Non–Small Cell Lung Cancer: Immunotherapy
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Learning Objectives

1. Discuss basic science behind the human immune response
2. Describe how the checkpoint inhibitors alter the body’s immune response to non–small cell lung cancer (NSCLC) cells
3. Describe potential toxicities associated with checkpoint inhibitors, including etiology of these toxicities and management and/or prophylaxis
4. Explain how checkpoint inhibitors differ from other available treatment options for metastatic NSCLC, including kinase inhibitors and cytotoxic chemotherapy
5. Identify FDA-approved checkpoint inhibitors and their indications, including relevant aspects of patient selection
Overview of Lung Cancer

- More than 200,000 new cases anticipated in 2015\textsuperscript{1}
- Leading cause of cancer death in both men and women\textsuperscript{1}
- More than one-quarter of all cancer deaths\textsuperscript{1}
- Higher mortality than breast, prostate, and colorectal cancers combined\textsuperscript{1}
- Five-year survival < 20\%\textsuperscript{2}

Percentage of Cases by Stage

- **Localized** (16%)
  Confined to primary site

- **Regional** (22%)
  Spread to regional lymph nodes

- **Distant** (57%)
  Cancer has metastasized

- **Unknown** (5%)
  Unstaged

Overview of Lung Cancer

Two major types

Small cell lung cancer (SCLC) 15%

Non–small cell lung cancer (NSCLC) 85%

Squamous

Adenocarcinoma

Large cell

Lung Cancer Treatment: Changing Paradigm

- Chemotherapy
  - Impacts all rapidly dividing cells
- Targeted therapy
  - Focuses on individual molecular targets
- Immunotherapy
  - Works on specific receptors to modulate immune system function
Immune System 101

- Cancers avoid detection by the immune system
- Immunotherapy enhances the ability to detect and destroy malignant cells
- Immunotherapy activates the immune system
- Provides stimulatory signals (step on the gas)
- Removes the inhibitory signals (lift off the brake)
PD-1

Programmed cell death protein 1 (PD-1)

- Immunosuppressive molecule that is expressed on many T cells
- Activated when it binds to its ligand, PD-L1
- Activation leads to impaired T-cell function

PD-L1

Programmed cell death ligand 1 (PD-L1)

- Ligand that binds to and activates PD-1
- PD-L1 is expressed on many cancer cells

T-Cell Immunity

- **T lymphocytes** are produced in hematopoietic tissue and differentiate and mature in the thymus.
- Important component of cell-mediated immunity.
- Reliant on antigen-presenting cells to “prime” the antigen for recognition.
- Several mechanisms of action:
  - Direct cytotoxicity through cell lysis by conversion to cytotoxic T lymphocytes (CTLs)
  - Secretion of cytokines that are directly cytotoxic or through recruitment of other immune-system cells
  - Facilitation of B-cell activity
Blockade of PD-1 or CTLA-4 Signaling in Tumor Immunotherapy

Immunotherapy Agents in NSCLC: Pembrolizumab

- Humanized monoclonal IgG4 kappa antibody against PD-1\textsuperscript{1}
- Inhibits the interaction between PD-1 and its ligands, PD-L1 and PD-L2\textsuperscript{2}
- FDA approved for patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy. Patients with \textit{EGFR} or \textit{ALK} genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab.\textsuperscript{2}

Pembrolizumab

- KEYNOTE-001 trial
- Phase IB study
- 495 patients with advanced NSCLC
- PD-L1 expression assessed using immunohistochemistry
- 81% squamous and 17% nonsquamous
- More than 80% had prior therapy
- Median overall survival: 12 months

Pembrolizumab (cont)

- **Dosing**
  - Various dosing schedules have been studied
  - 2 mg/kg, 10 mg/kg, fixed 200-mg dose
  - 2 mg/kg is the package insert dose for melanoma
  - 200-mg fixed dose being utilized in current studies

- **Administration**
  - 30-min infusion every 3 weeks

- **Side effects**
  - Most common side effects in KEYNOTE-001 were fatigue, pruritus, and decreased appetite
  - Immune-related side effects

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Nivolumab

- Human IgG4 monoclonal antibody that binds to the PD-1 receptor
- Inhibits PD-1 receptor interaction with PD-L1 and PD-L2
- FDA approved for metastatic squamous NSCLC with progression on or after platinum-based chemotherapy
- FDA approved for treatment of patients with metastatic NSCLC with progression on or after platinum-based chemotherapy; patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving nivolumab
Nivolumab (cont)

CHECKMATE-017

- A phase III study of nivolumab vs. docetaxel in previously treated advanced or metastatic squamous cell NSCLC
- 272 previously treated patients
- Overall survival 9.2 vs. 6 months favoring nivolumab
- Grade 3 or 4 adverse events only 7% of nivolumab patients vs. 55% in docetaxel arm

Nivolumab (cont)

CHECKMATE-057

- Phase III randomized trial of nivolumab vs. docetaxel in advanced nonsquamous NSCLC
- 582 patients who had received prior platin-based doublet and a tyrosine kinase inhibitor if eligible
- Overall survival 12.2 vs. 9.4 months favoring nivolumab
- Efficacy across subtypes

Nivolumab (cont)

- **Dosing and administration**
  - 3 mg/kg over 60 minutes every 2 weeks\(^1\)

- **Side effects**
  - Most common side effects in CHECKMATE-017 were fatigue, decreased appetite, and asthenia\(^2\)
  - Immune-related side effects

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Role of PD-L1 Staining

- PD-L1+ status
  - May or may not be predictive and/or prognostic
  - No difference in response rates or survival with nivolumab in CHECKMATE-017\(^1\)
  - Better response rates and survival with nivolumab in CHECKMATE-057 and with pembrolizumab in KEYNOTE-001\(^2,3\)

- Multiple assays and tumor heterogeneity an issue
- Utility is still to be determined

Immunotherapy and Pseudopropgression

- Imaging studies may demonstrate\(^1\)
  - Development of new lesions
  - Inflammatory infiltrates
  - Increase in size of baseline lesions
- Immune-related response criteria (irRC)\(^2\)
  - Takes into account total disease burden, including new measurable lesions
  - Requires confirmatory imaging not less than 4 weeks later

Immunotherapy: Future Directions

- Adjuvant setting
- Oligometastatic disease
- Small cell lung cancer
- In combination with radiation
- In combination with other immunotherapy and targeted agents
Immune-Mediated Side Effects

- Pneumonitis
- Colitis
- Nephritis/renal dysfunction
- Endocrine dysfunction
- Hepatitis
- Miscellaneous
Pneumonitis

- Rate: 2%–6%\textsuperscript{1,2}
- Onset: Median 2–5 months\textsuperscript{1,2}
- Often reversible
- Management
  - Hold treatment and administer corticosteroids for moderate grade 2)\textsuperscript{1,2}
  - 1–2 mg/kg/day prednisone equivalent followed by corticosteroid taper\textsuperscript{1}
  - Permanently discontinue for severe (grade 3) or life-threatening (grade 4)\textsuperscript{1,2}

Colitis

- Rate: 1%–2%\(^1,2\)
- Onset: Approximately 2–6 months\(^1,2\)
- Management
  - Hold treatment for moderate (grade 2) or severe (grade 3)\(^1,2\)
  - Permanently discontinue for grade 4\(^1,2\)
  - Administer corticosteroids for grade 2 or greater
  - Grade 3 or 4: 1–2 mg/kg/day prednisone equivalent followed by corticosteroid taper\(^1\)
  - Grade 2 if > 5 days’ duration: 0.5–1 mg/kg/day prednisone equivalent followed by corticosteroid taper; can increase to 1–2 mg/kg/day if worsening or no improvement\(^1\)

Nephritis/Renal Dysfunction

- Incidence: < 1%\textsuperscript{1,2}
- Onset: Variable; weeks to months\textsuperscript{1,2}
- Management
  - Withhold for grade 2 or 3\textsuperscript{1}
  - Permanently discontinue for grade 4\textsuperscript{1,2}
  - For grade 2 or 3 serum creatinine elevation: Corticosteroids at a dose of 0.5–1 mg/kg/day prednisone equivalent followed by corticosteroid taper; if worsening or no improvement occurs, increase dose of corticosteroids to 1–2 mg/kg/day prednisone equivalent\textsuperscript{1}
  - For grade 4: corticosteroids at a dose of 1–2 mg/kg/day prednisone equivalent followed by corticosteroid taper\textsuperscript{1}

Thyroid Dysfunction

- Incidence
  - Hypothyroidism: 4%–8%\textsuperscript{1,2}
  - Hyperthyroidism: 1%–3%\textsuperscript{1,2}

- Onset: 1.5–5 months\textsuperscript{1,2}

- Management
  - Hypothyroidism
    - Administer hormone replacement therapy\textsuperscript{1,2}
  - Hyperthyroidism
    - Initiate medical management\textsuperscript{1}
    - Administer corticosteroids for grade 3 or greater hyperthyroidism\textsuperscript{2}
    - Withhold treatment for grade 3 and permanently discontinue for grade 4 hyperthyroidism with pembrolizumab\textsuperscript{2}
  - There are no recommended dose adjustments of nivolumab for hypothyroidism or hyperthyroidism\textsuperscript{1}

Hepatitis

- Incidence: 0–1%\textsuperscript{1,2}
- Onset: Weeks to months\textsuperscript{1,2}

Management
- Hold treatment and administer corticosteroids for moderate (grade 2)\textsuperscript{1,2}
- Discontinue for grade 3 or 4\textsuperscript{1}
- Corticosteroid dosing: 1–2 mg/kg/day prednisone equivalent\textsuperscript{1}

Case 1

- AB is a 55-year-old male with a history of stage IIIA squamous cell NSCLC
- Initially treated with concurrent chemoradiotherapy with weekly paclitaxel and carboplatin
- Three months after completion of chemoradiotherapy, he developed new pulmonary metastases
Audience Response Question

What is the best treatment option for AB at this point?

A. Docetaxel JL192
B. Nivolumab JL193
C. Erlotinib JL194
D. Gemcitabine JL195
Case 1 (cont)

- AB begins treatment with nivolumab 3 mg/kg every 2 weeks
- After the 4th cycle, he presents to the office with complaints of diarrhea 2 to 3 times a day for the past 3 days
What would you recommend for AB?

A. Continue nivolumab and add an antidiarrheal agent such as loperamide  JL196
B. Continue nivolumab and add prednisone 0.5–1 mg/kg  JL197
C. Hold nivolumab and add prednisone 0.5–1 mg/kg  JL198
D. Hold nivolumab and add prednisone 1–2 mg/kg  JL199
NCI Common Terminology Criteria for Adverse Events v.4.0: Diarrhea

- Grade 1: Increase of < 4 stools per day over baseline
- Grade 2: Increase of 4–6 stools per day over baseline
- Grade 3: Increase of > 7 stools per day over baseline; incontinence; hospitalization indicated
- Grade 4: Life-threatening consequences; urgent intervention indicated
Case 1 (cont)

- AB is treated with loperamide, and nivolumab is continued
- One week later, he presents to the office with diarrhea up to 10 times over the past 24 hours and is found to have renal failure
- He is urgently admitted to the hospital
What recommendations would you have for the general medicine hospital team caring for AB?

A. Administer octreotide at a dose of 1 mg/kg  JL200
B. Administer prednisone 0.5–1 mg/kg   JL201
C. Administer diphenoxylate-atropine every 4 hours  JL202
D. Administer prednisone 1–2 mg/kg  JL203
Case 2

- JM is a 70-year-old female with metastatic squamous NSCLC with bone and hepatic involvement
- She developed progressive disease after 3 cycles of paclitaxel and carboplatin
- Her oncology team begins second-line treatment with nivolumab
Case 2 (cont)

- JM begins treatment with nivolumab and completes 6 cycles, with stable disease noted on CT scan
- Following the 8th cycle, she develops a progressive cough and shortness of breath when walking around her house
- She is evaluated by the APRN, who recommends obtaining a chest CT
- The chest CT scan shows patchy infiltrates consistent with an inflammatory process
What should the advanced practitioner recommend for JM?

A. Continue nivolumab and begin prednisone 1–2 mg/kg
   JL204
B. Hold nivolumab and begin prednisone 1–2 mg/mg
   JL205
C. Permanently discontinue nivolumab and begin prednisone 1–2 mg/kg
   JL206
D. Continue nivolumab and begin levofloxacin for presumed pneumonia
   JL207
NCI Common Terminology Criteria for Adverse Events v.4.0: Pneumonitis

- Grade 1: Asymptomatic; clinical or diagnostic observations only
- Grade 2: Symptomatic; medical; intervention indicated; instrumental activities of daily living (ADLs) limited
- Grade 3: Severe symptoms; self-care ADLs limited; oxygen indicated
- Grade 4: Life-threatening respiratory compromise; urgent intervention indicated

NCI CTCAE v.4.03, 2010.
References

References (cont)


Hi, everyone. Welcome this morning. I’m so glad to see everybody bright
eyed and bushy tailed at 8:00 a.m. this morning. I came in from the east coast,
so I’m a little bit off this morning. I came in yesterday late in the day and I kind of
am still on that east coast time trying to get started. So just a little bit about my
background. I’m a nurse practitioner and I’ve been working in thoracic oncology
for almost the past 20 years, and in that period of time I’ve seen a tremendous
amount of changes in the way we are managing our patients, and its really
exciting nowadays to see just a newer class of drug, our immunotherapy drug. I
also teach at the University of Pennsylvania School of Nursing in our oncology
minor and I have a colleague actually who teaches with me who is here today
who I just ran into, Anne Markham. Raise your hand, Anne. And I just started a
PhD program at the University of Arizona, so I was out in Tucson in August and it
was 107 degrees, so it’s so nice to be here today when the temperature is a little
bit more I guess temperate you would call it. So that’s a little bit on my
background and today we are going to talk about immunotherapy and how it
relates to non–small cell lung cancer.

Financial disclosure, and these are some objectives that I’m not going to
go through. Okay, just a brief overview of lung cancer. There are about 200,000
cases expected for 2015 and it’s the leading cause of cancer death in both men
and women and accounts for more than a quarter of all cancer deaths. I think a
lot of people don’t realize that it has a higher mortality than breast, prostate and
colorectal cancers combined and the five-year survival is about 20%. And that hasn’t changed – it is actually a little less than 20% and that hasn’t really changed significantly since I have been doing lung cancer work, but I’m hopeful that with some of our emerging targeted therapies and our immunotherapy agents we will definitely see an increase in that survival the next time the statistics are reported out.

Most of our cases occur at an advanced stage, unfortunately, so more than 50% occur when patients have presented with metastatic disease and about almost a quarter with regional spread. So that’s why our systemic therapies are so important in this disease. Just a quick overview on the types of lung cancer that I am sure you are all familiar with. Small–cell lung cancer represents a little less than 15% of cases, and then what we are going to talk about today is non–small cell lung cancer which represents about 87 or so percent of cases. We really think about non-small cell lung cancer as squamous and non-squamous. And non-squamous would consist of adenocarcinoma and large cell because some of our treatments vary depending upon type of histology. And I was asked to include this slide just so we could meet the objectives, but when I first started working in lung cancer almost 20 years ago we had chemotherapy only and we only had a couple of agents at our disposal.

And chemotherapy as you know impacts all rapidly dividing cells and we see those commensurate toxicities. And then our targeted therapies have emerged and those are focusing on individual molecular targets and now we have our immunotherapy drugs, which work on specific receptors to modulate
immune system function. And I stole this slide from my collaborating physician, Dr. Evan Alley, so I will give a shout out to Evan, because I really liked how the gas pedal and brake analogy was illustrated here. So basically we can think of the immune system as providing stimulatory signals or which would be stepping on the gas pedal or removing those inhibitory signals by lifting off the brake. Today we are really going to be focusing on a couple of those aspects of the immune system that are really pertinent to some of the FDA approved drugs that we have at our disposal.

You may have all heard of PD-1 and PD-L1 and when we first started conducting some of the clinical trials in our practice. I kept getting confused with the PD-1, PD-L1, aren’t they the same thing? Well, they’re a little bit different and I’ll verbally explain them and then I’ll have a little illustrative slide a couple of slides down the line. But PD-1 is a programmed cell death protein and it’s an immunosuppressive molecule that’s expressed on many T cells. It’s activated when it binds to its ligand, PD-L1 which as you will see in the next slide is expressed on some cancer cells. And when those two areas bind, there’s an impairment in T cell function. PD-L1 is the programmed cell death ligand 1 that binds to and activates PD-1 that we just talked about. It is expressed on many cancer cells including lung cancer cells. So why is T cell immunity so important? Well, just a little refresher in that the T lymphocytes are produced in the hematopoietic system and then they mature in the thymus and they are an important component of cell mediated immunity.
It’s important to note that they do rely on these antigen presenting cells in order to recognize the foreign object and a lot of those would be dendritic cells, you probably have heard of those, and those are the primary antigen presenting cells that we think of. T lymphocytes have several mechanisms of action. They can be directly cytotoxic or they can recruit or secrete cytokines, they can also recruit other immune system cells and they can also facilitate B cell activity. This is that illustration that I had alluded to earlier. So I wanted to point out here there are kind of two phases that we think of. We think of a priming phase where the antigen presenting cell presents to the T cell, and then our effector phase here where we have the T cell connecting with the cancer cell, and it’s in this area here that – everybody’s familiar with ipilimumab – so ipilimumab works on the CTLA4 connection here. So it’s a little bit less specific, which is why we can see a lot more side effects with ipilimumab than with some of our newer agents, our anti-PD-1 agents, like nivolumab and pembrolizumab who work over here on this section. The two drugs that I just alluded to, the nivolumab and pembrolizumab work on PD-1 here to prevent that binding to PD-L1.

Basically, this here is CTLA4 and that’s what ipilimumab works on. It works on where that antigen presenting cell hooks up with the T cell. So it’s a little less specific. And then over here, is where PD-1, where nivolumab and pembrolizumab work to prevent that binding here. I wanted to move forward now that we have an understanding of how some of these agents work, on what those agents are. And we’ll talk a little bit about pembrolizumab and I have actually had
to change these slides in the last couple of weeks several times because there have been some changes in FDA approvals.

So pembrolizumab was actually just FDA approved within the last few weeks for use in non–small cell lung cancer. It’s a monoclonal antibody and it inhibits the interaction between PD-1 and its ligands PD-L1 and there’s another one called PD-L2, which we really didn’t talk about today. I have included the FDA approved indication and I really wanted to point out here that it’s FDA approved in patients who have failed a frontline platinum containing agent and also have over-expressed PD-L1. And there’s a companion test that has been FDA approved along with pembrolizumab. And so what we will talk about in another slide is about the significance of PD-L1 testing. A lot of the data that we have comes from the KEYNOTE-001 trial which was a phase 1B study, and it looked at almost 500 patients with advanced non–small cell lung cancer and it also looked at PD-L1 expression which is why it’s got its FDA approval in conjunction with the PD-L1 assay.

Most of the patients had squamous cell, but about 20% almost had non-squamous and most patients had had prior therapy. The median overall survival was about 12 months, which is pretty significant when you are thinking of second and third line setting. The FDA approved dosing for pembrolizumab is 2 mg per kg, but right now in some of our clinical trials we are looking at a fixed 200 mg dose. It’s nice because it’s a 30 minute infusion and it’s only administered every three weeks. We’ll talk a little bit about the immune-related side effects a little bit later, but some of the other side effects that were noted were fatigue, some
pruritus, and reduction in appetite. Nivolumab was FDA approved in March for squamous cell histology, but in the last couple of weeks it got its approval for non-squamous patients as well. And it’s similar to pembrolizumab in that it’s a monoclonal antibody directed against PD-1, so to prevent that connection between PD-1 and PD-L1. And it’s now FDA approved and I had to change this slide and I don’t think I had a chance to update it for squamous and non-squamous patients. And unlike pembrolizumab it was not FDA approved with a companion PD-L1 test so patients don’t have to express PD-L1 in order to be eligible for nivolumab. And there were two studies that were important in getting nivolumab its FDA approval and the first one is the CheckMate 017, and this was a study looking at nivolumab compared to docetaxel which is really our standard second line chemotherapy drug, and there was a significant improvement in overall survival, but more importantly the toxicity was much less than what we would see with docetaxel. And CheckMate 057 was important because it included non-squamous patients and once again improvement in survival.

I do want to point out that, you know, these survival rates might not sound huge, but patients who respond can have really durable responses and we still haven’t reached the peak of what those responses are. So in the melanoma literature up to 20% of patients who responded to immunotherapy may survive ten years or more. The non–small cell lung cancer literature is much less mature, but hopefully we’ll continue to see some of those durable responses which you are not going to see with chemotherapy. Nivolumab dosing is 3 mg per kg over 60 minutes every two weeks and other than the immune related side effects it is
very well tolerated; fatigue, reduction in appetite, and some asthenia. So I mentioned earlier that PD-L1 status can be important particularly if you want to start your patient on pembrolizumab. It’s a little bit controversial right now because some studies have shown that there can be improved response rates and survival in patients who are PD-L1 positive and some studies haven’t, so we are still trying to struggle in our practice as to what we are doing. The problem is you do need tissue for PD-L1 testing and so sometimes patients don’t have extra tissue. There can also be heterogeneity in the tumor, meaning that you may sample one part of it and the person may be negative and then you may sample another part and they might be positive. So I think the utility is still to be determined. Another important point is that even patients who aren’t PD-L1 positive can still respond. So I have a patient right now in my practice who was being evaluated for a chemotherapy plus pembrolizumab trial and she was PD-L1 negative and was ineligible and went on to receive standard chemotherapy, failed that, wasn’t interested in more chemotherapy, so she started nivolumab and she responded.

So do you really want to eliminate that group of patients that may still respond? We are still trying to figure it out. I don’t know if anybody is familiar with the terminology pseudo progression, but for those of you who aren’t, it’s a very important point to keep in mind when we are looking at patients responding to immunotherapy because pseudo progression is when it looks like somebody is progression radiographically, but in reality they are not. So the imaging studies may show new lesions, enlarging lesions or inflammatory infiltrates and it’s
important to repeat a scan at least four weeks later to confirm that the patient is indeed progressing. Because you may see a reduction or resolution in those lesions and I actually just have a patient now a few weeks ago, who had her reimaging study and it looked like she was progressing, but she was clinically stable so we kept going and then about four to six weeks later repeated and all of those areas had significantly improved.

So we know that usually patients aren’t going to respond for at least two months so it’s important to be careful as to when you are scanning patients and a lot of times we don’t scan until at least two to three months later unless they appear to be clinically progressing. There are some new criteria that are being utilized in some clinical trials to kind of account for the pseudo progression, and that’s the immune related response criteria, the IRRC. Some of our future directions – we are looking at immunotherapy in the adjuvant setting and in melanoma just in the last couple of weeks. Ipilimumab was FDA approved for adjuvant therapy, so perhaps down the line we will see the same thing in non–small cell lung cancer. We are looking at it in oligometastatic disease and we have a study at our center right now; small–cell lung cancer, we are also combining it with chemotherapy and radiation and in combination with other immunotherapy and targeted agents, particularly ipilimumab. Because if you think back to that picture that I showed you where ipilimumab works on the CTLA4 area, so kind of having a double blockade may improve hopefully response rates and survival.
So let’s talk about some of the immune mediated side effects that I mentioned earlier, and these would be our pneumonitis, colitis, nephritis, endocrine dysfunction primarily hypo or hyperthyroidism, and hepatitis. Okay, so the rates of these immune mediated side effects are actually very low so most of them are single digits around the region of 1 to 5%, but it’s still something to be aware of and for those of you who are already aware, I think it’s also important to make sure that non-oncology providers are aware so when patients present to the emergency room, are the emergency room providers going to know what to look for and how to manage these symptoms. And the maker – Bristol-Myers has a great thing for nivolumab – like a little wallet card that patients can keep with them so if they end up in the emergency room or at another provider’s office, the side effects and how to manage them are included. So for pneumonitis and particularly lung cancer, sometimes the symptoms can mimic some of the symptoms that patients with lung cancer have. So the median onset is about two to five months, so if you look at any of these immune mediated side effects, the timing can really be variable so sometimes in the first couple of months, but there have been some side effects that have been out even 12 months. So they really can occur at any time.

Many of them are reversible including pneumonitis, so if we can intervene early than they can be reversible. So management a lot of times depends on the grades and for grade 2 you would want to hold therapy and start corticosteroids and obviously if it’s grade 3 or grade 4 whereas grade 3 is requiring oxygen and grade 2 would be symptoms, but still able to function and grade 1 is
asymptomatic. Colitis we saw much more frequently with our CTLA4 drugs like ipilimumab and the rates appear to be pretty low with nivolumab and pembrolizumab, only about 1 to 2%, and once again the onset can be variable and some of the recommendations really depend on the significance. So grade 1 would be really an increase of about four stools per day and grade 2 and 3 would be like IV fluids and 4 would be hospitalization. So usually for grade 1 we can kind of keep going and symptomatically manage them, but once you start getting into grade 2 and further then we want to hold treatment and start steroids.

Nephritis or renal dysfunction can occur so it’s important to monitor labs and when we monitor labs it’s really kind of still up in the air as to whether we do it with each round or every other or you know just periodic management. So you can read some of these recommendations here. A lot of them include corticosteroids and either 0.5 to 1 mg per kg per day or 1 to 2 mg per kg per day depending upon the severity. Thyroid dysfunction, and a lot of our patients are already hypothyroid, occurs more commonly with hypothyroidism than hyperthyroidism. I actually have not I don’t think had a patient with hyperthyroidism, but I have had a few patients with mild progression of their hypothyroidism and a lot of times we can just manage medically with adjusting their dose of Synthroid or whatever they’re taking. I haven’t seen any severe cases, but in severe cases obviously you would hold.

Hepatitis: I have a patient right now who had elevated transaminases up to almost three times the upper limit of normal; three times upper limit of normal would be about a grade 2, so you would want to hold and administer
corticosteroids and a week later retested her LFTs and they had come back down to almost normal again. And so a lot of times you could resume therapy. So we are going to move into our cases. The first case is AB who is a 55-year-old male with a history of stage 3A squamous cell non–small cell lung cancer. Initially treated with concurrent chemotherapy and radiotherapy with weekly Taxol and carboplatin. And then after three months he developed new pulmonary metastasis. So the first audience response question would be what is the best treatment option for AB at this point? A) Dose of Taxol which is JL192; B) Nivolumab, JL193; C) Erlotinib, JL194; or D) Gemcitabine, JL195. Wow, 100%. YAY! Oh, no. Okay. So most people picked nivolumab. Okay. And that typically would be what we would do. You could consider second line chemotherapy, but I think we know what some of those limitations are based on the Brahmer study that compared nivolumab to docetaxel. In the second line setting we know that this is a better choice and there is less toxicity. So we start AB with nivolumab and after the fourth cycle he presents with complaint of diarrhea two to three times a day for the past three days.

Next question. What would you recommend for AB at this point? A) Continue nivolumab and add an antidiarrheal agent such as loperamide, JL196; B) Continue nivolumab and add prednisone 0.5 to 1 mg per kg, JL197; C) Hold nivolumab and add prednisone 0.5 to 1 mg per kg, JL198; or D) Hold nivolumab and add prednisone 1 to 2 mg per kg, JL199. I feel like we should have some Jeopardy music up here. Okay, so it looks like we have a smattering of answers. Continue nivolumab – Well we’re still tallying them a little bit. It looks like about
half of you picked continue nivolumab and add an antidiarrheal agent and then about a quarter to a fifth picked continue nivolumab or hold nivolumab and add a steroid. So we’ll talk about that. So a grade 1 would be an increase of less than four stools per day over baseline, and so typically for grade 1 we could continue and support the patient with an antidiarrheal such as loperamide. It’s really when we start into grade 2 where we would start holding the drug and initiating corticosteroids. You do have to be careful though because it can progress very quickly from grade 1 to grade 2. And I have a patient with some mental health issues who you know we reiterated multiple times, but he got confused, came in the next week for his next dose of nivolumab and was having diarrhea about every hour, at least ten times a day, and ended up in renal failure and it was a complete disaster. So it can go south pretty quickly.

So in this case AB was treated with loperamide and nivolumab was continued. One week later he presents to the office with diarrhea up to ten times over the past 24 hours and is found to have renal failure. He’s urgently admitted to the hospital. So in this particular situation what would you recommend to the general medicine team caring for AB in the hospital? Would it be, A) Administer octreotide at a dose of 1 mg per kg; B) Administer prednisone at 0.5 to 1 mg per kg; C) Administer Lomotil every four hours; or D) Administer prednisone at 1 to 2 mg per kg. And it looks like most people picked the correct answer, which would be to administer prednisone 1 to 2 mg per kg. This is a really significant toxicity and if somebody requires hospitalization we usually consider that a grade 4 and
would want to administer prednisone at 1 to 2 mg per kg. And then you can start tapering down once the diarrhea starts improving.

So let’s move on to our second case and we are getting to the end here, and then we might have a few minutes left for questions. So our second case is JM who is a 70-year-old female with metastatic squamous non–small cell lung cancer. She has bone and hepatic involvement and she developed progressive disease after three cycles of paclitaxel and carboplatin. And it’s recommended at that point that she begin second line treatment with nivolumab. She completes six cycles and has stable disease noted on CT. Following the eighth cycle, however, she develops a progressive cough and shortness of breath when walking around her house. She is evaluated by the APRN who recommends obtaining a new chest CT, worried about disease progression, and the chest CT shows patchy infiltrates consistent with an inflammatory process. I think this might be our last question. So what would the advanced practitioner recommend at this point for JM? A) Continue nivolumab and begin prednisone 1 to 2 mg per kg; B) Hold nivolumab and begin prednisone 1 to 2 mg per kg; C) Permanently discontinue nivolumab and begin prednisone 1 to 2 mg per kg; or D) Continue nivolumab and begin levofloxacin for presumed pneumonia.

Okay. So it looks like most people picked hold nivolumab and begin prednisone 1 to 2 mg per kg. So this would typically be considered a grade 2 which means the patient is symptomatic and intervention is indicated. It is impacting their ADLs. So for grade 2 you typically would hold and start steroids and in this case you may be able to go back to the nivolumab once the
symptoms have resolved and the patient is able to be off prednisone. So it’s very individualized. And I think that’s my last slide. These are my references. And I think we have some time for some questions. Yes?

**ATTENDEE:** Can you tell me how often when you have used nivolumab that you see patients having fever like within six hours?

**MS. WALKER:** Oh, I’m not sure that I’ve ever seen anybody – The question is how often have I seen somebody getting nivolumab have fevers within the first six hours and I have not had any patients report either with nivolumab or pembrolizumab that they’ve had a fever. I’ve had some patients say they felt fatigued for a couple of days afterwards. I don’t know, has anybody else in the audience experienced that? No?

**ATTENDEE:** Quick question regarding the pseudo progression. So symptomatically they seem clinically fine, but the picture doesn’t match with how they feel or do – Are you concerned because they seem like they’re progressing?

**MS. WALKER:** Right. Yeah, in most cases they are asymptomatic, but it gets tricky when they develop symptoms because sometimes they’re – I mean that still could be pseudo progression, and do you wait it out while they are symptomatic and wait another four to six weeks and repeat a scan and see if they’re getting even worse? I think it really depends on the clinical scenario. We had a patient once who had progression in her endobronchial disease and we just did not feel that we could wait and ended up starting her on radiation because things were progressing. But in a lot of cases they are asymptomatic and we are able to wait another four to six weeks and recheck a scan. Yes?
ATTENDEE: Do you ever do concurrent radiation with Opdivo?

MS. WALKER: Do we ever do concurrent radiation with Opdivo. Not - Well – Let’s – We have more for paliat – Like if somebody is getting you know palliative radiation to the brain or bone mets we have a clinical trial looking at the combination as sort of a rad BACs phenomenon, but outside of a clinical trial we wouldn’t really do like concurrent radiation, thoracic radiation, with immunotherapy for curative intent. So it’s more until that clinical trial data is available.

ATTENDEE: So when you have the patients that have changes in their thyroid function, I mean, I personally don’t like to get involved with that because it’s not my area of expertise.

MS. WALKER: Right.

ATTENDEE: Do you commonly refer those patients out to go back to their endocrinologist or do you take that on yourself?

MS. WALKER: I refer as much as I can because I have not done primary care in a long time. Every once in a while we have a couple of patients who really don’t see their primary care provider and in those cases we – You know we’ll do it for them, but in most cases we send them back. Just like if they get hyperglycemic from something we’ve done I usually try to refer them back. I just can’t keep track of all of the new anti-diabetic medications that are out there, but that’s probably more of an individual decision. Yes?
ATTENDEE: Say somebody has COPD and they have an exacerbation and they are on a steroid taper or something related to that, do you have to wait until they are completely off of steroids before you have them resume?

MS. WALKER: We don’t. So the question is if somebody has a COPD exacerbation and they are on steroids do you have to wait until that taper is finished before resuming and we haven’t. There is some controversy as to whether or not those corticosteroids could be counteracting the way these drugs work, but we have not wanted to withhold therapy altogether so we have kept going. We have a lot of patients that end up on steroids for one reason or another, it’s a lung cancer population and so we have kept going and there – I believe there is some preliminary data that perhaps the concomitant steroids aren’t as bad as we kind of initially thought. So that’s what we do.

ATTENDEE: What’s a typical imaging schedule you use for these patients?

MS. WALKER: So what we have been doing because we know that the median time to response isn’t until about a little over two months, we are waiting until at least eight to 12 weeks before scanning and more like 12 weeks as long as the patients are not clinically showing signs of progression, and that way we are not getting into a situation where we could be seeing a pseudo progression early on in the treatment course. There’s no right or wrong answer I don’t think. In the clinical trials that we have conducted, a lot of times they get their first scan at six to eight weeks and then if there’s evidence of pseudo progression repeating at four weeks thereafter, but in the clinical arena we are really waiting.
Plus, a lot of times these patients don’t really have that many other treatment options beyond immunotherapy because it’s already second or third line for them and so you know what are we going to do at that point anyway. Yes?

ATTENDEE: I have another strange question. We have one patient we started on that had several enlarged lymph nodes and where these lymph nodes were he got red blotchy circles around them. It wasn’t a rash, it was just redness. Have you seen that?

MS. WALKER: So there’s another interesting question. A patient had lymph nodes that were enlarged and they got red blotchy circles around them and have I seen that. I have not. I have had a couple of patients rarely get a mild rash, but that’s really rare. I think I’ve only had maybe two patients on immunotherapy several different kinds develop a rash. That can happen, and it’s reported in the literature, but in my practice it’s been very rare. Any other questions? Great. Thank you.