-101 and CMP-001 are both TLR9 agonists being investigated in melanoma.[60,61] SD-101, a synthetic CpG oligonucleotide, is currently being evaluated in a Phase Ib/II multicenter trial in combination with pembrolizumab for patients with unresectable or metastatic melanoma (NCT02521870). In the first phase of the dose escalation trial injections were generally well tolerated and led to a 78% overall response rate in patients naïve to anti-PD-1 therapy and a 15% overall response rate in patients that had prior anti-PD1 therapy, with responses seen in noninjected, distant lesions.[60] Immune expression profiling showed an increase in tumor infiltrates with CD4+ and CD8+ T cells, supporting the conversion of a cold to hot tumor microenvironment. Similarly, CMP-001, a CpG-A oligodeoxynucleotide encapsulated in a virus-like particle, is another TLR9 agonist that showed early promise in an interim analysis of a phase Ib study combining CMP-001 with pembrolizumab in 68 patients with advanced melanoma resistant to anti-PD-1 therapy.[61] Ongoing trials will further evaluate the safety

and efficacy of TLR agonists (NCT02521870, NCT03084640, NCT03618641, NCT02680184, NCT02668770, NCT03445533).

Summary/Discussion—Injectable therapies for melanoma are attractive due to the ease of intralesional delivery to cutaneous, subcutaneous and nodal metastases, limited systemic toxicity profiles and importantly the ability to convert cold, non-inflamed tumors into hot, inflamed tumors that may have better responses to systemic therapies.[62] As lack of T cell infiltration into the tumor microenvironment can be both a barrier to and predictor of response to ICB, there is significant interest in overcoming this immune evasion mechanism and modulating the tumor microenvironment.[63] Intralesional injection with oncolytic viruses such as T-VEC, immune modulators such as TLR agonists or inflammatory cytokines as well as numerous other substances under investigation can promote an inflammatory response in the tumor microenvironment. While multiple injectable treatments have been shown to have the ability to cause local antitumor effects such as direct cytotoxicity, local immune cell infiltration and clinical responses in injected lesions, the most promising intralesional therapies also lead to a systemic antitumor immune response causing responses in distant as well as injected lesions, particularly when combined with systemic therapy. Indeed, the majority of ongoing trials evaluating intralesional therapies are in combination with ICB and targeted therapies.

In the current landscape of melanoma treatment, in which we are seeing better responses to novel treatments than ever before, injectable therapies can be considered as part of a multifaceted approach to patients with IT melanoma as well as unresectable locally advanced and metastatic melanoma. The only FDA approved injectable therapy in wide clinical use currently is T-VEC, though there are many others being evaluated in the clinical trial setting. While injectable therapies as monotherapy have not yet been shown to lead to an improvement in melanoma specific or overall survival, they can be beneficial in subsets of patients.[26,35,64]

In patients with rapidly progressive disease, the use of locoregional therapies such as intralesional therapy or regional chemotherapy must be weighed with the risk of the development of distant metastases, and systemic therapies are often the preferred first line therapy. However, intralesional therapies may be used in patients with recurrent disease, those who have failed systemic therapy or those who are not candidates for systemic therapy. Special consideration for injectable therapies may be given to patients who are frail or have multiple comorbidities and may not be able to tolerate systemic therapies and their requisite side effects, as well as in a palliative setting to improve quality of life or for patients not interested in systemic therapies or morbid surgical resection. Future use of injectable therapies will likely be in conjunction with other systemic therapies or in sequence with surgical therapy to downstage tumors or prevent recurrence. Ongoing trials investigating novel intralesional therapies as well as the synergistic benefits of combination therapies will better guide which patients will benefit most from intralesional therapies in the future.

Funding:

There was no funding provided for this work.

Research Support:

- *NEF and KL receive research support from NIH funded Surgical Oncology research training grant (*T32 CA 93245)
- GMB receives clinical trial funding from Istari Oncology

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Synopsis

Patients with unresectable cutaneous, subcutaneous or nodal melanoma metastases are often candidates for injectable therapies, which are attractive for ease of intralesional delivery to superficial metastases and limited systemic toxicity profiles. Injectable or intralesional therapies can be part of multifaceted treatment strategies to kill tumor directly or to alter the tumor in a way as to make it more sensitive to systemic therapy. Talimogene laherparepvec (T-VEC) is the only FDA approved injectable therapy currently in wide clinical use in the United States, though ongoing trials are evaluating novel intralesional agents, as well as combinations with systemic therapies, particularly checkpoint inhibitors.

Key points

- Injectable therapies are a treatment option for patients with unresectable, recurrent or refractory melanoma with cutaneous, subcutaneous or nodal metastases
- Advantages include ease of delivery to superficial disease sites, relatively limited systemic side effect profile and the ability to promote conversion of cold, non-inflamed tumors to hot, immunologically engaged tumors
- Injectable therapies include intralesional injection of oncolytic viruses, immune modulators such as toll-like receptor agonists and inflammatory cytokines, gene therapy and vaccines, among others
- Talimogene laherparepvec (T-VEC), a modified oncolytic herpes virus, is the only FDA approved injectable treatment currently in wide clinical use in the United States, with many more in development
- In the future, injectable therapies will likely be most beneficial when used in conjunction with systemic therapies such as immune checkpoint blockade

Table 1.

Table showing number of total, completed (terminated, completed and withdrawn) and active (not yet recruiting, recruiting, enrolling by invitation and active, not recruiting) trials on clinicaltrials.gov in cutaneous melanoma when including search terms of virus, vaccine and regional chemotherapy

Search Term(s)	Status	Number of Trials
Injectable / Injection	TOTAL	90
	Complete/Active	55/32
Virus	TOTAL	44
	Complete/Active	23/19
Vaccine	TOTAL	144
	Complete/Active	113/44
Regional Chemotherapy	TOTAL	25
	Complete/Active	19/4