Does Use of Intratumoral Injections in Solid Tumor Malignancies Improve Outcomes and Reduce Adverse Events? An Integrative Review

MAGGIE MATYOLA, APRN, FNP-C, ASHLEY MARTINEZ, DNP, APRN, FNP-BC, JOYCE DAINS, DrPH, JD, APRN, FNP-BC, FNAP, FAANP, FAAN

From The University of Texas MD Anderson Cancer Center, Houston, Texas

Authors' disclosures of conflicts of interest are found at the end of this article.

Correspondence to: Maggie Matyola, APRN, FNP-C, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030
E-mail: mmatyola@MDAnderson.org

https://doi.org/10.6004/jadpro.2024.15.1.4

Abstract

The purpose of this review is to assess the efficacy and adverse events associated with intratumoral injection in the treatment of solid tumor malignancies. A literature review was conducted using PubMed, the Cochrane Database of Systematic Reviews, CINAHL, and Scopus databases from 2009 to 2022. A total of 588 articles were retrieved, with five selected based on inclusion and exclusion criteria. Inclusion criteria specified English language publications, in human trials, and use of intratumoral anticancer agents. The findings from this integrative review demonstrate treatment efficacy as measured by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria with increased stable disease and partial response in patients as well as a prolonged survival period. Additionally, findings show that this therapy is associated with predominantly mild adverse events.

The method of treatment delivery in cancer patients is frequently evaluated to determine the maximum efficacy of selected treatments. In delivering anticancer therapy for solid tumor malignancies, challenges are often encountered when evaluating drug penetrance and systemic adverse effects (Maeda & Khatami, 2018). The traditional method of administering cancer therapy via methods such as intravenous infusion allows the drug to be distributed throughout the body, which increases the potential of generalized systemic effects throughout the tissues and organs.

Intratumoral injections were introduced to overcome limitations in systemic therapies. One such limitation is the poor blood supply associated with solid tumor biological makeup, which is a limiting factor in

J Adv Pract Oncol 2024;15(1):36–42

the penetrance of anticancer agents. This treatment modality was observed as early as the 1900s when Dr. William Coley recorded the use of streptococcal organisms in a cancerous lesion of a living patient (Marabelle et al, 2017).

Intratumoral injections for local administration of drug therapies in solid tumors is one of the newer cornerstones of drug delivery. Local intratumoral medication delivery has the potential to elicit prolonged systemic immune responses by successfully delivering a high concentration of drug directly into the cancerous lesion (Houessinon et al., 2020). Compared with systemic infusions, local injections allow for significantly larger concentrations of immune-stimulating agents in the tumor microenvironment. Solid tumors present a unique challenge due to the requirement to maximize penetrance necessitating direct injection into the tumor lesions. Drug penetrance varies by location in solid tumor malignancies, and intratumoral injection can improve tissue permeability and boost treatment dose efficacy. Intratumoral injection offers the additional advantage of bioavailability without having to be metabolized through sites of the body such as the liver, avoiding first-pass effect.

Clinical trials are designed in drug development to assess safety, side effects, and how the novel treatment compares to existing standard-of-care drugs. Phase I clinical trials are essential to drug development and in establishing the safety profile of novel drugs. Phase II clinical trials include a more significant number of enrollees and test the efficacy and side effects of the novel drugs (Le Tourneau et al., 2009).

The purpose of this review is to determine if the use of intratumoral injection treatment increases the efficacy and reduces adverse events associated with the treatment of solid tumor malignancies.

METHODS

With the assistance of a research librarian, a literature review was conducted using PubMed, Cochrane, Scopus, and CINHAL databases from January 2009 to March 2022. The literature search yielded 588 articles with five meeting inclusion and exclusion criteria (Figure 1). Inclusion criteria specified were English language publications dealing with human subjects who received intratumoral injection as a cancer treatment. Articles that did not specifically identify intratumorally associated toxicities or efficacy measures that were not in unison with other studies were excluded. Search terms were intralesional injections, adverse events, efficacy, cancer treatments, and toxicities.

RESULTS

All five studies included in this review were clinical trials that explored the efficacy and adverse events associated with intratumoral injections. Two were phase I clinical trials (Janku et al., 2021; Hanna et al., 2012) with sample sizes ranging from 9 to 24 enrolled patients. There were two phase II clinical trials that included sample sizes of five and 15 patients, respectively (Hohenforst-Schmidt et al., 2013; Weide at al., 2017), and one phase III clinical trial with 90 patients (Table 1; Li et al., 2016).

Efficacy

For the purposes of this review, efficacy is defined by the Response Evaluation Criteria in Solid Tumor (RECIST 1.1), which measures disease or target lesions at baseline then compares response after the treatment. Within the RECIST 1.1 criteria, data are categorized by complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The modified World Health Organization (mWHO), which assesses tumor burden in response to treatment, was also used to define tumor response in the studies.

Four of the five studies used imaging to assess clinical outcomes after therapy (Hanna et al., 2012; Janku et al., 2021; Li et al., 2016; Weide et al., 2017). The fifth study, Hohenforst-Schimdt and colleagues (2013), did not detail measurable radiologic disease changes in patients.

In a phase I study of 24 patients with treatment refractory solid tumors who received intratumoral injection of *Clostridium novyi*-NT, Janku and colleagues (2021) reported efficacy outcomes including SD and PD consistent with the RECIST 1.1 criteria. In the 24 patients, 42% (10) showed radiologic tumor destruction from treatment with *C. Novyi*-NT in injected lesions with a decrease of –2% to –24% compared to baseline. Of the 22 evaluable patients, 86% (19) demonstrated SD and 13% (3) had PD.

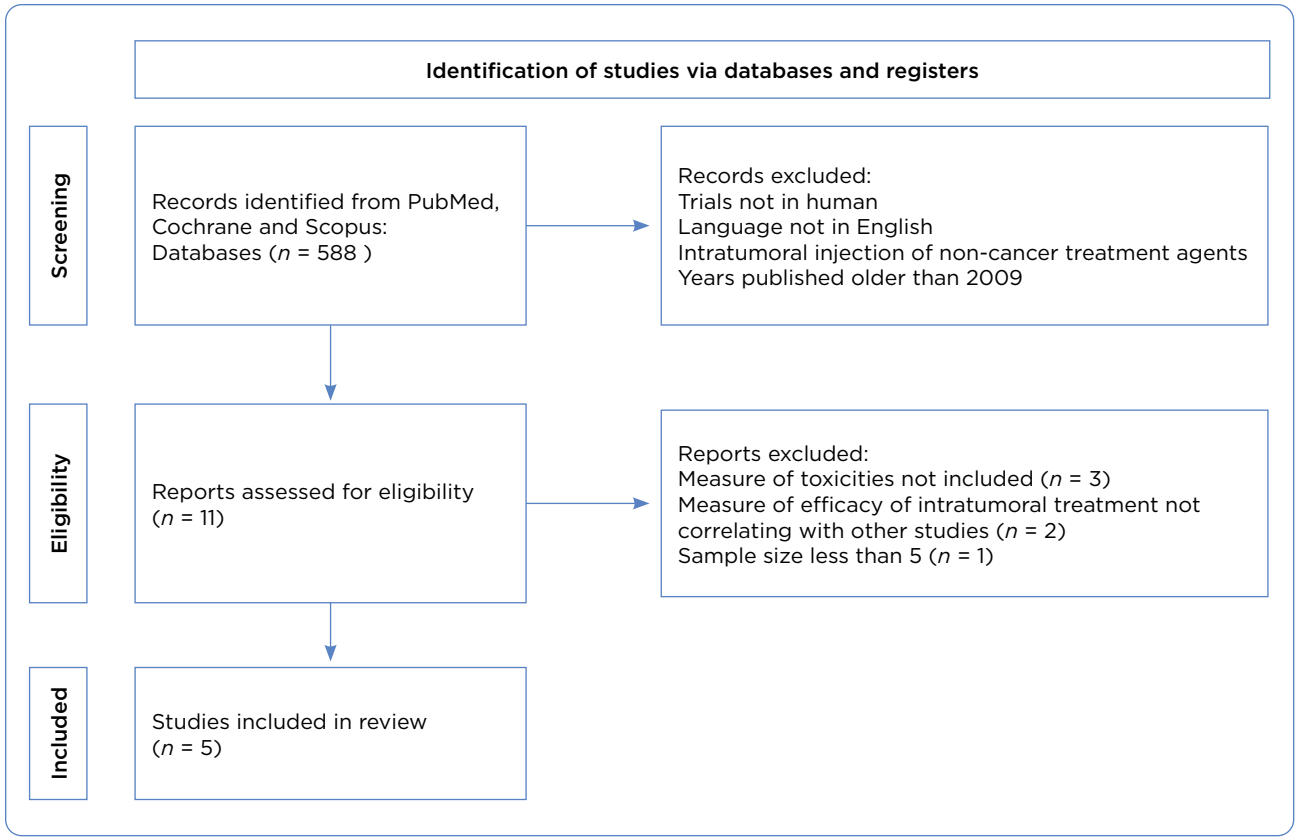

Figure 1. PRISMA flow diagram.

Similarly, Hanna and colleagues (2012) reported on another phase I clinical trial involving two cohorts of patients with unresectable, locally advanced, nonmetastatic pancreatic cancer treated with BC-819 (a DNA plasmid) intratumoral injection. Cohort 1 comprised three subjects who received a 4-mg dose of BC-819. Cohort 2 comprised six subjects who received an 8-mg dose of BC-819. Each cohort received twice-weekly dosing of BC-819 for a total of 2 weeks of imaging-guided intratumoral injection. Injections in cohort 1 participants were performed using CT, whereas intratumoral injections of BC-819 in cohort 2 were performed using endoscopic ultrasound (EUS). Using the RECIST 1.1 criteria, cohort 1 had 33% SD and 67% PD by radiologic evaluation. Cohort 2 demonstrated 67% SD and 33% PD by radiologic assessment using either CT or PET scan.

In their phase II study, which combined the immunotherapy drug ipilimumab (Yervoy) with intratumoral injection of interleukin-2 (IL-2) in 15 melanoma patients with distant metastases, Weide and colleagues (2017) were the only researchers to use a combination drug approach. Ipilimumab was dosed four times at 3-week intervals and IL-2 intratumoral injections were administered twice weekly for 4 weeks. Of their patients, 73% (11) received all four doses of ipilimumab, and one patient received three of four doses. Two patients received two out of four intended doses and one had a single dose administered. There were eight full courses of IL-2 doses, and 80% received the full course of the intended doses. Two of the patients received seven out of eight doses and one patient received one dose of IL-2 intratumoral injection. The authors reported that at 12-week follow-up, 20% (3) of their patients showed SD while 67% (10) had PD. Of their patients, 13% (2) had to be evaluated prior to the 12-week period due to early disease progression requiring transition to a different systemic therapy.

In Li and colleagues' phase III multicenter study (2016), 90 patients with non–small cell lung cancer (NSCLC) received para-toluenesulfonamide (PTS) intratumoral injection. Pre- and post-treatment changes were evaluated using objective

Table 1. Summary of Literature Review

Study	CR	PR	SD	PD	Survival	Adverse events
Janku et al., 2021 Phase I *N* (evaluable) = 21	0	0	86% (19)	13% (3)	22 alive at follow-up of 8 weeks or more	DLTs: 8.3% sepsis, 6.2% gas gangrene, 4% soft tissue infection, 13% tachycardia, 46% fever
Hanna et al., 2012 Phase I, cohort 1 *N* = 3	0	0	33% (1)	67% (2)	100% at 3 months 100% at 6 months 0% at 12 months	100% mild
Hanna et al., 2012 Phase I, cohort 2 *N* = 6	0	0	67% (4)	33% (2)	67% at 6 months 33% at 12 months	100% mild 1 grade 3 DLT
Li et al., 2016 Phase III *N* (evaluable) = 79	44% (39)	29% (26)	23% (12)	2% (2)	Median survival: 25th percentile: 180 days 75th percentile: 460 days	64% total adverse events 46% mild 7.9% severe
Hohenforst-Schmidt et al., 2013 Phase II *N* = 6	17% (1)	67% (4)	17% (1)	0	Median survival: Average in pts with partial response: 463 days Average in pts with progressive disease: 338 days	4/6 "not severe"
Weide et al., 2017 Phase II N (evaluable) = 13	0	0	20% (3)	67% (10)	Median survival = 231 days (188 days for patients who died, 940 days for those who lived)	100% localized symptoms 60% fatigue, 13% colitis, 40% exanthema rash

Note. CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; DLT = dose-limiting toxicity.

alleviation rate (OAR) based on the RECIST 1.1. or WHO criteria. The authors reported that at 30 days post treatment, 44% (39) had achieved CR, 29% (26) had achieved PR, 4% (2) had PD, and 23% (12) had SD.

In contrast, Hohenforst-Schmidt and colleagues' phase II clinical trial of five patients with NSCLC (2013), did not detail measurable radiologic disease changes during patients' treatment with intratumoral cisplatin therapy. The authors do mention using CT scans prior to therapy and post therapy but do not categorize information using WHO or RECIST 1.1 criteria.

Survival Outcomes

All five studies (Janku et al., 2021; Hanna et al., 2012; Li et al., 2016; Weide et al., 2017; Hohenforst-Schmidt et al., 2013) analyzed survival outcomes. The time from initiation of treatment to progression-free survival to disease progression or death was defined as the progression-free survival period. Analysis of survival was performed using the Kaplan-Meier method and log rank test.

In their phase I study of unresectable, locally advanced nonmetastatic pancreatic cancer, Hanna and colleagues (2012) reported that patients were followed every 3 months for up to 1 year post injection for survival and disease status. At the first 3-month follow-up, all patients in their cohort 1 were alive; however, two out of three (67%) had progressive disease. In their second cohort with an increased dose, two out of six (33%) had progressive disease. In the lower dose cohort, 100% of patients survived beyond 6 months; however, they had all succumbed at the 12-month mark. In the higher dose cohort, 67% (4/6) of their patients had survived at 6 months, and 33% (2/6) survived at 12 months or longer.

In their phase II study involving a combination drug approach with systemic ipilimumab and intratumoral IL-2 injections in 15 melanoma patients, Weide and colleagues (2016) reported the median survival period was 231 days, with 188 days for patients who died during follow-up (12 patients) and 940 days for those who were still alive (three patients). In the whole cohort,

the overall survival probability was 33.3% after 1 year and 26.7% after 2 years, using the Kaplan-Meier method.

Similarly, Li and colleagues (2016) performed an analysis of survival using the Kaplan-Meier method. They reported that 42% (37/88) of their patients succumbed with a median survival duration of 394 days.

In their phase II study involving use of cisplatin therapy in NSCLC, Hohenforst-Schmidt and colleagues (2013) reported average PR+ survival (a reduction of greater than 50% of initial disease volume) as 463 days and average PR– survival (a reduction of 25%–50% of initial disease volume) as 338 days.

In contrast, Janku and colleagues (2021) did not report scheduled time intervals of follow-up similar to the other two studies; instead, they reported on progression and mortality outcomes. Two of their patients succumbed during their follow-up period. The first patient died 56 days following the intratumoral injection as a result of disease progression. The second patient was reported to have progressed as well and died at 4.5 months after C. *novyi*-NT injection. They reported progression-free survival periods with a mean of 78.3 days across their 22 subjects ranging from a minimum of 26 days to maximum of 240 days in their patient population.

Adverse Events

All five articles addressed adverse events. Safety analysis was the primary aim of three out of the five studies (Hanna et al., 2012; Janku et al., 2021; Li et al., 2016), which used toxicity outcomes characterized as dose-limiting toxicities (DLTs), localized toxicities, and systemic toxicities. The Common Terminology Criteria for Adverse Events (CTCAE), which describes the severity of organ toxicity for patients receiving cancer therapy, was also used with categorization as mild, moderate, or severe. Two of the studies (Hohenforst-Schmidt et al., 2013; Weide et al. 2017) used non-standardized criteria for evaluating adverse events.

Li and colleagues (2016) and Hanna and colleagues (2012) both reported an aggregate of patients that suffered adverse events as 64% and 100%, respectively. Specifically, in a phase I clinical trial, Hanna and colleagues (2012) reported mild adverse events such as grade one anemia and grade two amylase elevation in cohort two. Of the patients included in the two cohorts, one dosed at 4 mg and another dosed at 8 mg, only one grade 3 or severe lipase elevation was reported as a DLT.

In their phase III multicenter study, Li and colleagues (2016) reported mild adverse events in 43% of their patients, which included coughing, bloody sputum, and injection site hemorrhage. Severe adverse events in 8% of their patients included airway stenosis, respiratory failure, major hemorrhaging, and heart failure.

A safety analysis by Janku and colleagues (2021) in the *C. novyi*-NT study revealed three patients with DLTs, which included grade 4 sepsis and grade 4 gas gangrene. It was reported that all patients recovered from these DLTs. Sepsis requiring additional supportive treatment in a male with metastatic osteosarcoma was reported 3 days after receiving intratumoral injection of *C. novyi*-NT. The same grade 4 sepsis was reported in a male patient who received injection into a thigh mass, which also required additional supportive treatment. Finally, they reported grade 4 gas gangrene in a male patient with myxofibrosarcoma of an upper extremity, which was unresponsive to supportive measures and eventually resulted in an amputation of the extremity, 11 days after receiving treatment with intratumoral *C. novyi*-NT.

In contrast to the aforementioned three studies, Hohenforst-Schmidt and colleagues (2013) in a phase II clinical trial of NSCLC reported adverse events not categorized by CTCAE or DLTs. Of their six evaluable patients, four had adverse effects, although none of these were noted to be severe adverse events. The adverse events were bleeding at injection site after intratumoral chemotherapy, vomiting and nausea, and leukopenia and fever lasting 3 days post injection in a patient.

Weide and colleagues (2017) reported that in all patients, localized injection site symptoms such as pain, edema, and erythema were observed. 60% of the patients noted fatigue or flu-like symptoms within 24 hours of injection. Colitis and exanthema were shown to be directly connected to therapy in 40% of the patients.

DISCUSSION

The strategy of localized delivery of therapy in intratumoral injections presents a novel method to target the tumor microenvironment more efficaciously (Goins et al., 2016). The studies in this review were clinical trials that explored the efficacy and toxicities associated with intratumoral injections.

In measuring efficacy, Li and colleagues' phase III study (2016) demonstrated stronger outcomes data as compared with others, with reports of complete remission. Hohenforst-Schmidt and colleagues (2013) did report PR, whereas the others reported only SD or PD. The larger sample increases the level of statistical significance and can account for these differences. Additionally, these clinical trials had a heterogenous representation of disease sites and patient status, which may explain the mixed results. In their study, Muñoz and colleagues (2021) highlighted the importance of improving efficacy of drug delivery by the use of CT-guided intratumoral immunotherapy to potentiate lesion targeting accuracy and improve drug efficacy, thus improving patient outcomes.

Differences in dosing can account for the variability of findings. Weide and colleagues' (2017) was the only study in this review that used a combination of ipilimumab, an immunotherapy drug, and intratumorally injected IL-2 in advanced melanoma patients, with 80% of the patients receiving a full dose of IL-2. Higher dosing in cohort two could be implicated as part of the reason patients had a higher rate of SD than PD in that cohort. In contrast, cohort one reported higher rates of PD vs. SD. Hanna and colleagues (2012) had two different dose levels in their dose-escalation trial, which could account for the differences in survival outcomes between the two population groups.

Four out of the five studies reported a prolonged survival period (months) post treatment, demonstrating lengthened survival periods in the various disease subtypes of patients treated with various intratumoral agents (Hanna et al., 2012; Li et al., 2016; Hohenforst-Schmidt et al., 2013; Weide at al.,2017). Hohenforst-Schimdt and colleagues (2013) reported that according to the International Union Against Cancer TNM Prognostic Factors Project, 7th edition (Mirsadraee et al., 2012), the expected median survival for patients with Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1 was 276 days. They were able to achieve a median survival of 378 days, which demonstrated a 44% surplus in median survival. Similarly, Hanna and colleagues (2012) also reported survival outcomes that demonstrated 67% of their patients were alive at the 6-month follow-up period. Similar to the other studies, Weide and colleagues (2017) reported a prolonged survival period of 231 days. These data demonstrate the commonality of prolonged survival periods across the studies.

Dose-limiting toxicities reported by Janku and colleauges (2021) included grade 4 sepsis in two of their patients and grade 4 gas gangrene occurring in one patient. This necessitated the use of additional treatment with IV antibiotics, hydration, and vasopressors. One of the patients with grade 4 sepsis succumbed after 56 days while the other recovered and had SD for a period of 4.5 months, at which time he died from disease progression.

Only one study (Hanna et al., 2012) reported DLTs. The other studies primarily reported mild to moderate adverse events. Most common were fatigue, colitis, and exanthem rash. Various patients included in these studies had advanced disease, which can account for the variety of adverse events that were reported in some of the studies.

IMPLICATIONS FOR PRACTICE

Intratumoral injections have a clinical benefit in improving overall survival in patients with solid tumor malignancies. Furthermore, directly targeting the malignant cells through this treatment modality offers an additional benefit of improved penetrance, which intends to increase the antitumor activity of whichever treatment agent is utilized.

With this knowledge, advanced practitioners play a role in the front line in presenting this treatment option to patients they encounter in practice. However, intratumoral injections still lie heavily in the clinical trial setting. In addition, advanced practitioners are often collaborators in clinical trials (Patterson & Barber, 2020). Therefore, seeking out treatment options with a marked clinical benefit, such as intratumoral injections, is highly beneficial to the oncology patient population.

However, there are a multitude of factors that affect the feasibility and administration process of

intratumoral injections. From a technical aspect, the tumor must be directly accessible to perform the intratumoral injection of any lesion (Bult et al., 2013). Training advanced practitioners on the proper administration of intratumoral injections with or without imaging guidance enhances accessibility for patients due to the increased number of providers available to provide this treatment.

Future research should also implicate the role of providers in astutely monitoring adverse events that arise from this therapy. Providers are primarily responsible for sequential follow-up visits and must keenly identify treatment-related adverse events to intervene appropriately (Ulrich et al., 2011).

CONCLUSIONS

Intratumoral injections as a treatment modality exist mainly in clinical trials, except for talimogene laherparepvec therapy, which is standard of care in melanoma patients. There must be further research to explore the efficacy and adverse events associated with this therapy in patients with solid tumor malignancies. In addition, patient enrollment in clinical trials must be expanded to fully explore the use of anticancer targeted therapy with intratumoral injections. Currently, no standardized guidelines exist on the use of intratumoral injections. However, with continued research, information exploration will yield more findings that can guide the effective use of this therapy and minimize the associated adverse event profile.

Disclosure

The authors have no conflicts of interest to disclose.

References

Bult, W., Kroeze, S. G. C., Elschot, M., Seevinck, P. R., Beekman, F. J., de Jong, H. W. A. M.,...Jans, J. J. M. (2013). Intratumoral administration of holmium-166 acetylacetonate microspheres: Antitumor efficacy and feasibility of multimodality imaging in renal cancer. *PloS One, 8*(1), e52178–e52178. https://doi.org/10.1371/journal.pone.0052178

Goins, B., Phillips, W. T., & Bao, A. (2016). Strategies for improving the intratumoral distribution of liposomal drugs in cancer therapy. *Expert Opinion on Drug Delivery, 13*(6), 873–889. https://doi.org/10.1517/17425247.2016.1167035

Hanna, N., Ohana, P., Konikoff, F. M., Leichtmann, G., Hubert, A., Appelbaum, L.,...Hochberg, A. (2012). Phase 1/2a, dose-escalation, safety, pharmacokinetic and preliminary efficacy study of intratumoral administration of BC-819 in patients with unresectable pancreatic cancer. *Cancer Gene Therapy, 19*(6), 374–381. https://doi.org/10.1038/cgt.2012.10

Hohenforst-Schmidt, W., Zarogoulidis, P., Darwiche, K., Vogl, T., Goldberg, E. P., Huang, H.,...Brachmann, J. (2013). Intratumoral chemotherapy for lung cancer: Re-challenge current targeted therapies. *Drug Design, Development and Therapy, 7*, 571–583. https://doi.org/10.2147/DDDT.S46393

Houessinon, A., Moreira, A., Bettoni, J., Schoonaker, M., Sauzay, C., Galmiche, A.,...Chauffert, B. (2020). Resensitization to nivolumab after intratumoral chemotherapy in recurrent head and neck squamous cell cancer: A report of 2 cases. *Case Reports in Oncology, 13*(2), 835–842. https://doi.org/10.1159/000507986

Janku, F., Zhang, H. H., Pezeshki, A., Goel, S., Murthy, R., Wang-Gillam, A.,...Gounder, M. M. (2021). Intratumoral injection of *Clostridium novyi*-NT spores in patients with treatment-refractory advanced solid tumors. *Clinical Cancer Research, 27*(1), 96–106. https://doi.org/10.1158/1078-0432.CCR-20-2065

Le Tourneau, C., Lee, J. J., & Siu, L. L. (2009). Dose escalation methods in phase I cancer clinical trials. *Journal of the National Cancer Institute, 101*(10), 708–720. https://doi.org/10.1093/jnci/djp079

Li, S., Li, Q., Guan, W., Huang, J., Yang, H., Wu, G.,...Zhong, N. (2016). Effects of para–toluenesulfonamide intratumoral injection on non-small cell lung carcinoma with severe central airway obstruction: A multi-center, non-randomized, single-arm, open-label trial. *Lung Cancer, 98*, 43–50. https://doi.org/10.1016/j.lungcan.2016.05.012

Maeda, H., & Khatami, M. (2018). Analyses of repeated failures in cancer therapy for solid tumors: Poor tumor-selective drug delivery, low therapeutic efficacy and unsustainable costs. *Clinical and Translational Medicine, 7*(1), e11. https://doi.org/10.1186/s40169-018-0185-6

Marabelle, A., Tselikas, L., de Baere, T., & Houot, R. (2017). Intratumoral immunotherapy: Using the tumor as the remedy. *Annals of Oncology, 28*(suppl_12), xii33–xii43. https://doi.org/10.1093/annonc/mdx683

Mirsadraee, S., Oswal, D., Alizadeh, Y., Caulo, A., & van Beek, E., Jr. (2012). The 7th lung cancer TNM classification and staging system: Review of the changes and implications. *World Journal of Radiology, 4*(4), 128–134. https://doi.org/10.4329/wjr.v4.i4.128

Muñoz, N. M., Williams, M., Dixon, K., Dupuis, C., McWatters, A., Avritscher, R.,...Sheth, R. A. (2021). Influence of injection technique, drug formulation and tumor microenvironment on intratumoral immunotherapy delivery and efficacy. *Journal for Immunotherapy of Cancer, 9*(2), e001800. https://doi.org/10.1136/jitc-2020-001800

Patterson, C., & Barber, F. D. (2020). Clinical trial subinvestigator: An emerging role for oncology nurse practitioners. *Clinical Journal of Oncology Nursing, 24*(5), 479–481. https://doi.org/10.1188/20.CJON.479-481

Ulrich, C. M., Zhou, Q., Ratcliffe, S. J., Ye, L., Grady, C., & Watkins-Bruner, D. (2011). Nurse practitioners' attitudes about cancer clinical trials and willingness to recommend research participation. *Contemporary Clinical Trials, 33*(1), 76–84. https://doi.org/10.1016/j.cct.2011.09.005

Weide, B., Martens, A., Wistuba-Hamprecht, K., Zelba, H., Maier, L., Lipp, H. P.,...Garbe, C. (2017). Combined treatment with ipilimumab and intratumoral interleukin-2 in pretreated patients with stage IV melanoma-safety and efficacy in a phase II study. *Cancer Immunology, Immunotherapy, 66*(4), 441–449. https://doi.org/10.1007/s00262-016-1944-0