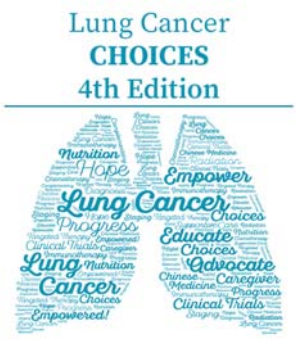

Chapter 3

Systemic Therapy for Non-Small Cell Lung Cancer (Chemotherapy, Targeted Therapy, and Immunotherapy)

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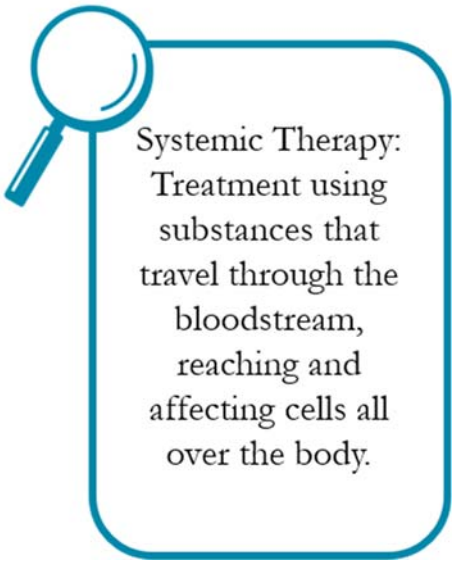
Introduction

The treatment of lung cancer depends upon the cell type, stage, and mutational characteristics identified. The first distinction is the tumor histology: small cell (SC) or non-small cell lung cancer (NSCLC). NSCLC accounts for approximately 85% of all lung cancer. The major sub-types are adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. NSCLC can be further characterized by specific mutations that "drive the growth" of the tumor. The stage describes the extent of disease present at diagnosis.

There are several treatment strategies available for non-small cell lung cancer (NSCLC). These include surgery, radiation therapy, chemotherapy, targeted therapy, immunotherapy, and palliative care. Patients may be treated with one type of treatment or a combination of treatments. Historically, chemotherapy has been the foundation of systemic treatment. However, over the past decade, clinical trials have led to the advancement of several new approaches to systemic therapy. Treatment decisions are based on the extent of disease, burden of disease (symptoms), histology (adenocarcinoma versus squamous cell carcinoma), the presence of driver mutations (EGFR, ALK, ROS1, BRAF), and level of PD-l expression. This chapter reviews the use of systemic therapies used in the treatment of NSCLC, including chemotherapy, targeted therapies, and immunotherapy.

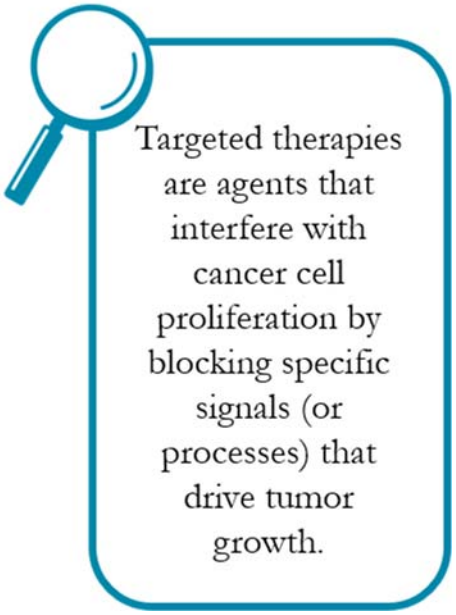


Chemotherapy

Chemotherapy agents that are selected to treat NSCLC have been approved for use after extensive clinical research. Some of these chemotherapy agents have been approved in combination with other therapies. Chemotherapy agents are identified by the generic name and brand names, and either name is used when treatment is explained to patients.[1] (Appendix 1)

Targeted Therapies

Targeted therapies are agents that interfere with cancer cell proliferation by blocking specific signals (or processes) that drive tumor growth. Targeted therapies include small molecules that disrupt cell division from inside cancer cells and monoclonal antibodies that target receptors on the tumor cell surface. Monoclonal antibody therapies function by inhibiting the blood supply to tumors and inhibiting growth factors needed for tumor growth. Cancerous tumors require blood supply for nutrition to survive. This process is referred to as angiogenesis. Some targeted therapies, such as monoclonal antibodies, prevent tumor cells from developing blood vessels, therefore, blocking nutrition, leading to tumor death. These agents are referred to as anti-angiogenic agents. The most common anti-angiogenic agents block the vascular endothelial growth factor (VEGF) and are administered intravenously.



Other targeted therapies, called small molecules, block growth factors, or "driver-mutations" that are needed for tumors to grow and spread. It is necessary to identify if tumor cell growth relies on a "driver-mutation" to survive. The most common driver mutation targets in lung cancer are epidermal growth factor receptor (EGFR), EML4-ALK, ROS-1, BRAF, MET, HER2, NTRK, and KRAS.[2] Each of these "driver mutations" occur independently. Therefore, patients do not harbor more than one mutation initially. However, tumors may mutate further after therapy and develop an additional mutation of resistance. Several targeted therapies have been approved that target specific mutations. These are taken orally. Targeted therapies may be referred to by their generic or brand names. Patients must follow directions carefully for how to take the oral targeted therapies. Taking with food and other medications may impact absorption and metabolism of the treatment, which may increase the risk of toxicity. (Appendix 2)

Immunotherapy

Ideally, the immune system in your body should recognize tumor cells as foreign, then seek and destroy or eliminate the cancer cells. However, cancer cells have developed mechanisms to "hide" or evade immune recognition by blocking specific immune checkpoints on the immune cells. In

effect, the tumor cells put the "breaks" on the immune system. Therapies that target these pathways are referred to as immune checkpoint inhibitors. Several immune "checkpoint inhibitors" have been investigated over the past several years that demonstrate an effect in restoring the immune system's ability to recognize tumor cells.[1, 3-4] Programmed Death 1 (PD-1) receptor is found on immune cells (T-cells), when activated, the immune cell function is suppressed. Programmed Death Ligand (PD-L1) is found on cancer cells in varying degrees. The interaction of the PD1 & PD-L1 pathway "halts" the immune response. Immune checkpoint inhibitors that attach to the PD1 receptor on immune T-cells or the PD-L1 ligand on tumor cells block the interaction of this pathway. This restores the pathway and eliminates the tumor's ability to escape. The level of PD-L1 expression can be tested on tumors. There is some evidence that higher expression of PD-L1 correlates with higher responses to therapy. However, even if the tumor has a low expression of PD-L1, responses to therapy have still been noted. Immune checkpoint inhibitors that have been approved may be referred to by the generic or brand names. (Appendix 3)

Treatment Team

Treatment of lung cancer requires a multidisciplinary approach. Several healthcare professionals are involved in patient care, and each has expertise in the treatment of lung cancer. It is valuable to seek treatment at a facility that has a lung cancer specialty program and a treatment team with which the patient is comfortable. It is also important for patients to be actively involved in treatment decision making. This patient-centered approach to care is called "shared decision making."

Medical Oncologist

Following a diagnosis of NSCLC, the patient is referred to a medical oncologist, a physician who specializes in the medical management of cancer. In cancer centers, hospitals, or large clinics, the physicians may specialize in one type of cancer. In smaller community practices, the oncologist may treat patients with a variety of cancers. It is important for the patient to see an oncologist who has a special interest in treating lung cancer.

The medical oncologist reviews the medical history, pathology, tumor mutational status, diagnostic tests, and performs a physical examination. Treatment recommendations are based on this information as well as the stage of the disease, physical condition, functional status, and history of previous treatment for cancer. Functional or Performance status is assessed by the ability of the patient to carry out their normal daily activities.[5] (Table 1)

The medical oncologist prescribes and monitors response to treatment and performs follow-up evaluations. The decision to administer systemic therapy does not depend on a patient's age, and many studies have shown that elderly patients can successfully receive chemotherapy.[1] However, the treatment of lung cancer varies from one person to another, and the type of systemic therapy prescribed will depend on the specifics of the patient's disease.

Table 1. Eastern Cooperative Oncology Group (ECOG) Performance Status[5]

Grade	Description
0	Fully active, able to carry out all daily activities
1	Decreased activity, but able to walk and carry out light activities (light house work or office work)
2	Able to walk and care for self, but unable to carry out any work activities, up and active more than 50% of waking hours.
3	Able to do only minimal self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair

Advanced Practice Provider (Nurse Practitioner or Physician's Assistant)
The oncology advanced practice provider is an integral member of the treatment team. An advanced practice nurse has received additional master's level education and certification beyond nursing school. Physician Assistants complete a master's level education beyond undergraduate education. The advanced practice provider is involved in the overall coordination of the cancer care, performs physical examinations, and may diagnose and treat health problems related to cancer and cancer treatment. The advanced practice provider may order diagnostic tests, perform specific procedures, prescribe medications, and other treatments.

Oncology Nurse
The oncology nurse works closely with the physician and advanced practice provider to provide optimal care to the patient and family. This nurse has special training and certification in administering chemotherapy, targeted therapy, and immunotherapy; and managing side effects. The oncology nurse may start the intravenous line, administer the therapy, and monitor for symptoms during and after the infusion. This nurse also reinforces education about managing side effects and coordinates additional nursing services needed in the home.

Social Worker
A licensed clinical oncology social worker specializes in assessing psychological, social, and emotional concerns, counseling support for cancer patients and families, and assisting with referrals to hospital and community resources. The oncology social worker may collaborate with the interdisciplinary team about care plans at different stages of illness. Many oncology social workers facilitate support groups for patients and families and may offer groups that address the needs of specific cancer patients such as those with lung cancer. The patient may find out about available social work services by asking their care providers, local hospital, or cancer organizations such as Caring Ambassadors and the American Cancer Society.

Pharmacist
A licensed pharmacist who specializes in oncology may be part of the treatment team if the patient is being treated at a large oncology practice, designated cancer center, or hospital. The pharmacist will review the treatment regimen, medications, and prepare the therapy for infusion or prepare and dispense oral therapy. In some cases, oral therapies must be ordered through specialty pharmacies as there is a restriction on their distribution. Specialty pharmacists can assist in assuring the timely delivery of these therapies. Pharmacists are available to help counsel the patient about how to take the medications/therapy, what the expected side effects are, and how to self-manage common side effects. As well as educate about when to seek medical care.

Nutrition
A licensed nutritionist specializes in assessing nutritional needs during treatment. This healthcare specialist may assist the patient and family in monitoring dietary intake and may provide suggestions to improve nutrition during and after treatment.

Other
Throughout therapy, other specialists may be consulted to help manage symptoms of the lung cancer or side effects of the treatment. Specialists include pulmonologist, cardiologist, endocrinologist, dermatologist, nephrologist, and others. The entire team collaborates to assure alignment of the patients' treatment goals.

It's always hard to deal with injuries mentally, but I like to think about it as a new beginning. I can't change what happened, so the focus needs to go toward healing and coming back stronger than before.

- Carli Lloyd

There are **71** NCI-Designated Cancer Centers, located in **36** states and the District of Columbia, that are funded by NCI to deliver cutting-edge cancer treatments to patients. Of these **71** institutions:

- **13** are Cancer Centers, recognized for their scientific leadership, resources, and the depth and breadth of their research in basic, clinical, and/or prevention, cancer control, and population science.
- **51** are Comprehensive Cancer Centers, also recognized for their leadership and resources, in addition to demonstrating an added depth and breadth of research, as well as substantial transdisciplinary research that bridges these scientific areas.
- **7** are Basic Laboratory Cancer Centers that are primarily focused on laboratory research and often conduct preclinical translation while working collaboratively with other institutions to apply these laboratory findings to new and better treatments.

Most of the NCI-Designated Cancer Centers are affiliated with university medical centers, although several are freestanding institutions that engage only in cancer research.

NCI also offers the National Clinical Trials Network, once known as cooperative groups. These large networks of researchers, doctors, and other health care professionals do clinical trials across the country. Review and search a complete list of NCI-designated cancer centers here: https://www.cancer.gov/research/nci-role/cancer-centers

Systemic Therapy for Lung Cancer

Goals of Treatment

The purpose of systemic therapy treatment may vary, depending on the patient's current status. Treatment goals may include curing the cancer, keeping the cancer under control and preventing it from spreading (metastasizing) to other areas of the body, decreasing tumor size to minimize pain and other negative symptoms (palliative), and treating recurrent disease.

The schedule of chemotherapy, targeted therapy, and immune therapy administration varies in time and sequence by the regimen selected and goals of therapy. Neoadjuvant therapy is given before surgery in an attempt to decrease tumor size, so surgery is more effective. Adjuvant therapy is given after surgery to kill tumor cells that might be remaining in the body. Concurrent is the administration of two modalities of therapy at the same time, such as chemotherapy given with

radiation therapy, done before or after surgical resection (tri-modality treatment). Chemotherapy, targeted therapies, and immunotherapy may be given in combination or can be administered alone.

Administration of Therapy

Chemotherapy, immune therapy, and some targeted therapies may be given in an infusion center clinic, a physician's office, or a hospital. The safest location for receiving treatment may depend on the type of therapy and duration of infusion. Specific therapy agents may be used alone or in combination with other agents. Treatment is given on a schedule, in blocks of time known as cycles. The specific cycles vary depending on the treatment combination. Each therapy cycle usually is followed by a recovery period to allow the normal cells to repair. However, the treatment schedule may be changed when the patient experiences severe side effects from treatment.

Chemotherapy, immune therapy, and some targeted therapies are usually given intravenously via the bloodstream throughout the entire body. Techniques for intravenous chemotherapy include:

Peripheral intravenous
A catheter or needle is inserted into an arm vein on the day of the treatment infusion and is removed at the end of treatment.

Infusion port
This is a more permanent device that is placed under the skin, includes a catheter that tunnels into a larger vein and remains in place throughout the treatment course. A specially trained oncology nurse places a needle into the port through the skin to administer treatment, give hydration, and draw blood samples. Only specially trained nurses or providers can access the port. When the needle is not in place, the patient may participate in normal activities, including showering.

Peripherally inserted central catheter (PICC)
This is a catheter placed through a large vein in the arm, neck, or chest for therapy, hydration, or drawing blood. The catheter extends outside the body, and only specially trained oncology nurses access this catheter. This catheter requires a bandage dressing over the exit site to prevent infections. The catheter must be protected from getting wet. The oncology nurse educates patients on how to care for the catheter and dressing at home.

Pump
Some treatments require a continuous infusion for several hours or days. An infusion pump ensures that the correct amount of therapy is infused into the body at a specific rate.

Some treatment drugs are given as an injection into the skin or muscle, and some are taken by mouth. Targeted therapies are usually taken by mouth in pill form daily.

Treatment Procedure

On the day of treatment, the patient is evaluated by the physician or advanced practice provider to assess and address any changes in the patient's status. The height and weight are measured because these measurements are used to calculate the dose of therapy. The oncology nurse will insert the intravenous line or access the infusion port. Intravenous fluids (hydration) may be given before the therapy. Other medications may be provided to help prevent side effects of treatment such as nausea or allergic reaction. The nurse administers the therapy through the intravenous line, either by syringe or pump infusion. During, and after treatment, the nurse monitors the patient closely for any possible adverse reactions. The patient must notify the nurse about any unusual symptoms. Information is given to the patient about the therapy and possible side effects, and a schedule for future appointments is provided.

Following treatment, the patient is routinely evaluated, for potential side effects, with a physical examination and blood tests. The healthcare team asks the patient about any possible side effects, symptoms of the disease, and strategies they have used for symptom management. The patient is encouraged to contact the healthcare team between visits for any unusual side effects or symptoms that develop post-treatment infusion. It may be necessary for the patient to come back to the clinic or office for further examination and evaluation.

Oral

Targeted therapies that are taken orally usually have to be ordered through a specialty pharmacy as they are closely regulated with restricted distribution. The processing of the prescription may take several days. In many cases, the medicine will be delivered to the patient via mail delivery. The patient needs to notify their healthcare team if there is a delay in obtaining the prescription. Once the patient receives the prescription for the targeted oral therapy, the health care provider may want to meet with the patient to review specific instructions for taking the therapy. Often targeted therapies need to be taken hours after or before meals and other medications. Taking with food may impair the absorption of the therapy. In addition, there is a potential for interactions between targeted therapies and other drugs, including over the counter medications. Patients should review all medications with their care team to minimize toxicities.

Evaluation before the start of therapy includes a physical examination to assess performance status and major organ functions such as pulmonary, cardiac, gastrointestinal and nervous system. (Table 1) Blood tests, diagnostic tests, and other procedures are necessary. Blood tests are obtained on a regular schedule to evaluate organ tolerance and potential side effects of treatment. The complete blood count assesses white blood cells, red blood cells (hemoglobin or hematocrit), and platelets. Complete metabolic chemistry panel includes the assessment of electrolytes (potassium, calcium, sodium, chloride, and magnesium), kidney function, and liver function. Additional tests may also

be necessary based on the specific therapy (i.e., further blood tests, urine tests, or electrocardiogram [ECG]).

Prior to starting treatment, prescriptions are provided for supportive care medications that may be required during chemotherapy. Supportive care medications are those that treat the side effects of your cancer treatment. The prescriptions should be filled before treatment. Patients should tell the healthcare team about any difficulties obtaining or starting the medications as prescribed. If you smoke, smoking should be stopped before therapy, and many centers offer smoking cessation counseling. Exercise is vital to maintain energy, and it is important to have a balance between maintaining physical activity and getting adequate rest. A normal, balanced diet is recommended during treatment. Patients should inform the healthcare team about all medications, including non-prescription ("over the counter") medication. Some medications may interfere with the chemotherapy, making treatment less effective or side effects more severe. See Chapter 7: *Supportive Care*, and Chapter 8: *Nutrition in the Patient with Lung Cancer*, and Chapter 11: *How to Quit Smoking Confidently and Successfully*.

The oncologist performs tests intermittently throughout the treatment course to assess the effectiveness of treatment. This evaluation may include computerized tomography (CT) scan, magnetic resonance imaging (MRI) scan, or positron emission tomography (PET) scan. The MRI and CT scans provide a 3-dimensional view of the organs examined, and the PET scan may distinguish normal cells from tumor cells that are rapidly dividing. The diagnostic tests may be compared with tests from the time of diagnosis. The radiologist and oncologist review the imaging tests to measure the tumor response to treatment.

If cancer has been surgically removed, the patient might receive a prescribed number of cycles of therapy with or without radiation therapy. After completing this regimen, repeat (restaging) scans are performed. However, if chemotherapy is the primary treatment modality, restaging scans are usually done after every two to three cycles of chemotherapy.

Precautions:
Chemotherapy, targeted therapy, and immune therapy agents can harm developing unborn babies. It is essential that patients (male and female) receiving chemotherapy, targeted therapy, or immune therapy, use effective birth control measures to prevent pregnancy while on therapy and for up to six months following completion of therapy. These treatment measures can cause congenital disabilities and or lead to the death of a fetus. In addition, women receiving therapy should not breastfeed as these therapies may be passed onto an infant in breast milk. The length of time for precautions will vary by the type of treatment and should be discussed in detail with your provider.

Oral targeted therapies and supportive therapies must only be handled by the patient. They must be kept out of reach of children in a secure childproof container. Oral therapies may be toxic to children and persons for whom it was not prescribed. In some cases, they can cause life-threatening events or death.

Treatment by Cancer Stages

Patients diagnosed with NSCLC will have their disease assessed for the size of the tumor (T), the extent of lymph node involvement (N) and the extent of metastasis to other regions (M). These three factors contribute to the TNM staging of the NSCLC. One of the initial treatment decisions is based on the TNM stage.

Early-Stage Lung Cancer (Stage I and II)

Stage I NSCLC is a small tumor with no lymph node involvement. Stage II NSCLC is a small or larger tumor with lymph node involvement confined to one lung. The initial treatment of choice for stage I and II NSCLC is surgery with lobectomy, segmentectomy, or pneumonectomy. Adjuvant (post-surgery) chemotherapy may be incorporated into the treatment plan for patients at high risk of recurrence.[1, 6,7] Radiation therapy, including stereotactic radiosurgery may be necessary if the primary tumor is not able to be surgically removed or if the patient is not able to undergo surgery.[8] Stage I NSCLC may recur at local (regional) or distant (metastatic) sites. If the disease recurs at the same location, the area may be treated with local radiation therapy. Patients may be asked to participate in clinical trials to investigate adjuvant (postoperative) chemotherapy.

For stage II NSCLC, chemotherapy and surgery are effective treatments and improve patient survival. Chemotherapy may be used before surgery (neoadjuvant) or after surgery (adjuvant). Neoadjuvant chemotherapy may decrease the tumor size so that surgery may be less extensive. Chemotherapy also may treat cancer cells that may have traveled to other parts of the body (micrometastasis) but cannot be identified with current diagnostic scans. Radiation therapy may be recommended following surgery and chemotherapy to minimize local recurrence.[9]

Stage IIIA Lung Cancer

Stage IIIA NSCLC is a large tumor with or without invasion or lymph node involvement in the central chest region (mediastinum). Most cases of stage IIIA NSCLC are not surgically resectable because of the vast extent of disease. Therefore, combination therapy will be employed to decrease the extent of disease and provide opportunity for surgical resection. Stage IIIA NSCLC often receives combination treatment, with four to six cycles of chemotherapy. The most common regimens used are cisplatin with etoposide and carboplatin with paclitaxel weekly.[10] Treatment is administered in one of the following schedules: [1, 6, 7, 10.]

Neoadjuvant chemotherapy: Chemotherapy before surgery
Induction chemotherapy before concurrent chemotherapy: Chemotherapy alone before a course of chemotherapy and radiation therapy.

Neoadjuvant chemotherapy with concurrent radiation
Chemotherapy and radiation therapy is given together before surgery. Neoadjuvant therapy may be given sequentially if the combination of both might not be tolerated. Chemotherapy is administered first, followed by radiation therapy.

Adjuvant chemotherapy or postoperative radiation therapy
May be used to minimize local recurrence.

For patients with unresectable stage III NSCLC, concurrent chemotherapy and radiation therapy is the first-line of therapy. Following the completion of this, adjuvant treatment with durvalumab (immunotherapy) may be recommended in select patients.[11] Durvalumab is an immune checkpoint inhibitor. It is administered every two weeks for up to one year.

Advanced-Stage Lung Cancer (Stages IIIB and IV)

Stage IIIB NSCLC is unresectable disease with local involvement. Stage IV NSCLC includes extensive local spread or metastasis of cancer to other regions in the body such as the brain, liver, or adrenal glands or the development of a malignant pleural or pericardial effusion. The treatment goals for advanced-stage disease include prolonging survival and controlling symptoms.[1, 12-14] Supportive care includes treatment that controls symptoms but may not necessarily treat cancer directly.

Patients with non-small cell lung cancer, of adenocarcinoma histology, who are being considered to receive systemic therapy, should have their tumor tissue assessed for genetic markers or mutations of the epidermal growth factor receptor (EGFR), EML4-ALK, ROS 1, BRAF, RET, ERB2 (HER2), KRAS, and MET.[1, 2] Also, tumor tissue should be assessed for the level of PD-L1 expression on the tumor surface.

Patients whose tumors harbor an EGFR-mutation should receive oral therapy with an EGFR inhibitor. EGFR inhibitors include osimertinib, erlotinib, gefitinib, and afatinib.[1, 12, 13, 15] Osimertinib is the preferred first-line treatment as this targets EGFR as well as a known mechanism of

resistance known as T790M.[1, 16, 17] If cancer progresses on first-line treatment, patients may be asked to undergo a repeat biopsy of the tumor to test for specific markers of resistance.[18] (Appendix 2)

Patients with an EML4-ALK mutation should receive oral therapy with an EML4-ALK inhibitor. Currently approved EML4-ALK inhibitors include alectinib (preferred first-line) and crizotinib.[1, 19-22] If there is progression of disease or resistance to therapy on alectinib or crizotinib, ceritinib or brigatinib may be utilized.[1, 20] Lorlatinib is a third-line of therapy available if progression on two prior lines of therapy.[23, 24] Dabrafenib & Trametinib in combination are approved for BRAF mutation.[25] Crizotinib and ceritinib for ROS1 rearrangements.[19, 26] Larotrectinib is approved for NTRK fusion mutations.[27] (Appendix 2)

There is much research on therapies that target other tumor driver mutations, including KRAS, which is the most common driver mutation. Currently, there is very little data on mutational drivers in NSCLC squamous histology. In the future, there are likely to be additional targets and targeted therapies for patients with lung cancer. If cancer progresses on first-line treatment with targeted therapy, patients may be asked to undergo a repeat biopsy of the tumor to test for specific markers of resistance.[18] In some cases, this information can be obtained through a "liquid biopsy", a blood test.

For patients who do not have a mutation for which there is an approved targeted therapy, treatment will be dependent upon the level of PD-L1 expression in the tumor and specific patient considerations that influence the use of immunotherapy.[1, 3, 12-14] Single agent immune checkpoint inhibitor may be recommended for those whose tumor PD-L1 expression is high. A combination of immune checkpoint inhibitor with chemotherapy (+/- an angiogenic targeted therapy), may be recommended for patients with lower PD-L1 expression, or for those in which the results are not available, or those with a high tumor burden. Potential contraindications to immune checkpoint therapy may include previous underlying auto-immune diagnosis, prior organ transplant, and requirement of high dose steroids.[1, 3, 12-14] (Appendix 3)

Combination chemotherapy is recommended in patients who are in relatively healthy condition, unable to receive immune checkpoint therapy and without a driver mutation.

Single-agent chemotherapy may be selected if the patient has a poor performance status. The selection of chemotherapy is based on the specific type of NSCLC (eg, adenocarcinoma vs. squamous cell carcinoma).[1, 28] Treatment is usually given for four to six cycles if there is tumor response or stable disease. It is standard for two chemotherapy drugs to be used together (doublet). The combination usually consists of a combination of a platinum chemotherapy agent (cisplatin or carboplatin) and a second chemotherapy agent. In some cases, a third agent, such as a monoclonal antibody targeted therapy is added if patients are eligible to receive. If the patient has a poor performance status, a single agent may be used. Approved treatment options for NSCLC are listed in Appendices 1-3.

Maintenance Therapy for Advanced NSCLC

Maintenance therapy consists of ongoing administration (beyond four to six cycles) of at least one immune checkpoint inhibitor, chemotherapy, or targeted agent given during the primary treatment. The goal is to extend long-term benefit from primary treatment. Examples of maintenance therapy include immune checkpoint inhibitors (pembrolizumab, atezolizumab), pemetrexed, bevacizumab, and cetuximab.[1, 28-30]

Switch maintenance is the initiation of a new chemotherapy agent after primary treatment is completed. Examples of switch maintenance therapy include pemetrexed or docetaxel.[1, 28-30]

Second-Line Treatment for Non-Small Cell Lung Cancer

Second-line treatment is a treatment for disease that has progressed or recurred. The physician does a complete review of the disease, treatment history, and reviews new and previous diagnostic scans. It is important for the physician to understand how well the patient tolerated the first-line of treatment and if there are any residual side effects. Several immune checkpoint inhibitors and chemotherapy agents are approved in the second-line setting.

For patients that are not eligible for treatment on immune therapy, a different combination of chemotherapy drugs is used. Radiation therapy and surgery may be considered depending on the site of recurrence.

Continuation After Disease Progression

Targeted agents such as erlotinib, afatinib, gefitinib, osimertinib, crizotinib, ceritinib and alextanib may be continued in the setting of disease progression in patients with EGFR and ALK mutations.[28] The chemotherapy portion of the regimen is discontinued.

Clinical Trials

Clinical trials are supervised research studies that investigate the effectiveness and safety of new cancer treatments or the combination of new treatments with established treatments. The trials are designed to compare new treatment strategies with the current standard of care and to improve survival outcomes. Patients may be invited to participate in clinical trials at any stage of disease. See Chapter 6: *Clinical Trials and Emerging Therapies for Lung Cancer*.

Chemotherapy and Targeted Therapy Side Effects

Chemotherapy and targeted therapies for NSCLC can cause many unwanted side effects. These side effects occur because chemotherapy drugs kill both cancer cells and rapidly dividing normal cells. Healthy cells that may be affected include bone marrow, blood, intestinal, oral, and hair cells. Not every side effect of chemotherapy may be experienced. Frequency and severity of side effects may depend on factors such as the dosage, route (intravenous or oral), frequency (how often chemotherapy is given), and response of the individual body to the chemotherapy. The patient should speak with the oncology team about specific side effects that may be expected and about how to prevent and treat them.

Side effects of chemotherapy and targeted therapy include and are not limited to anemia, leukopenia, thrombocytopenia, nausea, vomiting, diarrhea, constipation, mucositis, peripheral neuropathy, alopecia, infection, pain, and fatigue. The patient may also experience changes in appetite, skin, nails, vision, hearing, or cognition. The patient may have flu-like symptoms, including body and muscle aches, fever, chills, headache, and nasal congestion. (See Appendix 1 and 2)

Bone Marrow Suppression

Bone marrow is a thick, pasty liquid inside bones where new red blood cells, white blood cells, and platelets are formed. When bone marrow suppression occurs from chemotherapy, the production of these cells is decreased. Bone marrow suppression is diagnosed with a complete blood count, a blood test that measures the number of red blood cells, white blood cells, and platelets. Bone marrow suppression may include anemia (a decrease in red blood cells), leukopenia (a decrease in white blood cells), and thrombocytopenia (a decrease in platelets), and is more likely to occur with more cycles of chemotherapy.

Chemotherapy-induced anemia is caused by the impairment of the cellular products needed to make red blood cells in the bone marrow. The platinum chemotherapy agents such as cisplatin and carboplatin are well known to cause anemia. Signs and symptoms of anemia include weakness, fatigue, dizziness, lightheadedness, shortness of breath, and pallor of the fingernails, palms of the hands, eyelids, and inside of the mouth. Anemia may be prevented by eating a diet rich in iron and folate, including red meats and green leafy vegetables. Drink plenty of fluids and try doing mild exercise daily such as walking for 15 to 30 minutes. Medical evaluation is advised for symptoms of increased fatigue, inability to do normal activities, shortness of breath, chest pain, bleeding, or inability to think clearly. Treatment for anemia may include a blood transfusion.[31]

When leukopenia or neutropenia (a decrease in the white blood cell count) occurs, the body is prone to infections. There are many different types of white blood cells. The neutrophils make up most of the white blood cell count. Usually, the white blood cell count is lowest 10 to 14 days after chemotherapy. A decrease in the number of neutrophils (neutropenia) occurs during this time. Patients will be at risk of developing infections during this time.[32, 33]

It is extremely important to take measures to prevent infection during chemotherapy by washing the hands frequently, avoiding large crowds, limiting time spent with small children as they carry a lot of germs, and avoiding sick individuals. Most infections arise from bacteria from the patient's mouth, airway, skin, urinary tract, or rectum. It is important for the patient to bathe daily and perform oral care 3-4 times a day as well as good perineal care.

The patient should contact their healthcare provider immediately if they develop a high fever (temperature equal to or greater than 100.4OF), chills, new onset of cough or shortness of breath, burning with urination, vaginal discharge, or pain, swelling, redness, or warmth at an intravenous site, or any site of injury. Severe untreated neutropenia is very dangerous. Patients should be treated with antibiotics immediately.[32, 33] If the white blood cell count is expected to decrease, treatment with growth factors such as filgrastim or pegfilgrastim within 24 to 48 hours after chemotherapy may decrease the length of leukopenia and thus decreasing the risk of developing infections. There is an "on-body" infusion device for pegfilgrastim that may be applied at the end of your infusion. This device will automatically infuse pegfilgrastim at 24 hours post-chemotherapy completion and eliminates the need for you to have to return to the clinic for administration.

Platelets help the blood form clots in response to injury. With thrombocytopenia (low platelet count), blood clot formation is impaired. Signs include easy bleeding or bruising, purple or red spots (petechiae) on the skin, blood in the urine, bloody or black stools, and extreme weakness. Treatment may include a platelet transfusion or administration of growth factors. Patients should use a soft-bristle toothbrush, only use electric razors, and protect themselves from injury.

Nausea and Vomiting

The most common side effect of chemotherapy is nausea and vomiting. Nausea and vomiting are caused by different impulses received from the digestive tract and the brain. Anti-nausea medications block different pathways and neurotransmitter receptors.[34-36] Several antiemetic drugs are available and work differently to prevent and treat different types of nausea, including acute, delayed, anticipatory, breakthrough, or refractory nausea. (Table 2) Different antiemetic drugs commonly are used in combination and may be given before, during, or after chemotherapy. When the optimal antiemetic regimen is used, nausea or vomiting may be prevented.

Nausea and vomiting also may be managed by decreasing unnecessary motion, eating slowly, eating small frequent meals and avoiding large meals, and sipping on water, ginger ale, or electrolyte-rich fluids. Behavioral therapies useful for nausea induced by chemotherapy include acupuncture, acupressure, guided imagery, and relaxation methods. See Chapter 9: *Integrative Medicine, Complementary Therapies, and Chinese Medicine in Lung Cancer*. The patient should contact their provider if they experience uncontrollable or ongoing nausea, projectile vomiting, severe stomach pain or bloating, weight loss, or vomit that is bloody or appears like coffee grounds.

Risk factors for developing nausea and vomiting including the female gender, history of prior chemotherapy induced nausea and vomiting, younger than 50 years of age, dehydration, electrolyte

imbalances, history of motion sickness, brain metastases, anxiety, bowel obstruction or slow bowel transit, and use of opioids to control pain.[34]

Table 2. Common Antiemetic Drugs for Nausea and Vomiting Induced by Chemotherapy [34-36]

Serotonin (5-HT3) antagonists	Neurokinin-1 (NK1) antagonist
Dolasetron (Anzemet®) Granisetron (Granisol®, Kytril®, Sancuso®) Ondansetron (Zofran®) Palonosetron (Aloxi®) Netupitant/palonsetron (Akynzeo®) Fosmetopetent/palonesetron	Aprepitant or Fosaprepitant (Emend®) Rolapitant (Varubi®)
Other	
Dexamethasone (Decadron®) Dronabinol (Marinol®) Prochlorperazine (Compazine®) Promethazine (Phenergan®) Alprazaolam (Xanax®) Haloperidol (Haldol®) Lorazepam (Ativan®) Olanzapine (Zyprexa®) Metoclopramide (Reglan®) Scopolamine Transdermal Patch	

Diarrhea

Diarrhea is defined as two to three loose or watery bowel movements daily. When the intestines are not working properly, the fluid remains in the stool and causes loose or watery bowel movements. If untreated, diarrhea can cause dehydration and loss of essential electrolytes that are needed for normal function. Diarrhea can cause dizziness, weakness, fatigue, weight loss, nausea, abdominal pain, abdominal cramping, or bloating.

The primary treatment for diarrhea is fluid replacement and stool bulking. Drink electrolyte-rich fluids such as water, juice, soup broth, or commercially available electrolyte drinks and consume

bulking foods such as bananas, rice, apple sauce, oat cereal, toast, crackers, or potatoes. Patients with diarrhea should avoid consuming caffeinated beverages, alcohol, milk products, and high fiber, high fatty, spicy, and gas-producing foods such as beans, nuts, raw vegetables, corn, dried fruits, or hot peppers. Many nonprescription products can help stop diarrhea, including loperamide (Imodium®) or bismuth subsalicylate (Pepto-Bismol®). However, sometimes, diarrhea can be so severe that prescription medications are prescribed such as diphenoxylate and atropine (Lomotil®).[37, 38]

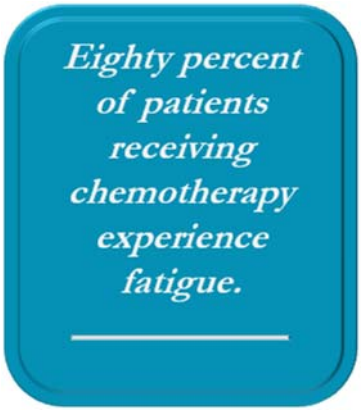
The patient should keep a record of the number of loose stools per day and clean the area around the rectum thoroughly. The patient's provider should be notified immediately for diarrhea that does not resolve and is associated with fever, inability to eat or drink, decreased urination, or bloody or black stools.

Constipation

Constipation occurs when bowel movements are infrequent (no bowel movement in 3 days) or stool is difficult to pass. Cancer-related constipation is mainly caused by chemotherapy and medications to treat cancer pain.[39, 40] Prevention of constipation includes eating a diet high in fiber (grains, beans, and vegetables), drinking eight glasses of fluids daily, walking or exercising regularly, and establishing a bathroom routine. Medications to treat and prevent constipation include stool softeners and laxatives. The provider should be contacted if a patient develops constipation that is associated with abdominal pain, vomiting, or inability to eat, hard impacted stool that will not come out, or absence of a bowel movement in 4 to 5 days. These symptoms occur with stool impaction and bowel obstruction, which are serious complications of constipation.

Fatigue

Eighty percent of patients receiving chemotherapy experience fatigue. Fatigue is the feeling of overwhelming tiredness.[41] Fatigue can be caused by cancer, treatments for cancer such as chemotherapy or radiation therapy, and the side effects of therapy including anemia, electrolyte abnormalities, dehydration, malnutrition, lack of physical activity, lack of sleep, pain, or emotional distress.[41] Fatigue can affect how patients feel physically, emotionally, and spiritually, as well as interfere with the ability to function or socialize. Patients usually report having fatigue within 1 to 2 days after the first chemotherapy treatment, throughout therapy, and weeks to months and sometimes even a year after treatment.



Since many varied factors can cause fatigue, a combination of treatment approaches is necessary. Fatigue can be managed by, maintaining a healthy diet avoiding long naps during the day (keep under 1 hour), postponing activities that are not essential, doing a moderate physical activity such as walking, and participating in relaxation activities such as yoga, massage, or acupuncture. Treating

problems such as pain, sleep disturbance, infection, or anemia also decrease fatigue. Symptomatic anemia related fatigue is sometimes treated with blood transfusions or red blood cell-stimulating products. Steroids or medications that increase the patient's appetite can also be helpful. It is useful to keep a record or weekly diary of the onset of fatigue, factors that aggravate or improve fatigue, and the effect of fatigue on activities of daily living. Patients should contact their provider if they experience an increase in their fatigue, the inability to get out of bed or think clearly, or fever, or chills.

Alopecia

Alopecia is temporary or permanent hair loss. Alopecia occurs because chemotherapy damages the hair follicle, causing the hair to break. Some chemotherapy drugs cause thinning of the hair without complete hair loss. Chemotherapy may affect the hair on the head, eyelashes, eyebrows, face, underarm, leg, and pubic area. Most people report a tingling sensation before the hair falls out, usually two to three weeks after the first chemotherapy treatment.

Hair loss cannot be prevented, so being prepared is important. Before starting chemotherapy, the patient may purchase hats, scarves, or wigs. After hair loss, it is important to protect the skin from extreme warm (sunburn) or cold temperatures and to keep the skin lubricated with ointments and creams to avoid dryness. After chemotherapy completion, the hair may grow back; however, this usually begins within three months after the last treatment.[27]

Cutaneous (Skin and Nail) Changes

Changes to the skin and nail may occur due to chemotherapy, especially if a patient is being treated with targeted therapies (EGFR inhibitors, ALK inhibitors, monoclonal antibodies, and immune therapies).[42, 43] Rash is the most common skin-related side effect from targeted therapies.[28] The rash is usually acneiform (looks like acne with pustules or whiteheads) and is located on the face, chest, abdomen, or thighs.[42, 43] It is important for the patient not to pop the pustules as this could lead to infection requiring antibiotics. The patient's skin can also become itchy, scaly, rough, and dry. Bathing with nonirritating soaps and water as well as applying fragrance-free emollients, creams, and lotions to moisturize the skin can provide symptom relief. Patients should avoid bath salts or lotions that contain alcohol as they can dry out the skin. Epidermal growth factor receptor inhibitors can cause paronychia or nail fold swelling and cracking in the fingers and toes. Skin and nail changes can wax and wane or spontaneously resolve. For the most part, reducing the dose or interrupting therapy for a brief period is the most effective way to manage moderate to severe cutaneous reactions related to targeted therapies. At times topical or oral antibiotics may be given to help reduce symptoms related to targeted therapy-induced acneiform rashes. Both targeted and non-targeted based chemotherapies can cause the skin to become sensitive to sunlight, therefore, staying out of direct sunlight and wearing sunscreen is essential.

Mucositis

Mucositis is inflammation and ulceration of the lining of the mouth, throat, and digestive tract. Mucositis occurs due to direct cellular kill by chemotherapy, as well as the release of oxidative, inflammatory, and metabolic by-products.[44-46] Mucositis can be very painful and irritating, requiring pain medications and alteration in nutritional intake. Symptoms may include an abnormal sensation in the mouth, redness, swelling, sores, difficulty swallowing, bleeding, and mouth pain. Mucositis can also cause nausea and vomiting. Medications can be used to prevent mucositis from developing or becoming worse. It is important to maintain good nutrition and oral hygiene to prevent abnormal bacteria or fungi from growing inside the mouth. It also is important to keep the mouth and lips moist to prevent cracking, which can lead to infection. The patient should avoid using a hard-bristle toothbrush and alcohol-based mouthwash, which can irritate the lining of the mouth and gums. The patient should notify the practitioner for any changes in the mouth, inability to swallow, pain or discomfort when swallowing, sores or white patches in the mouth or on the tongue, bleeding from the gums, fever, or other signs of infection. Medications and oral rinses (saline solutions, baking soda solutions) may alleviate symptoms.

Ototoxicity

The platinum-based chemotherapy drugs that are used to treat NSCLC, such as cisplatin and carboplatin, may cause inner ear damage, high pitch hearing loss, and ringing in the ears (tinnitus).[28, 47, 48] Other medications such as antibiotics and diuretics can produce the same effects. Hearing loss is painless and may not be noticed until it becomes severe and irreversible. Signs and symptoms of hearing loss include turning the head while having a conversation, increasing the volume of the television or radio, or unclear, muffled, or quiet sounds. The patient should report changes in hearing to the practitioner, who may examine the ears and determine if hearing loss has occurred. A hearing test (audiogram) may be done before, during, or after chemotherapy to assess hearing.

Ocular Toxicities

Changes in vision and eye toxicities are side effects of systemic chemotherapies as well as targeted therapies. Some of the most common eye problems experienced by patients include: blepharitis (inflammation of the eyelids, redness, crusting and flaking of the skin on the lids); conjunctivitis (inflammation and redness of the conjunctiva); epiphora (excessive tear production); photophobia (sensitivity to light); photopsia (ocular pain); trichomegaly (long eyelashes that get misdirected or go inward instead of outward); diplopia (double vision), visual floaters and blurry vision. Treatment for vision changes includes artificial tears or lubricants, topical steroids, anti-inflammatory medications, good eye hygiene, warm compresses, avoiding light exposure, and occasionally discontinuation of chemotherapy. Prompt referral to an ophthalmologist is important when a patient experiences severe pain, swelling, redness, or sudden onset of any visual impairment.[49, 50]

Cognitive Dysfunction

The cognitive change, also known as "chemo brain," is a decrease in mental sharpness. Chemotherapy is one of the many causes of cognitive dysfunction. Patients can develop memory impairment, difficulty completing tasks, the inability to learn new skills, trouble with word-finding or completing sentences, misplacing objects, confusing dates, and overall feeling mentally slow. Cognitive changes can be short or long term. The patient should notify their providers when "chemo brain" interferes with their normal daily activities and their ability to work.[51, 52]

Peripheral Neuropathy

Some chemotherapy drugs can cause damage to nerve fibers and lead to peripheral neuropathy, causing numbness, tingling, burning, and loss of vibratory sensation in the hands and feet.[28, 53] Peripheral neuropathies may interfere with normal activities and may cause difficulties performing fine motor movements such as buttoning a shirt, writing, or picking up utensils. When experiencing pain or changes in temperature, driving, walking, cooking, or brushing the teeth may also become difficult. Extremely hot or cold temperatures may aggravate numbness and tingling and may cause severe burns or frostbite injury. Therefore, extreme caution is necessary. It is recommended patients wear gloves near the refrigerator/freezer and potholders when cooking. Falls should be avoided by removing objects from the floor, securing area rugs, cleaning spills, and illuminating a room before entering.

Some medications may be given for peripheral neuropathy. Although several medications are not approved by the United States Food and Drug Administration for the treatment of peripheral neuropathy, they may decrease the unpleasant symptoms of numbness and tingling. These medications include antidepressants, anti-seizure medication such as gabapentin, topical creams that contain capsaicin, and anesthetic creams, or patches that contain lidocaine. Other helpful therapies may include acupuncture, physical therapy, massage, occupational therapy, and transcutaneous electrical nerve stimulation (TENS) a therapy that uses low-voltage electrical current for pain relief. See Chapter 9: *Integrative Medicine, Complementary Therapies, and Chinese Medicine in Lung Cancer.*

The patient should contact the provider if the peripheral neuropathy becomes worse, interferes with self-care or activities of daily living, or causes stumbling, falling, loss of balance, injury, or muscle spasms in the mouth, jaw, fingers, or toes.

Immunotherapy Side Effects

Side effects of immune therapy will be discussed separately, as the mechanism of how they develop, and the necessary management is usually different than the side effects of other systemic treatments. Immune therapy treatments are typically well-tolerated. The most common side effects are fatigue and myalgias. These are usually low grade. Immune-related adverse events (IrAE's) are unique class-specific effects of the inflammatory response on healthy cells. These are caused by

inflammation and attack on healthy cells and organs. In general, these are low grade or mild. However, if left unmanaged, they can proceed to severe and even life-threatening. IrAes can affect any body organ system. The pattern of occurrence can be immediately after a dose, after several doses, or even after discontinuation of therapy. They can affect more than one organ system at a time. The severity may increase with combination therapy. Systems affected include (but not limited to) those in Table 3.[28, 54-60]

Management of IrAE's includes delaying or stopping the immune checkpoint inhibitor therapy. In many cases, the IrAe will resolve on its own. However, it may be necessary to undergo further evaluation, testing, and treatment to prevent more serious progression of the IrAE. As these are inflammatory in nature, steroids are used to control and reverse the inflammation of most of the irAEs. Steroid dosing is dependent on the seriousness of the IrAE and typically continue over several weeks.[54-60] It is important to adhere to the steroid schedule, as missing or discontinuing doses, can lead to a flare of the toxicity that can be life-threatening. Additional supportive medications may be prescribed to minimize the side effects of the steroids.

In some cases, additional immunosuppressant therapy may be required to treat the IrAE. Endocrine irAEs are usually treated with replacement of the endocrine hormone that is deficient. In most cases, the patient will require hormone replacement for the rest of their life. The healthcare team may consult with other sub-specialists to assist in the management of the irAE. It is imperative that patients notify the healthcare team immediately of the onset of any symptoms so that these can be properly evaluated and treated.

Table 3: Immune Related Adverse Events

Organ system	**IrAE**	**Symptoms**	**Self-Strategies**
Gastrointestinal	Diarrhea, colitis, nausea, mucositis, perforation	Abdominal pain or cramping, loose stools	Maintain adequate hydration; Avoid spicy foods
Dermatologic	Rash, Mucositis	Rash, itching, blistering, skin peeling, mouth tenderness	Sunscreen & protection, sunglasses; emollient lotions
Pulmonary	Pneumonitis	Shortness of breath, difficulty breathing, cough, chest pressure	Smoking cessation; avoid inhaled irritants
Endocrine	Hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, hyperglycemia, diabetes	Fatigue, palpitations, sluggishness, headache, decreased focus, anxiety	Maintain adequate rest

Organ system	IrAE	Symptoms	Self-Strategies
Liver	Hepatitis (inflammation of the liver)	Decreased function of liver, increase in liver enzymes	Avoid taking over the counter medications that are metabolized by liver (i.e. acetaminophen); Avoid alcohol consumption
Kidneys	Nephritis	Decreased function of kidneys, increase in fluid retention	Avoid taking over the counter medications that are metabolized by kidney (i.e. NASAIDS); Maintain adequate hydration
Pancreas	Pancreatitis	Nausea, abdominal discomfort, emesis	Avoid alcohol and high fat food content
Cardiac	Pericarditis, Myocarditis	Increased shortness of breath, arrythmias, chest pressure or pain	Minimize drug-drug reactions by reviewing all new medications with health care team
Musculoskeletal	Myalgias, Arthralgias	Muscle or joint aches or inflammation, decreased range of motion of joint	Maintain health exercise and range of motion
Nervous System	Peripheral Neuropathy, myasthenia gravis, Guillain Barre	Decreased sensation, impaired ambulation	Use caution when handling hot/cold materials; May need walking aide
Eyes	Uveitis, iritis, conjunctivitis	Impaired vision, dryness, itching, pain, swelling	Lubricating eye drops

Conclusion

The patient should speak with the oncology provider or nurse about specific side effects that may be expected from the chemotherapy, targeted therapy, and immune therapy. Discuss how these side effects might be prevented and how they will be monitored and treated. It is important to keep a list of the presence and severity of all side effects experienced. This list may give the oncology provider valuable information about how to treat the symptoms. In addition, the patient should keep the telephone numbers of their providers and clinic available in case of severe illness, high fever, or symptoms that require immediate medical attention.

Questions to Ask Your Doctor about Chemotherapy

- What type of chemotherapy will I receive?
- How long will treatment last?
- What are the side effects of chemotherapy?
- What are the potential benefits?
- What are the potential risks?
- How can chemotherapy affect my daily routine and hobbies? Can I still go to my job, exercise, see my friends, etc.?
- How will we manage nausea?

Questions to Ask Your Doctor about Targeted Therapy

- Can my tumor be treated with targeted therapy?
- What type of testing of the tumor is required?
- What side effects can I expect with this treatment?
- What are the potential benefits?
- What are the potential side effects?
- How can targeted therapy affect my daily routine and hobbies? Can I still go to my job, exercise, see my friends, etc.?

Questions to Ask Your Doctor about Immunotherapy

- Is immunotherapy right for me? Do I need to be tested in order to be put on an immunotherapy treatment?
- What are the potential benefits?
- What are the potential side effects?
- How can immunotherapy affect my daily routine and hobbies? Can I still go to my job, exercise, see my friends, etc.?
- How is immunotherapy given, and how often do I undergo treatment? Where do I undergo treatment?
- How long will I have to receive immunotherapy treatment?
- How can I prepare myself before beginning immunotherapy? Can I eat, drink, etc. before or after receiving the medicine?
- Are there any lung cancer support programs where I can speak with other people who received immunotherapy?

Appendix 1. Chemotherapy Drugs for Non-Small Cell Lung Cancer and Common Side Effects*

Chemotherapy Drug	Common Side Effects
Cisplatin (Cis-diamminedichloroplatinum, CDDP, Platinol®)	Kidney damage (nephrotoxicity), nausea and vomiting, decrease in the red cell, white cell, and platelet counts (bone marrow suppression), nerve damage (neurotoxicity), high pitch hearing loss and ringing in the ears (ototoxicity), eye damage (ocular toxicity), metallic taste of foods, loss of appetite, hair loss (alopecia), infertility, liver function changes, possible vascular events (heart attack, stroke, clot formation), SIADH (syndrome of inappropriate antidiuretic hormone secretion)
Etopiside (VP-16, VePesid®)	Decrease in the red cell, white cell, and platelet counts (bone marrow suppression), nausea and vomiting, anorexia, hair loss (alopecia), inflammation and ulceration in the mouth, throat, and intestines (muscositis), infusion reaction (fever, chills, shortness of breath, increased heart rate, facial and tongue swelling, low blood pressure), metallic taste in the mouth during infusion, redness at the injection site, skin changes (radiation recall reaction – skin reaction that occurs on an areas that has been previously radiated)
Carboplatin (Paraplatin®)	Kidney damage (nephrotoxicity), nausea and vomiting, decrease in red cell, white cell, and platelet counts (bone marrow suppression), nerve damage (neurotoxicity), hair loss (alopecia), infertility, liver function changes, allergic reaction (skin rash, itchiness, hives, shortness of breath, low blood pressure)
Paclitaxel (Taxol®)	Decrease in red cell, white cell, and platelet counts (bone marrow suppression), infusion reaction (skin rash, flushing, redness, shortness of breath, low blood pressure), nerve damage (neurotoxicity), heart rate changes, hair loss (alopecia), inflammation and ulceration in the mouth, throat, and intestines (muscositis), diarrhea, liver and kidney function changes, nail bed changes (onycholysis)
Vinorelbine (Navelbine®)	Decrease in the red cell, white cell, and platelet counts (bone marrow suppression), nausea and vomiting, constipation, diarrhea, inflammation and ulceration in the mouth, throat, and the intestines (muscositis), liver function changes, injury and inflammation the vein, nerve changes (neurotoxicity), hair loss (alopecia), general fatigue, infusion reaction (shortness of breath, low blood pressure, facial flushing, rash), SIADH (syndrome of inappropriate antidiuretic hormone secretion)

Chemotherapy Drug	Common Side Effects
Gemcitabine (Gemzar®)	Decrease in the red cell, white cell, and platelet counts (bone marrow suppression), nausea and vomiting, flu like symptoms (fever, muscle and body aches, chills, headaches), liver function changes, pulmonary toxicities(shortness of breath or drug induced pneumonitis), infusion reaction (facial flushing and swelling, headache, shortness of breath, low blood pressure), protein or blood in the urine, skin rash on the chest and extremities, swelling of the lower extremities, radiation recall skin reactions
Docetaxel (Taxotere®)	Decrease in the white blood cell count (neutropenia), allergic reaction (skin rash, skin redness, low blood pressure, shortness of breath), fluid retention, dry itchy skin rash (maculopapular rash), hair loss (alopecia), inflammation and ulceration in the mouth, throat, and intestines (muscositis), diarrhea, nausea and vomiting, generalized fatigue, liver and kidney function changes, phlebitis or swelling at the injection site
Pemetrexed (Alimta®)	Decrease in the red cell, white cell, and platelet counts (bone marrow suppression), skin rash, diarrhea, nausea and vomiting, inflammation and ulceration in the mouth, throat and intestines (mucositis), fatigue, changes in the liver and kidney function
Albumin-Bound Paclitaxel (Abraxane®)	Myelosupression (decrease in white blood cells, red blood cells, and platelets), ocular or visual disturbances, fatigue, weakens, alopecia, nausea, vomiting, mucositis, liver toxicities, neurotoxicity's (peripheral neuropathy and paresthesias), injection site reactions, cardiac toxicities (chest pain, high blood pressure, elevated heart rate, blood clot in the lungs), peripheral edema (swelling of the extremities)
Topotecan (Hycantin®)	Myelosuppression, nausea, vomiting, diarrhea, abdominal pain, headache, fever, fatigue, alopecia (hair loss), liver toxicities, blood in the urine

*Adapted from Chu E and Devita VT. Physicians' Cancer Chemotherapy Drug Manual (2019).28

Appendix 2. Targeted Therapy Drugs for Non-Small Cell Lung Cancer and Common Side Effects*

Targeted Therapy	Dose	Side Effects
EGFR Inhibitors		
Osimertinib (Tagrisso™)	80mg orally, daily, with or without food	Diarrhea, rash, dry skin, nail changes (redness, swelling, pain, nail breakage). Severe lung and cardiac effects
Erlotinib (Tarceva®)	150mg orally, once daily. Take 1 hour before or 2 hours after a meal	Dry and itchy skin, acneiform rash on face and chest, diarrhea, nausea and vomiting, mucositis, increased cough, shortness of breath, fever, liver function changes, anorexia, pink eye (conjunctivitis), inflammation of cornea (keratitis), nail changes (paronychia), hair growth abnormalities (alopecia, thinning of hair with increased fragility, darkening and increased thickness of eyelashes and eyebrows), possible gastro intestinal(GI) hemorrhage
Afatinib (Gilotrif®)	40mg orally, once daily Take 1 hour before or 2 hours after a meal	Diarrhea, rash, nail fold swelling in the fingers and toes (paronychia), dry skin, bullous and exfoliative skin disorders, decrease appetite, stomatitis, lung toxicity (interstitial lung disease), liver toxicities, inflammation of cornea (keratitis), visual changes, increase risk for heart dysfunction
Gefitinib (Iressa®)	250mg orally, daily, with or without food	High blood pressure, dry itchy skin, acneiform rash, liver function changes, anorexia, nausea and vomiting, mucositis, conjunctivitis, inflammation of cornea (keratitis), abnormal eyelash growth, inflammation of the eyelash follicle (blepharitis), possible coughing up blood or gastro intestinal (GI) hemorrhage
Dacomitinib (Vizimpro®)	45mg orally once daily without food	Diarrhea, rash, nail/cuticle changes, mouth sores, decreased appetite, dry skin, weight loss, hair loss, cough, interstitial lung disease

Targeted Therapy	Dose	Side Effects
Cetuximab (Erbitux®)	Given intravenously, usually weekly	Itchy and dry skin, acne skin rash on face and chest, nail fold swelling in the fingers and toes (paronychial inflammation), lung toxicity (cough, shortness of breath, interstitial lung disease), infusion reaction (fever, chills, rash, flushing, fatigue, headache, shortness of breath, lip swelling, low blood pressure), low magnesium, generalized malaise
Necitumumab (Portrazza™)	Intravenously over 60 minutes on days 1 & 8 of each 3-week cycle	Skin rash, inflammation of the eyes & fingers (conjunctivitis & paronychia). magnesium deficiency, muscle weakness, blood clots, infusion reaction
EML4-ALK Inhibitors		
Alectinib (Alecensa®)	Take 600mg every 12 hours (2 times daily). Take four- 150mg capsules at each dose for total of 8 capsules daily. Take with food	Fatigue, constipation, swelling in hands, feet, ankles, and eyelids; Muscle weakness or tenderness, lung (pneumonitis), liver, or cardiac toxicities
Crizotinib (Xalkori®)	250mg orally, twice daily with or without food	Liver and kidney toxicities decrease heart rate and contractility, lung toxicity (decrease in pulmonary function, pneumonia, interstitial lung disease/pneumonitis, shortness of breath, cough) visual disturbances (double and blurry vision, floaters/flashes, visual brightness, reduced visual acuity), diarrhea, nausea, vomiting, decrease appetite, fatigue, peripheral neuropathy
Ceritinib (Zykadia™)	750mg orally, once daily on an empty stomach, do not take within 2 hours of a meal	Diarrhea, nausea, vomiting, abdominal pain, liver toxicities, lung toxicity (interstitial lung disease/pneumonitis), heart dysfunction, decreased heart rate, high blood sugar (hyper-glycemia), fatigue, decrease appetite, constipation

Targeted Therapy	Dose	Side Effects
Brigatinib (Alunbrig®)	90mg orally, once daily for 7 days, if tolerated increase to 180mg orally once daily.	Nausea, diarrhea, fatigue, cough, headache, lung toxicity (interstitial lung disease/pneumonitis), hypertension, decreased heart rate, visual disturbances, increase in blood sugar levels (hyperglycemia), increase in pancreatic enzymes
Lorlatinib (Lorbrena®)	100mg orally once daily	Fluid retention, peripheral neuropathy, cognitive effects, shortness of breath, fatigue, weight gain, joint aches, mood changes, diarrhea, increased lipid, heart arrythmias
BRAF V600E Inhibitors		
Dabrafanib (Tafinlar®) & Trametinib (Mekinist®)	Dabrafanib: 150mg orally twice daily, at least 1 hour before or 2 hours after a meal Trametinib:2mg orally once daily, at least 1 hour before or 2 hours after a meal.	Headache, fever, joint aches, hair loss, hand-foot redness, swelling & pain; secondary cancers; bleeding, enlargement of heart (cardiomyopathy), visual disturbances, rash, hyperglycemia, anemia, colitis, deep vein thrombosis & pulmonary embolism (blood clotting), interstitial lung disease
ROS 1 Inhibitors		
Crizotinib (Xalkori®)	250mg orally, twice daily with or without food	Liver and kidney toxicities decrease heart rate and contractility, lung toxicity (decrease in pulmonary function, pneumonia, interstitial lung disease/pneumonitis, shortness of breath, cough) visual disturbances (double and blurry vision, floaters/flashes, visual brightness, reduced visual acuity), diarrhea, nausea, vomiting, decrease appetite, fatigue, peripheral neuropathy

Targeted Therapy	Dose	Side Effects
Ceritinib (Zykadia™)	750mg orally, once daily on an empty stomach, do not take within 2 hours of a meal	Diarrhea, nausea, vomiting, abdominal pain, liver toxicities, lung toxicity (interstitial lung disease/pneumonitis), heart dysfunction, decreased heart rate, high blood sugar (hyper-glycemia), fatigue, decrease appetite, constipation
Lorlatinib (Lorbrena®)	100mg orally once daily	Fluid retention, peripheral neuropathy, cognitive effects, shortness of breath, fatigue, weight gain, joint aches, mood changes, diarrhea, increased lipid, heart arrythmias
NTRK Inhibitor		
Larotrectonib (Vitrakvi®)	100mg orally twice daily	Fatigue, nausea, dizziness, vomiting, cough, impaired liver function, constipation, diarrhea, neurotoxicity, peripheral neuropathy
VEGF Inhibitors		
Bevacizumab (Avastin®)	Given intravenously over 90 minutes for the first dose and 30mg for subsequent doses, every 3 weeks.	Nose bleeds (epistaxis), high blood pressure, decreased wound healing, gastrointestinal perforation, protein in the urine (proteinuria), infusion reaction (fever, chills, hives, facial flushing, fatigue, headache, shortness of breath, lip swelling, low blood pressure), possible lung bleeding (pulmonary hemorrhage) or vascular events (heart attack, stroke), dizziness, depression
Ramucirumab (Cyramza®)	Intravenously over 60 minutes every 2 weeks	High blood pressure; diarrhea; bleeding, blood clots, fistula formation and delayed wound healing

Targeted Therapy	Dose	Side Effects
Sunitinib (Sutent®)	50mg orally daily for 4 weeks every 6 weeks	Decrease in the red cell, white cell, and platelet counts (bone marrow suppression), high blood pressure, yellowish discoloration in the skin, skin rash, dryness or cracking of the skin, nose bleeds (epistaxis), fatigue, diarrhea, altered taste, abdominal pain, inflammation and ulceration in the mouth, throat, and intestines (mucositis), increase risk for heart dysfunction, adrenal insufficiency, low thyroid function (hypothyroidism)

*Adapted from Chu E and Devita VT. Physicians' Cancer Chemotherapy Drug Manual (2019).[28]

Appendix 3: Immune Therapy Drugs Approved for Non-Small Cell Lung Cancer

Drug	Target	Dosing
Pembrolizumab (Keytruda®)	PD-1	Intravenous over 30 minutes every 3 weeks First-line: Combination with chemotherapy or monotherapy every 3 weeks Second-line: monotherapy every 3 weeks
Nivolumab (Opdivo®)	PD-1	Intravenous over 60 minutes every 2-or 4-weeks monotherapy second-line
Atezolizumab (Tecentriq®)	PD-L1	Intravenous over 30 minutes First-Line: Combination with chemotherapy & Bevacizumab every 3 weeks; or monotherapy every 2, 3 or 4 weeks Second-line: single agent
Durvalumab (Imfinzi®)	PD-L1	Intravenous over 30 minutes every 2 weeks, monotherapy following chemotherapy & radiation therapy

*Adapted from Chu E and Devita VT. Physicians' Cancer Chemotherapy Drug Manual (2019).[28]

Notes

References

1. National Comprehensive Cancer Network (2019). *NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer.* [v1.2019-August 12, 2019]. Retrieved from http://www.nccn.org
2. Lindeman, NI, Cagle PT, Aisner DL, Arcila ME et al (2018). Updated molecular testing guideline for selection of lung cancer patients for treatment with targeted tyrosine kinase inhibitors. *Journal of Thoracic Oncology.* 13 (3): 323-358.
3. Brahmer JR, Govindan R, Anders RA, et al. (2018). Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of non-small cell lung cancer (NSCLC). *Journal for ImmunoTherapy of Cancer.* 6 (75). doi.org/10.1186/s40425-018-0382-2
4. Davies MJ. (2019). PD-1/PD-L1 inhibitors for non-small cell lung cancer: incorporating care step pathways for effective side-effect management. *J Adv Pract Oncol.* 10 (Suppl 1): 21-35.
5. Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982; 5:649-655
6. Postmus, PE, Kerr, KM, Oudkerk M, Senan, S., Waller, DA, Vansteenkiste J, Escriu C & Peters S, on behalf of the ESMO Guidelines Committee. (2017). Early and locally advanced non-small cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow up. *Annals of Oncology 28* (Suppl 4): iv1-iv21.
7. Kris MG, Gaspar LE, Chaft JE et al. (2017). Adjuvant systemic therapy and adjuvant radiation therapy for stage I to IIIa completely resected non-small-cell lung cancers: *American Society of Clinical Oncology/Cancer Care Ontario Clinical Practice Guideline Update. Journal of Clinical Oncology.* 35(25): 2960-2974.
8. Schneider BJ, Daly ME, Kennedy EB, et al. (2018). Stereotactic body radiotherapy for early-stage non-small cell lung cancer: American Society of Clinical Oncology endorsement of the American Society for Radiation Oncology evidence-based guideline. *J Clin Oncol* 36: 710.
9. Kann BH, Miccio JA, Stahl JM, Ross R, Verma V, Dosoretz AP, Parck HS, Shafman TD, Gross CP, Yu JB & Decker RH. (2019). Stereotactic body radiotherapy with adjuvant systemic therapy for early-stage non-small cell lung carcinoma: a multi-institutional analysis. *Radiother Oncol.* 132: 188-196.
10. Liang J, Bi N, Wu S, et al. (2017). Etoposide and cisplatin versus paclitaxel and carboplatin with concurrent thoracic radiotherapy in unresectable stage III non-small cell lung cancer: a multicenter randomized phase III trial. *Ann Oncol* 28:777.
11. Antonia SJ, Villegas, A, Daniel D, Vicente D, et al. PACIFIC Investigators. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med.* 379 (24): 2342-2340.
12. Hanna N, Johnson D, Temin S, et al (2017). Systemic therapy for stage IV non-small cell lung cancer: *American Society of Clinical Oncology Practice Guideline update. Journal of Clinical Oncology.* 35 (30): 3484-3515.
13. Planchard D., Popat S., Kerr K., et al. (2018). Metastatic non-small cell lung cancer: *ESMO Clinical Practice Guidelines for diagnosis, treatment and follow up. Ann Oncol.* 29 (suppl 4): iv192-iv237. Updated version published 18 September 2019 by the ESMO Guidelines Committee.
14. Arbour KC & Riely GJ. (2019). Systemic therapy for locally advanced and metastatic non-small cell lung cancer: a review. *JAMA.* 322 (8): 764-774.
15. Girard J. (2019). Optimizing outcomes and treatment sequences in EGFR mutation-positive non-small-cell lung cancer: recent updates. *Future Oncology.* 15 (25): 2983-2997.
16. Soria JC, Ohe Y, Vansteenkiste J, et al. (2018). Osimertinib in untreated EGFR-mutated advanced non-small cell lung cancer. *N Engl J Med.* 378 (2): 113-125.
17. Carlisle JW & Ramalingam SS. (2019). Role of osimertinib in the *treatment of EGFR-mutation positive non-small cell lung cancer. Future Oncol.* 15 (8): 8805-816.
18. Oxnard GR, Hu Y, Mileham KF et al. (2018). Assessment of resistance mechanisms and clinical implications in patients with EGFR T790M-positive lung cancer and acquired resistance to osimertinib. *JAMA Oncol.* 4:1527-1534.
19. Sqambarto A, Casaluce F, Maine P & Gridelli C. (2018). Targeted therapies in non-small cell lung cancer: a focus on ALK/ROS1 tyrosine kinase inhibitors. *Expert Rev Anticancer Ther. 18 (1): 71-80.*
20. Lin JJ & Shaw AT. (2019). Refining precision cancer therapy in ALK-positive NSCLC. *EBioMedicine.* 41: 9-10.
21. Hida T, Nokihara H, Kondo M. et al. (2017). Alectinib versus crizotinib in patients with ALK-positive non-small cell lung cancer (J-ALEX): an open-label, randomized phase 3 trial. *Lancet.* 390 (10089): 29-39.

22. Peters S., Camidge DR, Shaw AT, et al (2017). Alectinib versus crizotinib in untreated ALK-positive non-small cell lung cancer. *N Engl J Med.* 377 (9): 829-38.
23. Solomon BJ, Beese F, Bauer TM, Felip E, Soo RA, Camidge DR DR….Shaw, AT. (2018). Lorlatinib in patients iwht ALK-positive non-small cell lung cancer: results from a global phase 2 study. *Lancet Oncol.* 19 (12): 1654-1667.
24. Shaw AT, Solomon BJ, Besse B, Bauer TM, Martini JF. (2019). ALK resistance mutations and efficacy of lorlatinib in advanced anaplastic lymphoma kinase positive non-small cell lung cancer. *J Clin Oncol.* 37 (16); 1370-1379.
25. Planchard D, Smit EF, Growe HJM, Mazieres JM, Besse B, Helland A. et al. (2017)). Dabrafenib plus trametinib in patients iwht previously untreated BRAF V600E mutant metastatic non-small cell lung cancer: an open-label phase 2 trial. *The Lancet Oncology.* 18 (10): 1307-1316.
26. Shaw AT, Riely GJ, Bang Y-J, Kim, D-W, et al. Crizotinib in ROS1 rearranged advanced non-small cell lung cancer (NSCLC): updated results, including overall survival, from PROFILE 1001. *Annals of Oncology.* 30 (7): 1121-1126.
27. Drilon A, Laetsch TW, Kummar S, DuBois SG……Hyman DM (2018). Efficacy of larotrectinib in TRK Fusion-positive cancers in adults and children. *N Engl J Med.* 378 (8): 731-739.
28. Chu E. & DeVita VT. (2019). Physicians' Cancer Chemotherapy Drug Manual. Sudbury, MA. Jones & Bartlett.
29. McMullen S, Hess LM, Kim ES, et al. (2019). Treatment decisions for advanced non-squamous non-small cell lung cancer: patient and physician perspectives on maintenance therapy. *Patient.* 12 (2): 223-233.
30. Ramalingam SS, Dahlberg SE, Belani CP, et al. (2019). Pemetrexed, bevacizumab, or the combination as maintenance therapy for advanced nonsquamous non-small cell lung cancer EC) G-ACRIN 5508. *J Clin Oncol.* 37:2360-2367.
31. National Comprehensive Cancer Center Network (2019). NCCN *Clinical Practice Guidelines in Oncology: Cancer and Chemotherapy induced Anemia* [V2.2019-March 27, 2019]. Retrieved 9.22.19.
32. National Comprehensive Cancer Network (2019). NCCN Clinical Practice Guidelines in Oncology: Prevention and Treatment of Cancer Related Infections. [V1.2019-October 25, 2018].
33. Wilson BJ, Zitella LJ, Erb CH., et al. (2018). Prevention of infection: a systematic review of evidence-based practice interventions for management in patients with cancer. *CJON.* 22(2): 157-168.
34. National Comprehensive Cancer Network (2019). *NCCN Clinical Practice Guidelines in Oncology Antiemesis.* [v.1.2019-February 28, 2019]
35. Hesketh PJ, Kris MG, Basch E. et al. (2017). Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline update. *J Clin Oncol.* 35 (28): 3240-3261.
36. Razvi Y, Chan S, McFarlane T. et al (2019). ASCO, NCCN, MASCC/ESMO: a comparison of antiemetic guidelines for the treatment of chemotherapy-induced nausea and vomiting in adult patients. *Support Care Cancer.* 27 (1): 87-95.
37. Krishnamurthi SS & Macaron C. (2019). Management of acute chemotherapy-related diarrhea. *UpToDate.* May 23, 2019.
38. Bossi P, Antonuzzo A, Cherny NI. Et al. (2018). Diarrhoea in adult cancer patients: ESMO clinical practice guidelines. *Ann Oncol.* 29 (Suppl 4): iv126-iv142.
39. Larkin PJ, Cherney NI, LaCarpia D. et al ((2018). Diagnosis, assessment and management of constipation in advanced cancer: ESMO clinical practice guidelines. *Ann Oncol.* 29 (Suppl 4): iv111-iv125.
40. Wickham RJ. (2017). Managing constipation in adults with cancer. *J Adv Pract Oncol.* 8 (2): 149-161.
41. National Comprehensive Cancer Network (2019). NCCN Clinical Practice Guidelines in Oncology: Cancer Related Fatigue. [V.1.2019-Marhc 12, 2019].
42. Beech, J, Germetaki T, Judge M. et al. ((2018). Management and grading of EGFR inhibitor-induced cutaneous toxicity. *Future Oncology.* 14 (24): 2531-2541.
43. Lacouture ME, Anadkat MJ, Bensadoun RJ. Et al. (2011). Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. *Supportive Care in Cancer.* 19 (8): 1079-1095.
44. Peterson DE, Boers-Doets CB, Bensadoun RJ & Herrstedt J. (2015). Management of oral and gastrointestinal mucosal injury: ESMO clinical practice guidelines. *Ann Oncol.* 26 (suppl 5): v139-v151.
45. Eilers, J., Harris, D., Henry, K., & Johnson, LA. (2014). Evidence-based interventions for cancer treatment related mucositis: Putting evidence into practice. *CJON.* 18 (6): 80-96.

46. Lalla RV, Bowen J, Barasch A et al. (2014). MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. *Cancer.* 120:1453-1461.
47. Ganesan P, Schmiedge J, Manchaiah V. et al. (2018). Ototoxicity: a challenge in diagnosis and treatment. J Audiol Otol. 22 (2): 59-68.
48. Landier W. (2016). Ototoxicity and cancer therapy. *Cancer.* 122: 1647-58.
49. Noble CW, Gangaputra SS, Thompson IA. Et al. (2019). Ocular adverse events following immune checkpoint inhibitors for metastatic malignancies. *Ocul Immunol Inflamm.* Apr 23:1-6.
50. Huillard O, Bakalian S, Levy C. et al. Ocular adverse events of molecularly targeted agents approved in solid tumours: a systematic review. *Eur J Cancer.* 50 (3): 638-48.
51. Von Ah D., Jansen CE & Allen DH. (2014). Evidence-based intervention for Cancer and treatment related cognitive impairment. *CJON.* 18 (6): 17-25.
52. Loh KP, Janelsins MC, Mohile SG. Et al. (2016). Chemotherapy related cognitive impairment in older patients with cancer. *J Geriatr Oncol.* 7 (4): 270-80.
53. Hou S, Huh B, Kim HK. Et al. (2018). Treatment of chemotherapy-induced peripheral neuropathy: systematic review and recommendations. *Pain Physician.* 21 (6): 571-592.
54. Postow MA, Sidlow R, Hellman MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med.* 2018. 378 (2): 158-168.
55. Puzanov I, Diab A, Abdallah K, et al & Society for Immunotherapy of Cancer Toxicity Management Working Group. Managing toxicities associated with immune checkpoint inhibitors: Consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *J Immunother Cancer.* 2017. 5 (1):1-28.
56. AIMwithImmunotherapy Immuno-Oncology Essentials (IO Essentials). Retrieved from: https://aimwithimmunotherapy.org/ Approved November 2018. Accessed April 5, 2019.
57. Brahmer JR, Lacchetti C, Schneider BJ, et al in collaboration with the National Comprehensive Cancer Network. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guidelines. *J Clin Oncol.* 2018. 36: 1714-1768.
58. Haanen JBAG, Carbonnel F, Robert C, et al & ESMO Guidelines Committee Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up: Corrigendum. Ann Oncol. 2017. 28 (suppl 4): 119-142.
59. Haanen JBAG, Carbonnel F, Robert C. et al & ESMO Guidelines Committee. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann *Oncol. 2018.* 29 (suppl 4): 264-266.
60. Thompson JA, Schneider BJ, Brahmer J, et al. Management of Immunotherapy-related toxicities, version 1.2019. *J Natl Comp Canc Netw.* 17 (3): 255-289.