Medical Coverage Policy

Effective Date.....**11/15/2021**
Next Review Date.....**11/15/2022**
Coverage Policy Number **0225**

Adoptive Immunotherapy

Table of Contents

Related Coverage Resources

Chimeric Antigen Receptor T-Cell (CAR-T) and Advanced Cellular/Immune Effector Cell Therapy
Donor Lymphocyte Infusion and Hematopoietic Progenitor Cell (HPC) Boost
Oncology Medications

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This Coverage Policy addresses proposed indications for adoptive immunotherapy, also called adoptive cellular therapy, including the use of lymphocyte activated killer (LAK) cells, tumor Infiltrating lymphocytes (TILs), and antigen-loaded dendritic cells.

Coverage Policy

Each of the following adoptive immunotherapy techniques is considered experimental, investigational or unproven, except as noted below in the related Coverage Policies:

- lymphokine activated killer (LAK) cells activated in vitro by recombinant or natural interleukin-2 (IL-2) or other lymphokines
- tumor infiltrating lymphocytes (TILs)
- antigen-loaded dendritic cells

Note:

- For information on coverage of Sipuleucel-T (Provenge®) refer to Cigna Coverage Policy Oncology Medications.
- For information on coverage of Axicabtagene Ciloleucel (Yescarta™) and Tisagenlecleucel (Kymriah™) see Cigna Coverage Policy Chimeric Antigen Receptor T-Cell (CAR-T) and Advanced Cellular/Immune Effector Cell Therapy

General Background

Adoptive immunotherapy, also called adoptive cellular therapy, is the transfer of immune cells with antitumor activity into a patient to mediate tumor regression. The therapy involves the removal of lymphocytes (white blood cells) from an individual, stimulation of those lymphocytes to increase their immune capabilities, and the transfer of those cells back into the patient. T-Cells, B-Cells and NK cells are types of lymphocytes. The potential benefit of this therapy depends on the availability of recombinant human cytokines and the ability to collect large enough quantities of stimulated lymphocytes for therapeutic transfer. Cytokines are cell signaling protein molecules that aid cell to cell communication in immune responses and stimulate the movement of cells towards sites of inflammation, infection and trauma. Examples of cytokines include interleukin and interferon which aid in regulating the immune system's response to inflammation and infection.

Adoptive immunotherapy has been proposed as a treatment option for numerous conditions including cancer, human immunodeficiency virus, type I diabetes mellitus and rheumatoid arthritis. Several techniques have been investigated, including the use of lymphocyte activated killer (LAK) cells, tumor Infiltrating lymphocytes (TILs), and T-cell lymphocytes/dendritic cells (DCs). At the present time, the high-dose bolus IL-2 regimen remains the treatment of choice for appropriate patients with access to such treatment and is the gold standard to which other IL-2–based regimens should be compared. The addition of tumor-infiltrating lymphocytes, other cytokines, or chemotherapeutics have failed to improve on the durable partial and complete responses observed with high-dose IL-2 treatment.

Lymphocyte Activated Killer (LAK) Cells
LAK cells are developed by removing peripheral blood lymphocytes and stimulating them with high concentrations of interleukin 2 (IL-2), a cytokine produced by lymphocytes that stimulates both T-cells and natural killer cells. Once there is a large enough quantity of stimulated cells, the cells are transferred back into the patient. Studies have suggested that LAK cells are limited in therapeutic efficacy and have demonstrated no advantage for the administration of LAK plus IL-2 over administration of IL-2 alone (Kasslin, 2014). Newer concepts in tumor immunology have lessened the importance of the continuing debate over the merits of IL-2/LAK therapy. The role of this therapy has not been established for any indication.

Literature Review: There is insufficient evidence to demonstrate the safety and effectiveness of adoptive immunotherapy with lymphocyte activated killer cells for the treatment of any condition, including malignancy and human immunodeficiency virus. Studies have primarily been in the form of case series with small patient populations (n=17–33) (Dillman, et al., 2009; Thionuun, et al., 2002).

Kimura et al. (2018) reported on the final results of a phase III, randomized control (RCT) investigating post-surgical adjuvant chemotherapy plus immunotherapy (group A) (n=50) vs. chemotherapy alone (group B) (n=51) for the treatment of non-small cell lung cancer (NSCLC). The trial was first reported by Kimura et al (2015). The objective of the continued research was to evaluate how long immunotherapy in combination with adjuvant chemotherapy or molecular targeted therapy improved the prognosis in post-surgical advanced lung cancer patients with poor prognosis. The authors noted that the target of immunotherapy in this trial was not the primary lesion, but the undetectable tumor cells remaining after the resection of primary carcinoma of the lung. Patients were age < 76 years; Eastern Cooperative Oncology Group performance status 0 or 1; with adequate liver, renal and bone marrow function; primary NSCLC histology (including combined type small cell carcinoma); and pathological of stage IB with tumor sizes larger than five centimeters or with severe vessel invasion and stages II–IV (including non-curative resection cases). Patients were excluded if they had exploratory thoracotomies or macroscopic residual tumors. Immunotherapy was comprised of the adoptive transfer of autologous activated killer T cells and dendritic cells (AKT-DC) from the patient's own regional lymph nodes. Group A received AKT-DC intravenously one week after each course of chemotherapy, once a month for the first six months after

resection and then every two months for two years after surgery. Group B was the control group who received chemotherapy alone. Primary outcomes measured were overall survival (OS) rate and recurrence-free survival (RFS) rate. Median follow up was 59.6 months. The 2, 5, and 7-year OS rates were 96.0%, 69.4%, and 55.1% in group A and 64.7%, 45.1% and 38.1% in group B, respectively. The results were statistically significant in favor of group A (p=0.0005). The 2, 5, and 7-year RFS rates were 70.0%, 57.9%, and 47.5% in group A and 43.1%, 31.4%, and 28.5% in group B, respectively, in favor of group A (p=0.0044). Adverse events were not reported. Author noted limitations included the small, heterogeneous patient population; single institution, and non-blinded study design. Patient selection criteria for post-surgical adjuvant chemotherapy plus immunotherapy has not been established. Additional well-designed, multi-institutional studies with large patient populations are needed to determine the safety and efficacy of this treatment.

Kimura et al. (2015) conducted a phase III, randomized controlled trial (RCT) to investigate postsurgical adjuvant chemotherapy plus immunotherapy (group A) (n=50) vs. chemotherapy alone (group B) (n=51) for the treatment of non-small cell lung cancer (NSCLC). Patients were age < 76 years, Eastern Cooperative Oncology Group (ECOG) performance status 0–1; had adequate bone marrow function, liver function, and renal function; primary NSCLC (including combined-type small cell carcinoma) histology; and pathological of stage IB with tumor sizes larger than five centimeters or with severe vessel invasion and stages II–IV. Non-curative resection cases were included. Immunotherapy consisted of the adoptive transfer of autologous activated killer T (AKT) cells and dendritic cells (DC) obtained from the patients' own regional lymph nodes. The autologous AKT-DC from the regional lymph nodes of patients had to grow enough to provide more than 7×10^9 cells for each course of the therapy. Undetectable tumor cells remaining after the resection of the primary tumor were the target of the immunotherapy. Group A received 12–15 courses of treatment over a two-year period and group B received four courses of chemotherapy. Stage IIIA patients received two courses of induction chemotherapy prior to surgery. Follow-ups occurred for up to five years. The primary end point was overall survival with recurrence-free survival, toxicity, and adverse effects of immunotherapy as secondary end points. The two-year overall survival rates in groups A and B were 93.4% and 66.0%, and the five-year rates were 81.4% and 48.3%, respectively, statistically significant in favor of group A (p=0013). The two- and five-year recurrence-free survival rates were also statistically significant in favor of group A (p=0.0020). Adverse events included chills, shivering and fever. There were 19 cases of recurrence in group A and 33 cases in group B. Thirty-five stage IIIB and IV patients were excluded from the study because macroscopic residual tumors remained after surgery, and enough T cells could not be obtained for dosage. Limitations of the study include the small patient population, heterogeneity of the disease stages and lack of sufficient numbers of lymphocytes obtained from patients with stage N2 and N3. Additional data from a large-scale multi-center RCT is needed before the clinical importance of this therapy is determined. The most effective dose for immunotherapy in this population has not been determined.

Tumor Infiltrating Lymphocytes (TILs)
Tumor tissue contains its own immune system cells called tumor infiltrating lymphocytes. In TIL therapy, tumor infiltrating lymphocytes are removed from the tumor itself and treated with IL-2. These activated cells are then returned to the patient to attack the tumor (American Cancer Society [ACS], 2019). There is insufficient evidence to support the safety and effectiveness of adoptive immunotherapy using tumor infiltrating lymphocytes for the treatment of any condition including melanoma and renal cell cancer. Study populations were small and heterogeneous, and outcomes related to overall survival are variable. At this time, the role of this therapy has not been established for any indication.

Literature Review: Khammari et al. (2020) conducted a randomized control trial of adult patients (n=49) with stage III melanoma with one invaded lymph node after complete resection. The intervention (n=26) was treatment with tumor-infiltrating lymphocytes (TIL) therapy and interleukin-2 (IL-2) administered within eight weeks after lymph node resection and again four weeks later. The comparator (n=23) was no other melanoma treatment (abstention). The primary outcome was disease-free survival (DFS). Secondary outcomes were overall survival rate (OS), tolerance to treatment with TIL + IL2, immunological response, analysis of clinical, biological and histological factors on survival: age, gender, localization of the melanoma lesion, Breslow thickness, Clark score and capsular breaking, ulceration of the primitive lesion and lactate dehydrogenase (LDH) level. Length of follow up was five years. There was no statistical difference in relapse rates (p=0.25) between the TIL + IL2 group (11/26) and abstention group (13/23). Death occurred in 9/26 of TIL + IL2 group and 11/23 of abstention group with no statistical difference in OS (p=0.35). No differences for progression-free survival, for age, gender, localization of melanoma lesion, Breslow thickness, Clark score and capsular breaking were observed. No

significant difference was found between the groups with primary melanoma with ulceration (p=0.14) or without ulceration (p=0.94). Adverse events included fever, tiredness, flu-like symptoms, myalgia, arthralgia, nausea, vomiting, diarrhea, headache, and injection site reaction. Serious adverse events included reactivation of the human herpes virus-6, pulmonary embolism and hypereosinophilia. Author noted limitations included the small patient population and lower number of tumor-specific TIL used to treat compared with previous trials. This study did not demonstrate any beneficial effects of treating patients with stage III melanoma with TIL + IL2.

Dafni et al. (2019) conducted a systematic review and meta-analysis of 13 studies (n=332) to determine the efficacy of adoptive cell therapy (ACT) using autologous tumor-infiltrating lymphocytes (TIL) and recombinant interleukin-2 (IL-2) following non-myeloablative chemotherapy in previously treated metastatic melanoma patients. Included were studies administering TILs with the addition of full non-myeloablating (NMA) chemotherapy regimen (or cyclophosphamide before 2000) and IL-2 (low dose [LD]: <720 000 IU/kg; high dose [HD]: 720 000 IU/kg) without total body irradiation (TBI). Reporting of tumor response was required. The target population were patients with advanced cutaneous-melanoma, refractory to several treatment lines, such as DTIC/temozolomide, bio-chemotherapy and high-dose IL-2. Exclusion criteria included: uveal/mucosal melanoma, genetically engineered T cells, TBI, intratumoral injections of TIL-ACT combined with kinase inhibitors (e.g. vemurafenib) and single-case reports. The primary outcome measured was the objective response rate (ORR). Secondary outcomes were complete response rate (CRR), overall survival (OS), duration of response (DOR) and toxicity. Median follow up was 40 months. The pooled overall ORR estimate was 41% (n=170/410) (p=0.049) and the overall CRR was 12%. For the high dose (HD)-IL-2 group (n=141/332), the ORR was 43% (p=0.075) and the low dose (LD)-IL-2 group (n=29/78) was 35% (p=0.15). The pooled estimates for HD-IL-2 group CRR were 14% (n=49/332) (p=0.0024) and LD-IL-2 was 7% (n=7/78) (p=0.52). Median overall survival was reported as 17 months for the HD-IL-2 cohort. The OS rate at one year for the HD-IL-2 group was 56.5%. DOR for the HD-IL-2 cohort (n=100, complete response [CR] =28, partial response [PR] =72), 55% progressed and 45% sustained their response during a median follow up of 36 months. Of the HD-IL-2 complete responders, 27 of 28 remained in remission for the duration of the follow up period (median follow up 40 months). The LD-IL-2 cohort had 12 PR who progressed. Toxicity was reported as adverse events (AE). The most frequent AEs reported were febrile neutropenia (from NMA chemotherapy), diarrhea, thrombocytopenia and vitiligo. Author noted limitations included the lack of information on patients with non-successful TIL expansion and lack of individual patient data requiring the use of aggregate data. Although tumors regressed in advanced cutaneous melanoma with TIL-ACT regimens, questions about best practices remain including the duration of TIL culture, the number of TILs infused and the optimum IL-2 dose. Further studies are needed to determine the safety and efficacy of TIL-ACT in the management of melanoma.

Rosenberg et al. (2011) reported on a trial of 93 patients with measurable metastatic melanoma who were treated with the adoptive transfer of autologous TILs administered in conjunction with interleukin-2 following a lyphodepleting preparative regimen on three sequential clinical trials. Ninety-five percent of the patients had progressive disease following prior treatment. About 85% of study participants had surgically resectable disease. Objective response rates by Response Evaluation Criteria in Solid Tumors (RECIST) in the three trials using chemotherapy alone or with two or 12 Gy irradiation were 49%, 52%, and 72%, respectively. Twenty of the 93 patients (22%) achieved complete tumor regression, and 19 have ongoing complete regressions beyond three years. The actuarial three- and five-year survival rates for the entire 93 patients were 36% and 29%, respectively. For the 20 complete responders, three- and five-year survival rates were 100% and 93%, for the 32 partial responders 31% and 21%, and for the 41 non-responders were 7% and 5%, respectively. Overall follow-up was 62 months. Limitations of the study are the uncontrolled design and lack of comparator.

Dreno et al. (2003) conducted a randomized controlled trial to demonstrate the use of TILs as adjuvant therapy for stage III (metastasis to regional lymph nodes) melanoma. After lymph node excision, patients without any detectable metastases were randomly assigned to receive a two-month course of either TIL plus IL-2 or IL-2 only. The primary endpoint was the duration of the relapse-free interval. Eighty-eight patients eligible for treatment were enrolled in the study. After a median follow-up of 46.9 months, the analysis did not show a significant extension of the relapse-free interval or overall survival for the study population**.** Khammari et al. (2007) reported long-term results of the Dreno study. After a median follow-up of 114.8 months, there was no change in the non-significant extension of relapse free interval or overall survival.

T-Cell Lymphocytes/Dendritic Cells (DCs)

T-cell (also known as dendritic cell [DC]) adoptive immunotherapy involves isolating the DCs, harvesting and exposing the cells to a variety of immunologic stimuli, then re-infusing the cells back into the patient. This process is also called autolymphocyte therapy. Phase I and II trials have explored the use of DCs in treating hormone-resistant prostate cancer. The studies reported that therapy was well-tolerated and resulted in a reduction of prostate-specific antigen (PSA) levels. The role of antigen-loaded dendritic cells has also been explored for the treatment of other malignancies (e.g., lymphoma, myeloma, subcutaneous tumors, melanoma, renal cell, uterine, cervical and non-small cell lung cancer) and autoimmune disorders, such as type I diabetes mellitus and rheumatoid arthritis.

Overall, the benefit of DCs to health outcomes has not been established for most indications. Exceptions include Sipuleucel-T (Provenge®) (see Cigna Coverage Policy Oncology Medications)

Randomized controlled trials are needed to determine safety and effectiveness, patient eligibility criteria, and treatment protocols, including optimal dosing, route of delivery, and source of antigens for the treatment of other malignancies and autoimmune disorders, including type I diabetes mellitus and rheumatoid arthritis.

Literature Review: Chen et al. (2018) conducted a systematic review and meta-analysis of the literature to evaluate the clinical efficacy of dendritic cell (DC)-based immunotherapy when used as an adjunct in the treatment of hepatocellular carcinoma (HCC). Nineteen clinical trials on DC-based immunotherapy for HCC were selected, including seven randomized control trials (RCT) and 12 non-RCT (n=1276 cases, range 18-160 per study). Inclusion criteria were patients of all ages with a diagnosis of HCC and the use of either DC vaccine or dendritic cells and cytokine-induced killer cells (DC-CIK) immunotherapy. The primary intervention was the adjunctive treatment of DC based immunotherapy. All studies used mature DCs, different antigen-loading methods and different injection routes (intravenous, intradermal, subcutaneous and intra-tumoral). The number of injection times ranged from 1–7 and the number of cells ranged from $4x10^6$ to $2x10^{10}$. The control groups were those patients who would not accept DC vaccine or DC-CIK. Primary outcomes measured were immunologic changes including CD4+ T/CD8+ T ratio, progression free survival (PFS) rate, overall survival (OS) rate, median PFS time and median OS time. Outcome results reported statistically significant improved CD4+ T/CD8+ T ratio ($p<0.001$), increased one–year, 18– months and five–year PFS rate ($p<0.05$) and OS rate ($p<0.05$). Median PFS time was 1.98 times that of control ($p<0.001$) and median OS time was 1.72 times that of control ($p<0.001$), both statistically significant. Adverse reactions were low-grade fever, skin reaction, myalgia, shiver, vomiting, hyperpyrexia, and fatigue. Author reported limitations included: small patient populations; heterogeneity of the study designs and intervention methodology; and variations in the timing of medication, cell dose and the number and route of administration of treatments. Patient selection criteria for this therapy has not been established. Studies have reported that DC immunotherapy is not effective for every patient. Additional well-designed, multi-center randomized controlled trials with large patient populations per study are needed to confirm the safety and efficacy of this treatment.

Wang et al. (2018) conducted a systematic review and meta-analysis to evaluate the safety and efficacy of cytokine-induced killer cell (CIK)/dendritic cell–cytokine-induced killer cell (DC-CIK) treatment in comparison to conventional chemotherapy for the treatment of gastric cancer (GC) after surgery. A total of nine studies met the inclusion criteria: seven randomized control trials and two controlled trials. Included studies reported on the clinical efficacy and safety comparing CIK cell therapy and conventional chemotherapy for patients with GC (stage I to IV) after surgery. Excluded were books, letters, expert opinions, case reports, editorials, and studies in animals and cell lines. Also excluded were studies not aimed at investigating the association between CIK cell therapy and GC. The intervention was CIK/DC-CIK combined with chemotherapy. The major adoptive cellular treatments utilized in all trials contained CIK cells, expanded activated autologous lymphocytes (EAALs), and tumor-associated lymphocytes (TALs) (n=562 patients).The number of adoptive cells transfused into patients in these studies exceeded $1.0x10^9$. The comparator was chemotherapy alone (n=597 patients). Primary outcomes were hazard ratio (HR), overall survival (OS) rates, disease-free survival (DFS) rates and immune function. A small HR value indicates a better therapeutic effect and a HR <1 indicates lower risk. Length of follow up was five years. The survival status in the treatment group was significantly better than that in the control group with an HR of 0.712 for OS and HR of 0.66 for overall DFS. The treatment group had higher OS and DFS than the control group at both three and five years follow up. Immune function was evaluated by comparing changes in T lymphocytes before and after treatment. The number of CD3+, CD4+, CD4+/CD8+, and NK cells in patients of the treatment group were reported to be significantly increased. Adverse events were fever, chills, rashes,

headaches, and nausea. Limitations of the study include the small heterogeneous (e.g., tumor state I-IV) patient populations, differences in the use of immune cells, and heterogeneity of the chemotherapy and surgical procedures. Patient selection criteria for post-surgical adjuvant chemotherapy plus immunotherapy have not been established. Additional multicenter randomized control trials with large patient populations are needed to verify efficacy of this therapy.

Xiao et al. (2018) conducted a meta-analysis to evaluate whether DC-CIK therapy repairs and reconstructs the antitumor immunity and improves the tumor responses, reveals its optimal usage and combination with chemotherapy, and provides the optimal evidence for individualized immunotherapy for non-small cell lung cancer (NSCLC). A total of 28 randomized control trials (n=2242 patients) met inclusion criteria. Inclusion criteria were: diagnosis with NSCLC using histopathological and cytological diagnostic criteria and TNM staging system; adequate kidney and liver function; and no other therapy including surgery, radiotherapy, CIK cells alone, traditional Chinese medicines, monoclonal antibody, or other cell therapies. Exclusion criteria included: duplicate studies patent, generic, abstracts, and reviews without specific data; in vitro or animal studies; studies about other tumors or nursing; studies with CIK cells or DC-CIK alone; and studies with DC-CIK plus radiotherapy, Chinese herbs, targeted therapy, surgery, or other cytotherapy. Studies with DC-CIK in two groups; non-randomized controlled studies; and unrelated systematic reviews or meta-analysis; studies without data of peripheral blood lymphocytes were also excluded. The experimental groups were DC-CIK plus chemotherapy. DC-CIK therapy included DC-CIK cells and Ag-DC-CIK cells (n=1127). The control groups received chemotherapy alone without restrictions on the type of chemotherapy used (n=1115). The primary outcome measured was antitumor immunity using the peripheral blood lymphocytes that included T lymphocyte subsets and natural killer cells (NK cells). T lymphocyte subsets were measured by using the proportions of CD3+ T cells, CD3+ CD4+ T cells, CD3+ CD8+ T cells, CIK cells (CD3+ CD56+ cells), and regulatory T cells (CD25+ CD4+ T cells, Treg cells) and the ratio of CD4+/CD8+ T cells. The secondary outcome was the tumor responses and was measured using the objective response rate (ORR) and disease control rate (DCR). Length of follow-ups ranged from one to four months after treatment. Antitumor immunity showed statistical significance in all of the study group subsets compared to the control groups:

- CD3+ T cells ($p<0.00001$)
- CD3+ CD4+ T cells ($p<0.00001$)
- CD3+ CD8+ T cells ($p<0.00001$)
- CIK cells ($p<0.00001$)
- regulatory T cells ($p=0.003$)
- CD4+/CD8+ T cells ($p=0.002$)
- NK cells ($p<0.00001$)

The tumor responses showed that DC-CIK plus chemotherapy increased both the ORR and the DCR and was statistically significant ($p<0.00001$, each). Adverse events were not reported. Author noted limitations included all trials were conducted in one country (China), not all trials reported on the random allocation or blinding method and there was heterogeneity in cell numbers used. Additional limitations include: the small patient populations; unclear risk of bias; the heterogeneity of the chemotherapy and the usage and combinations of the CIK therapy. Some trials failed to report the tumor response. Patient selection criteria and dosage regimens and combinations remain unclear. Additional randomized control trials with large populations and long term follow up are needed to establish the clinical efficacy of this treatment method.

Han et al. (2014) reported results of a systematic review and meta-analysis of six randomized controlled trials involving 428 individuals with non-small cell lung cancer (NSCLC). Patients in the control group received chemotherapy alone while the experimental group received chemotherapy combined with DC-cytokine-induced killer cells (CIK) immunotherapy. One-year overall survival (OS) was improved in the chemotherapy combined with DC-CIK immunotherapy group compared to that of the chemotherapy alone group ($p=0.02$); however, the two-year OS was not significantly different between groups $p= 0.21$). Likewise, one-year progression-free survival (PFS) was significantly prolonged in the DC-CIK immunotherapy group compared to the chemotherapy alone group ($p= 0.005$); however, there was no significant difference in two-year PFS ($p=0.10$). Partial response (PR), overall response rate (ORR) and disease control rate (DCR) were considered to assess treatment efficacy. Analysis of the DCR showed significant improvement for the group receiving combination treatment ($p=0.06$), but no statistically significant improvement between groups was noted for PR ($p=0.22$) or ORR ($p=0.76$). Although data suggest short-term improvement in OS and PFS, longer-term outcomes do not reflect sustained benefit.

Additional studies reflecting long-term benefit of DC immunotherapy are needed to establish the role of this therapy for the treatment of NSCLC.

Draube et al. (2011) performed descriptive analyses at a study level and individual patient data level on twenty-nine studies involving the use of immunotherapy with mature monocyte derived dendritic cells or immature monocyte derived dendritic cells in 906 patients with prostate or renal cell cancer (RCC). Three studies were randomized phase II studies; the remaining studies were phase I/II. Analysis at study data level revealed that dendritic cell (DC) vaccination led to an antigen-specific cellular immune response in 77% of patients with prostate cancer and 61% of patients with RCC. Specific humoral immune response was detected in 55% of patients with prostate cancer and no patients with RCC. Overall, objective response (complete response + partial response+ mixed response) was observed in 7.7% of patients with prostate cancer and in 12.7% of patients with RCC. The authors concluded that results demonstrated an association between specific cellular immune response and clinical benefit in both prostate cancer and RCC trials. However, there was heterogeneity regarding DC purity and dose, DC subtype, antigen delivery, route of vaccination and quality controls between the studies. DC immunotherapy warrants further investigation in phase III randomized trials.

Kimura et al. (2008) evaluated the efficacy and toxicity of adjuvant chemo-immunotherapy using autologous dendritic cells and activated killer cells obtained from tissue cultures of tumor-draining lymph nodes for the post-surgical treatment of primary lung cancer (n=28). All patients received four courses of chemotherapy along with immunotherapy every two months for two years. Two and five-year survival rates were 88.9% and 52.9%, respectively. The authors concluded that adoptive transfer of activated killer cells and dendritic cells from the tumor-draining lymph nodes of primary lung cancer patients is safe and feasible, and that a large-scale multi-institutional study is needed to evaluate the efficacy of this treatment.

Systematic Review of Multiple Adoptive Immune Cells

Hepatocellular Cancer: Zhao et al. (2018) conducted a systematic review and meta-analysis to evaluate the safety and efficacy of adoptive immunotherapy (AIT) for patients with hepatocellular carcinoma (HCC). AIT using lymphokine-activated killer (LAK) cells and cytokine-induced killer (CIK) cells are proposed therapies for HCC following curative treatment. Recurrence rate and mortality were the primary outcome measures. Studies were included if they met the following criteria: (a) were a randomized controlled trial (RCT) comparing patients receiving AIT to patients who did not; (b) patients received curative treatment before immunotherapy; (c) patients received otherwise similar treatments both in AIT and non-AIT arms; and (d) the study showed estimating risk ratios (RRs) with 95% confidence intervals. Eight RCTs (n=964) met inclusion criteria. All patients had undergone hepatic resection prior to receiving AIT. Five trials (n=685) used CIK, two trials (n=43) used LAK plus interleukin-2 (IL-2), and one study used transcatheter arterial chemoembolization (TACE) and LAK plus IL-2. The overall analysis showed that AIT treatment significantly decreased the one-year ($p<0.00001$), two-year ($p<0.00001$), and three-year ($p= 0.0001$) recurrence rate (RR). Data also showed a significant decrease in mortality at the one-year ($p=0.00001$), two-year ($p<0.00001$) and three-year ($p=0.03$) follow-ups. The groups treated with lymphokine-activated killer (LAK) cells showed lower pooled RR values compared to those treated with cytokine-induced killer cells. However, AIT treatment failed to affect the five-year recurrence rate and mortality ($p>0.05$). The most frequent reported adverse events were fever and chills. Additional rare adverse events included myalgia, headache, dizziness, fatigue, and nausea. Adverse events varied with the type of AIT received. No serious adverse events were reported. Author noted limitations of the studies included the small patient populations (n=12–112), short-term follow-ups, heterogeneity of tumor size and hepatitis B/C infection and lack of information on the clinic random allocation concealment process. It was also noted that all studies were from Asian countries and therefore, the results may not be generalizable. Larger randomized controlled studies for the various types of AIT therapies for the treatment of postoperative HCC are needed to confirm results of this analysis.

Mo et al. (2017) conducted a systematic review and meta-analysis on the efficacy of adoptive immunotherapy (AIT) for hepatocellular carcinoma patients after curative therapy. This analysis included the same studies as Zhao et al. (2018) above plus one additional retrospective review (n=1031). Due to the heterogeneity of the AIT therapies, the limited number of studies in total and the limited number of studies addressing the same outcomes, the authors concluded that additional randomized controlled trials with long-term follow-ups are needed and should aim to expand the range of relevant endpoints examined (e.g., quality of life, duration of hospital stay) and the possible clinical benefits of multi-modal immune therapies.

Yuan et al. (2017) conducted a systematic review and meta-analysis of the literature to evaluate the evidence on the safety and efficacy of adoptive immunotherapy (AIT) for postoperative hepatocellular carcinoma. Eight randomized controlled trials (RCTs) and two retrospective reviews (n=2120) met inclusion criteria. The studies were the same as reviewed by Mo et al. (2017) and Zhao et al. (2018) above plus one additional retrospective review. Eight studies reported that adjuvant AIT significantly improved disease free survival (DFS) or progression-free survival (PFS) ($p< 0.05$). One small RCT and two retrospective studies reported that adjuvant AIT significantly improved overall survival (OS) ($p<0.05$). Meta-analysis for the RCTs (n=483) showed significant recurrence benefit of AIT at one year, two years and three years ($p<0.05$, each) but not at five years. Adverse events included: fever, chills, headache, nausea, myalgia, fatigue, dizziness, itching and tachycardia. All events were grade 1 or 2 and self-limiting. Five patients delayed or stopped treatment due to persistent fever. No hospital deaths or serious adverse events were reported. Limitations of the studies include: short-term follow-up; heterogeneity of the type of AIT and treatment regimen (e.g., route of administration, number of cycles used); outcomes reported varied by studies and some were conflicting; lack of reporting procedures for randomization or allocation concealment; limited data on some outcomes; and lack of external validity of the result for populations other than Asian. The authors stated that these results should be viewed with caution.

Non-small Cell Lung Cancer: Zhao et al. (2017) conducted a systematic review and meta-analysis to evaluate adoptive immunotherapy (AIT) for the treatment of non-small cell lung cancer (NSCLC). Thirteen randomized controlled trials and two observational studies met inclusion criteria. Regarding pre-treatment, seven studies included pre-surgical patients, two studies included patients treated with chemotherapy, and one study included patients treated with surgery or chemotherapy or radiotherapy. Regarding AIT regimen, three studies used lymphokine-activated killer cells (LAK) plus IL-2 (or rIL-2), seven studies used dendritic cells/cytokine-induced killer cells (DC/CIK), two studies used CIK alone, two studies used activated killer T cells (AKT) alone, and one study used tumor infiltrating lymphocytes (TIL) alone. The regimen included > 4 cycles in eight studies and ≤ 4 cycles in four studies. The precise cycle used was not identifiable in the remaining studies. Compared to the control therapy group, the AIT group exhibited significantly better overall survival (OS) rates as follows: a) one-year (fifteen studies; n=1684) ($p=0.001$) b) two-years (13 studies; n=1548) ($p<0.001$) c) three-years (ten studies; n=1266) ($p<0.001$) and d) five-years (six studies; n=925) ($p=0.032$). AIT groups also showed significantly better progression-free survival (PFS) rates at one-year (five studies; n=519) ($p<0.001$), and two-years (three studies; n=353) ($p=0.029$). The difference in the objective response rate (ORR) (four studies; n=323) ($p=0.293$) and the disease control rate (DCR) (four studies; n=323) ($p=0.123$) were not significant between the groups. Subgroup analysis for one and two-year OS showed that CIK and DC/CIK significantly enhanced survival compared with LAK plus IL-2. Author-noted limitations included: heterogeneity of the studies and variation in the AIT cycles precluding a determination of the appropriate duration of AIT for maximum effectiveness; lack of reporting of adverse events (n=four studies); and the number of studies included were not adequate to yield credible results. All the studies included Asian participants, except for one which limits generalizability. Also, all the studies used AIT in combination with chemotherapy or radiotherapy making it difficult to estimate the efficacy of AIT alone. Further multicenter randomized controlled trials are needed to identify the clinical effectiveness of AIT and which therapy is associated with the greatest efficacy.

Zhu et al. (2017) conducted a Cochrane systematic review of the literature to evaluate the safety and effectiveness of immunotherapy (excluding checkpoint inhibitors) in patients with localized non-small cell lung cancer (NSCLC) (stages I to III) who received surgery or radiotherapy with curative intent. Included studies were randomized controlled trials, patients age ≥ 18 years, with histology confirmed NSCLC after surgical resection and patients with unresectable locally advanced stage III NSCLC who had received radiotherapy with curative intent. Nine randomized controlled trials (n=4940) met inclusion criteria. Immunological interventions included: Bacillus Calmette-Guérin (BCG), adoptive cell transfer (i.e. transfer factor, tumor-infiltrating lymphocytes, dendritic cell-cytokine induced killer), and antigen-specific cancer vaccines (melanoma-associated antigen 3 [MAGE-A3} and L-BLP25). Meta-analysis showed no statistically significant improvement in overall survival ($p=0.35$) or progression-free survival ($p=0.19$) with immunotherapy. There was no statistically significant increased risk in adverse events. In conclusion, the data do not support a clinical benefit of the use of immunotherapy for patients with localized NSCLC (stages I to III).

Qian et al. (2016) conducted a systematic review and meta-analysis of studies that compared chemoradiotherapy alone to chemoradiotherapy plus adoptive immunotherapy for the treatment of non-small-cell

lung cancer (NSCLC). Seven articles met inclusion criteria. The articles included clinical trials that investigated the treatment of NSCLC with adoptive immunotherapy with a mean follow-up longer than two years. Outcomes included: death, tumor recurrence, or metastasis. Studies with a sample size of less than 20 subjects were excluded. There was no significant difference in the two-year progression-free survival (PFS) in the combination of adoptive immunotherapy group and the chemoradiotherapy-alone group ($p=0.284$). The addition of immunotherapy did improve the two-year overall survival rate ($p<0.001$) of early stage NSCLC patients ($p<0.01$) but not for patients with advanced disease ($p=0.057$). Self-limited adverse effects of immunotherapy included: fever, shivers, nausea, fatigue and retention of water and sodium. Limitations of the studies include: the heterogeneity of the types of adoptive immune cells (LAK, TIL, CIK, cytotoxic T lymphocyte, γδ T cells); the combination regimen of the cells; and the short-term follow-ups. The authors noted that multicenter randomized controlled trials with large patient populations are needed to provide reliable data on which to develop guidelines for clinical practice.

Professional Societies/Organizations
American Cancer Society (ACS): In a statement regarding tumor infiltrating lymphocyte (TIL) therapy, the ACS noted that some early studies have been promising, but its use may be limited due to the inability to get TILs from patients. Treatments using TILs are being tested in clinical trials in patients with melanoma, kidney cancer, ovarian cancer, and other cancers (ACS, 2019).

National Comprehensive Cancer Network® (NCCN®): In the 2021 NCCN Guideline® on hepatobiliary cancers, NCCN states that data are currently too preliminary for the panel to provide specific recommendations regarding immunotherapy treatment in an adjuvant setting.

The 2020 NCCN Guideline® on non-small cell lung cancer does not include any information regarding the use of adoptive immunotherapy.

Use Outside of the US
Adoptive immunotherapy is noted to be of research interest in the published, peer-reviewed scientific literature.

Medicare Coverage Determinations

	Contractor	Policy Name/Number	Revision Effective Date
NCD		No National Coverage Determination found	
LCD		No Local Coverage Determination found	

Note: Please review the current Medicare Policy for the most up-to-date information.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Experimental/Investigational/Unproven when used to report the adoptive immunotherapy techniques listed in this Coverage Policy for any indication:

CPT®* Codes	Description
38999	Unlisted procedure, hemic or lymphatic system

HCPCS Codes	Description
S2107	Adoptive immunotherapy, i.e., development of specific anti-tumor reactivity (e.g., tumor-infiltrating lymphocyte therapy) per course of treatment

References

1. American Cancer Society. Immunotherapy. Jul 23, 2015. Revised Dec 27, 2019. Accessed Oct 11, 2021. Available at URL address: http://www.cancer.org/treatment/treatmentsandsideeffects/treatmenttypes/immunotherapy/index

2. American Cancer Society. What's new in melanoma skin cancer research? Aug 14, 2019. Accessed Oct 11, 2021. Available at URL address: https://www.cancer.org/cancer/melanoma-skin-cancer/about/new-research.html

3. Andersen R, Donia M, Ellebaek E, Borch TH, Kongsted P, Iversen TZ, Hölmich LR, Hendel HW, Met Ö, Andersen MH, Thor Straten P, Svane IM. Long-Lasting Complete Responses in Patients with Metastatic Melanoma after Adoptive Cell Therapy with Tumor-Infiltrating Lymphocytes and an Attenuated IL2 Regimen. Clin Cancer Res. 2016 Aug 1;22(15):3734-45.

4. Benlalam H, Vignard V, Khammari A, Bonnin A, Godet Y, Pandolfino MC, et al. Infusion of Melan-A/Mart-1 specific tumor-infiltrating lymphocytes enhanced relapse-free survival of melanoma patients. Cancer Immunol Immunother. 2007 Apr;56(4):515-26.

5. Besser MJ, Shapira-Frommer R, Treves AJ, Zippel D, Itzhaki O, Hershkovitz L, et al. Clinical responses in a phase II study using adoptive transfer of short-term cultured tumor infiltration lymphocytes in metastatic melanoma patients. Clin Cancer Res. 2010 May 1;16(9):2646-55.

6. Besser MJ, Shapira-Frommer R, Treves AJ, Zippel D, Itzhaki O, Schallmach E, et al. Minimally cultured or selected autologous tumor-infiltrating lymphocytes after a lympho-depleting chemotherapy regimen in metastatic melanoma patients. J Immunother. 2009 May;32(4):415-23.

7. Bregy A, Wong TM, Shah AH, Goldberg JM, Komotar RJ. Active immunotherapy using dendritic cells in the treatment of glioblastoma multiforme. Cancer Treat Rev. 2013 Dec;39(8):891-907

8. Centers for Medicare and Medicaid Services (CMS). Local Coverage Determinations (LCDs) alphabetical index. Accessed Oct 11, 2021. Available at URL address: https://www.cms.gov/medicare-coverage-database/search.aspx

9. Centers for Medicare and Medicaid Services (CMS). National Coverage Determinations (NCDs) alphabetical index. Accessed Oct 11, 2021. Available at URL address: https://www.cms.gov/medicare-coverage-database/search.aspx

10. Chen C, Ma YH, Zhang YT, Zhang F, Zhou N, Wang X, Liu T, Li YM. Effect of dendritic cell-based immunotherapy on hepatocellular carcinoma: A systematic review and meta-analysis. Cytotherapy. 2018 Aug;20(8):975-989. doi: 10.1016/j.jcyt.2018.06.002. Epub 2018 Jul 30.

11. Clark J, Atkins M, Urba W, Creech S, Figlin R, Dutcher J, et al. Adjuvant high dose bolus interleukin-2 for patients with high risk renal cell carcinoma: a Cytokine Working Group Randomized Trial. J Clin Oncol. 2003 August;21(16):3133-40.

12. Dafni U, Michielin O, Lluesma SM, Tsourti Z, Polydoropoulou V, Karlis D, Besser MJ, Haanen J, Svane IM, Ohashi PS, Kammula US, Orcurto A, Zimmermann S, Trueb L, Klebanoff CA, Lotze MT, Kandalaft LE, Coukos G. Efficacy of adoptive therapy with tumor-infiltrating lymphocytes and recombinant interleukin-2 in advanced cutaneous melanoma: a systematic review and meta-analysis. Ann Oncol. 2019 Dec 1;30(12):1902-1913. doi: 10.1093/annonc/mdz398. PMID: 31566658.

13. Delacroix SE, Wood CG, Jonasch E. Renal neoplasia. In: Taal MW, Chertow GM, Marsden PA, Skorecki K, Yu ASL, Benner BM, editors. Brenner and Rector's The kidney, 9th ed. Saunder's Elsevier; 2011.

14. Dillman RO, Duma CM, Ellis RA, Cornforth AN, Schiltz PM, Sharp SL, DePriest MC. Intralesional lymphokine-activated killer cells as adjuvant therapy for primary glioblastoma. J Immunother. 2009 Nov-Dec;32(9):914-9

15. Dotti G, Brenner MK. T-cell therapy of hematologic diseases. In: Hoffman R, Benz EJ, Silberstein LE, Heslop HE, Weitz JI, editors. Hoffman: Hematology: Basic principles and practice, 6th ed. Churchill Livingstone, an imprint of Elsevier; 2013

16. Draube A, Klein-Gonzalez N, Mattheus S, Brillant C, Hellmich M, Engert A, et al. Dendritic cell-based tumor vaccination in prostate and renal cell cancer: a systematic review and meta-analysis. PLoS One. 2011 Apr 20;6(4):e18801.

17. Dreno B, Nguyen J, Khammari A, Pandolfino M, Tessier M, Bercegeay S, et al. Randomized trial of adoptive transfer of melanoma tumor infiltrating lymphocyte as adjuvant therapy for stage III melanoma. Cancer Immunol Immunother. 2002 Sep;51:539-46.

18. Dunn G, Oliver K, Loke D, Staford N, Greenman J. Dendritic cells and HNSCC:A potential treatment option? (Review). Oncol Rep. 2005 Jan;13: 3-10.

19. Figlin R, Thompson J, Bukowski R, Vogelzang N, Novick A, Lange P, et al. Multicenter, randomized, phase III trial of CD8(+) tumor infiltrating lymphocytes in combination with recombinant IL-2 in metastatic renal cell carcinoma. J Clin Oncol. 1999 Aug;17(8):2521-9.

20. Gooden MJM, de Bock GH, Leffers N, Daemen T, Nijman HW. The prognostic influence of tumor-infiltrating lymphocytes In cancer-a systematic review with meta-analysis. Br J Cancer. 2011 June 28;93-103.105(1):93-103.

21. Han RX, Liu X, Pan P, Jia YJ, Yu JC. Effectiveness and safety of chemotherapy combined with dendritic cells co-cultured with cytokine-induced killer cells in the treatment of advanced non-small-cell lung cancer: a systematic review and meta-analysis. PLoS One. 2014 Sep 30;9(9):e108958.

22. Hargadon KM. Strategies to Improve the Efficacy of Dendritic Cell-Based Immunotherapy for Melanoma. Front Immunol. 2017 Nov 20;8:1594. doi: 10.3389/fimmu.2017.01594. eCollection 2017.

23. Kasslin AA, Neelapu SS, Kwak LW, Van Kaer L. Immunotherapy. In: Greer JP, Arber DA, Glader B, List AF, Means RT, Paraskevas F, Rodgers GM, Foerster J, editors. Wintrobe's clinical hematology. 13th Ed. Lippincott Williams & Wilkins; 2014.

24. Khammari A, Nguyen JM, Leccia MT, Guillot B, Saiagh S, Pandolfino MC, Knol AC, Quéreux G, Chiffolettau A, Labarrière N, Dréno B. Tumor infiltrating lymphocytes as adjuvant treatment in stage III melanoma patients with only one invaded lymph node after complete resection: results from a multicentre, randomized clinical phase III trial. Cancer Immunol Immunother. 2020 Aug;69(8):1663-1672. doi: 10.1007/s00262-020-02572-1. Epub 2020 Apr 18. PMID: 32306076.

25. Khammari A, Nguyen JM, Pandolfino MC, Quereux G, Brocard A, Bercegeay S, et al. Long-term follow-up of patients treated by adoptive transfer of melanoma tumor-infiltrating lymphocytes as adjuvant therapy for stage III melanoma. Cancer Immunol Immunother. 2007 Nov;56(11):1853-60.

26. Kim JH, Lee Y, Bae YS, Kim WS, Kim K, Im HY, et al. Phase I/II study of immunotherapy using autologous tumor lysate-pulsed dendritic cells in patients with metastatic renal cell carcinoma. Clin Immunol. 2007 Dec;125(3):257-67.

27. Kim W, Liau LM. Dendritic cell vaccines for brain tumors. Neurosurg Clin N Am. 2010 Jan;21(1):139-57.

28. Kimura H, Lizasa T, Ishikawa A, Shingyouji M, Yoshino M, Kimura M, Inada Y, Matsubayashi K. Prospective phase II study of post-surgical adjuvant chemo-immunotherapy using autologous dendritic cells and activated killer cells from tissue culture of tumor-draining lymph nodes in primary lung cancer patients. Anticancer Res. 2008 Mar-Apr;28(2B):1229-38.

29. Kimura H, Matsui Y, Ishikawa A, Nakajima T, Iizasa T. Randomized controlled phase III trial of adjuvant chemoimmunotherapy with activated cytotoxic T cells and dendritic cells from regional lymph nodes of patients with lung cancer. Cancer Immunol Immunother. 2018 Aug;67(8):1231-1238. doi: 10.1007/s00262-018-2180-6. Epub 2018 May 31.

30. Kimura H, Matsui Y, Ishikawa A, Nakajima T, Yoshino M, Sakairi Y. Randomized controlled phase III trial of adjuvant chemo-immunotherapy with activated killer T cells and dendritic cells in patients with resected primary lung cancer. Cancer Immunol Immunother. 2015 Jan;64(1):51-9.

31. Kondo H, Hazama S, Kawaoka T, Yoshino S, Yoshida S, Tokuno K, Takashima M, Ueno T, Hinoda Y, Oka M. Adoptive immunotherapy for pancreatic cancer using MUC1 peptide-pulsed dendritic cells and activated T lymphocytes. Anticancer Res. 2008 Jan-Feb;28(1B):379-87.

32. Kono K, Takahashi A, Ichihara F, Amemiya H, Iizuka H, Fuji H, et al. Prognostic significance of adoptive immunotherapy with tumor associated lymphocytes in patients with advanced gastric cancer: a randomized trial. Clin Cancer Res. 2002 Jun;8(6):1767-71.

33. Lange JR, Fecher LA, Sharfman WH, Alani RM, Mikkilineni R, Topalian SL, et al. Melanoma. In: Abeloff MD, Armitage JO, Lichter AS, Niederhuber JE, editors. 4th ed. Clinical oncology. New York, NY: Churchill Livingstone; 2008.

34. Lotze MT. Interleukin therapy. In: Devita VT, Lawrence TS, Rosenberg SA, editors. Devita, Hellman, and Rosenberg's Cancer: Principles & practice of oncology. 9th ed. Philadelphia, PA: Lippincott, Williams & Wilkins, Churchill Livingstone; 2011.

35. Mackensen A, Meidenbauer N, Vogl S, Laumer M, Berger J, Andreesen R. Phase I study of adoptive T-cell therapy using antigen-specific CD8+ T cells for the treatment of patients with metastatic melanoma. J Clin Oncol. 2006 Nov 1;24(31):5060-9.

36. Mitchell M, Darrah D, Yeung D, Halpern S, Wallace A, Voland J, et al. Phase 1 trial adoptive immunotherapy with cytolytic lymphocytes immunized against a tyrosine epitope. J Clin Oncol. 2002 Feb;20(4):1075-86.

37. Mo HY, Liao YY, You XM, Cucchetti A, Yuan BH, Li RH, Zhong JH,4, Li LQ. Timely meta-analysis on the efficacy of adoptive immunotherapy for hepatocellular carcinoma patients after curative therapy. PLoS One. 2017 Mar 24;12(3):e0174222.

38. National Comprehensive Cancer Network® (NCCN®): NCCN GUIDELINES® Clinical Guidelines in Oncology™. © National Comprehensive Cancer Network, Inc 2020, All Rights Reserved. Hepatobiliary cancers. V 5.2021-Sept 21, 2021. Accessed Oct 11, 2021. Available at URL address: https://www.nccn.org/professionals/physician_gls/default.aspx#site

39. National Comprehensive Cancer Network® (NCCN®): NCCN GUIDELINES® Clinical Guidelines in Oncology™. © National Comprehensive Cancer Network, Inc 2019, All Rights Reserved. Non-small cell lung cancer. V 6.2021-Sept 30, 2021. Accessed Oct 11, 2021. Available at URL address: https://www.nccn.org/professionals/physician_gls/default.aspx#site

40. Nencioni A, Brossart P. Cellular immunotherapy with dendritic cells in cancer: current status. Stem Cells. 2004;22(4):501-13.

41. Qian H, Wang H, Guan X, Yi Z, Ma F. Adoptive immunotherapy combined chemoradiotherapy for non-small-cell lung cancer: a meta-analysis. Anticancer Drugs. 2016 Jun;27(5):433-8.

42. Ribas A, Butterfield L, Glaspy J, Econonomou J. Current developments in cancer vaccines and cellular Immunotherapy. J Clin Oncol. 2003 Jun;21(12):2415-32.

43. Rosenberg SA. Cell transfer immunotherapy for metastatic solid cancer-what clinicians need to know. Nat Rev Clin Oncol. 2011 Aug 2;8(10)577-85.

44. Rosenberg S, Lotze M, Yang J, Topalian S, Chang A, Schwartzentruber D, et al. Prospective randomized trial of high dose interleukin-2 alone or in conjunction with lymphokine activated killer cells for the treatment of patients with advanced cancer. J Natl Cancer Inst. 1993 Apr;85(8):622-32.

45. Rosenberg SA, Yang JC. Sherry RM, Kammula US, Hughes MS, Phan GQ, et al. Durable complete responses in heavily pretreated patients with metastatic melanoma using T-cell transfer immunotherapy. Clin Cancer Res. 2011 Jul 1;17(13): 450-7.

46. Sereti I, Lane H. Immunopathogenesis of human immunodeficiency virus: implications for immune based therapies. Clin Infect Dis. 2001 Jun; 32(12):1738-55.

47. Tang X, Liu T, Zang X, Liu H, Wang D, Chen H, Zhang B. Adoptive cellular immunotherapy in metastatic renal cell carcinoma: a systematic review and meta-analysis. PLoS One. 2013 May 7;8(5):e62847.

48. Tanyi JL, Chu CS. Dendritic cell cell-based tumor vaccinations in epithelial ovarian cancer: a systematic review. Immunotherapy. 2012 Oct;410:995-1009.

49. Thiounn N, Pages F, Mejean A, Descotes JL, Fridman WH, Romet-Lemonne JL. Adoptive immunotherapy for superficial bladder cancer with autologous macrophage activated killer cells. J Urol. 2002 Dec;168(6):2373-6.

50. Tuma R, Giannino R, Guirnalda P, Leiner I, Pamer E. Rescue of CD8 T cell mediated antimicrobial immunity with a nonspecific inflammatory stimulus. J Clin Invest. 2002 Nov;110(10):1493-501.

51. Unverzagt S, Moldenhauer I, Nothacker M, Roßmeißl D, Hadjinicolaou AV, Peinemann F, Greco F, Seliger B.Immunotherapy for metastatic renal cell carcinoma. Cochrane Database of Systematic Reviews 2017, Issue 5. Art. No.: CD011673. DOI:10.1002/14651858.CD011673.pub2.

52. Wang X, Tang S, Cui X, Yang J, Geng C, Chen C, Zhou N, Li Y. Cytokine-induced killer cell/dendritic cell-cytokine-induced killer cell immunotherapy for the postoperative treatment of gastric cancer: A systematic review and meta-analysis. Medicine (Baltimore). 2018 Sep;97(36):e12230. doi: 10.1097/MD.0000000000012230.

53. Xiao Z, Wang CQ, Zhou MH, Li NN, Sun YP, Wang YZ, Liu SY, Yu HS, Li CW, Zeng XT, Chen L, Yao XS, Feng JH. The Antitumor Immunity and Tumor Responses of Chemotherapy with or without DC-CIK for Non-Small-Cell Lung Cancer in China: A Meta-Analysis of 28 Randomized Controlled Trials. J Immunol Res. 2018 Dec 13;2018:9081938. doi: 10.1155/2018/9081938. eCollection 2018. PMID: 30648123

54. Yuan BH, Li RH, Yuan WP, Yang T, Tong TJ, Peng NF, Li LQ, Zhong JH. Harms and benefits of adoptive immunotherapy for postoperative hepatocellular carcinoma: an updated review. Oncotarget. 2017 Mar 14;8(11):18537-18549.

55. Zhao H, Zheng M, Wang K, Wang L, He H, Wang M, Shi Y, Huang S, Ji F, Li X, Zhu H, Wang L, Zhang X, Shi X, Zhao S, Fu B, Wu T. A meta-analysis of adoptive immunotherapy in postoperative hepatocellular carcinoma. J Can Res Ther [serial online] 2018 [cited 2018 Oct 2];14:807-814. Accessed Oct 11, 2021. Available from: http://www.cancerjournal.net/text.asp?2018/14/4/807/235101

56. Zhao B, Zhang W, Yu D, Xu J, Wei Y. Adoptive immunotherapy shows encouraging benefit on non-small cell lung cancer: a systematic review and meta-analysis. Oncotarget. 2017 Jul 19;8(68):113105-113119.

57. Zhu J, Li R, Tiselius E, Roudi R, Teghararian O, Suo C, Song H. Immunotherapy (excluding checkpoint inhibitors) for stage I to III non-small cell lung cancer treated with surgery or radiotherapy with curative intent. Cochrane Database of Systematic Reviews 2017, Issue 12. Art. No.: CD011300. DOI: 10.1002/14651858.CD011300.pub2.