Understanding the Current Landscape of Immune Checkpoint Inhibitor Therapy in Advanced NSCLC: A Resource for Patients

OVERVIEW OF ADVANCED NSCLC

- Approximately 80% of lung cancers are non-small-cell lung cancer (NSCLC)—57% with metastatic disease (stage IV) at diagnosis[1,2]
  - Metastasis is common in lung, adrenal glands, liver, brain, bones; symptoms are site-specific[3]
- Histologic and biomarker assessments are critical for guiding therapeutic selection and assist in predicting treatment response[4]
  - For nonsquamous histology, tumor testing for EGFR mutations, ALK and ROS1 rearrangements, BRAF V600E mutation, and PD-L1 expression level is required
  - For squamous histology, tumor testing for PD-L1 expression level is required
- Systemic therapy is standard of care for metastatic NSCLC, including chemotherapy, targeted therapy, immune checkpoint inhibitors (anti–programmed death-1 [PD-1]/programmed death-ligand 1 [PD-L1] monoclonal antibodies), and combination therapy with chemotherapy plus an immune checkpoint inhibitor[5]

WHAT ARE IMMUNE CHECKPOINT INHIBITORS AND HOW DO THEY WORK?

- Immunotherapy works by boosting your body’s immune system to attack and kill tumor cells—which is in contrast with cancer treatments such as chemotherapy that directly kill tumor cells
- Immune checkpoint inhibitors are a type of immunotherapy that target cell surface molecules known as immune checkpoint proteins (PD-1/PD-L1 or cytotoxic T-lymphocyte–associated protein 4 [CTLA-4]), with the goal of promoting tumor detection by the immune system[6,7]
- Mechanism of action (Figure)[6,7]
  - The CTLA-4 and PD-1/PD-L1 immune checkpoint pathway normally functions to suppress T-cell immune function to prevent autoimmunity and minimize damage to healthy tissue during an immune response to an infection
  - Unfortunately, certain cancers can express these cell surface molecules (eg, PD-L1) and co-opt this system to inactivate immune T-cells, avoiding detection and allowing tumor cells to survive and grow
  - Checkpoint inhibitor therapy interferes with T-cell inactivation and enhances the vigilance of the immune system, making it more likely to detect and eliminate cancer
  - In other words[8]:
    ○ PD-L1 on the tumor cell interacts with PD-1 on an immune T-cell to “put the brakes” on immune system surveillance and allow tumor evasion
    ○ Checkpoint inhibitors work to “release the brake” on your immune system, restoring immune surveillance and immune-mediated tumor cell killing by T-cells

Figure. Checkpoint inhibitors “release the brake” on the immune system.
As of April 2019, there are 3 immune checkpoint inhibitors approved for advanced NSCLC: nivolumab, pembrolizumab, and atezolizumab (Table 1)

- First line: pembrolizumab monotherapy approved in some patients with advanced NSCLC; both pembrolizumab and atezolizumab approved in combination with chemotherapy for specific populations as defined in Table 1
- Second line: all 3 agents approved as monotherapy in patients who have not received prior immunotherapy, pembrolizumab in patients with ≥1% tumor PD-L1 expression and nivolumab and atezolizumab for all patients regardless of tumor PD-L1 expression

Table 1. FDA-Approved Immune Checkpoint Inhibitors for Metastatic NSCLC (April 2019)[9-16,18,19,23,24]

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosing Guidelines</th>
<th>Approved Indications in Metastatic NSCLC</th>
<th>Efficacy</th>
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| Nivolumab              | IV every 2 or 4 weeks over 30 minutes | • Single-agent therapy, regardless of PD-L1 expression, in patients with disease progression:  
  - On or after platinum-based CT, or  
  - On an FDA-approved therapy targeting an EGFR mutation or ALK rearrangement | Compared with CT:  
  • Squamous[12,25]:  
    - RR: 20% vs 9%  
    - 1-year PFS: 21% vs 6%  
    - 1-year OS: 42% vs 24%  
  • Nonsquamous[12,25]:  
    - RR: 19% vs 12%  
    - 1-year PFS: 19% vs 8%  
    - 1-year OS: 51% vs 39%  

Pembrolizumab          | IV every 3 weeks over 30 minutes | • First-line single-agent therapy in patients with PD-L1 tumor expression ≥ 50% and no EGFR or ALK aberrations  
  - FDA indication recently expanded to include patients with PD-L1 ≥ 1%  
  - However, the data supporting this indication are controversial and suggest that the much greater benefit of pembrolizumab in patients with high PD-L1 drives the benefit in the broader population, and that those with low PD-L1 are far less well served by pembrolizumab monotherapy.  
  - For patients with low PD-L1, there is broad and strong consensus among thoracic oncology specialists that pembrolizumab monotherapy is an inferior choice compared with pembrolizumab/CT in combination  
  - First-line therapy, regardless of PD-L1 expression, in combination with:  
    - Pemetrexed and platinum-based CT for patients with nonsquamous NSCLC and no EGFR or ALK aberrations  
    - Carboplatin plus paclitaxel or nab-paclitaxel for patients with squamous NSCLC  
  - Single-agent therapy in patients with PD-L1 tumor expression ≥ 1% and progression:  
    - On or after platinum-based CT, or  
    - On an FDA-approved therapy targeting an EGFR mutation or ALK rearrangement | Compared with CT in nonsquamous[16]:  
  • RR: 48% vs 19%  
  • 1-year PFS: 34% vs 17%  
  • 1-year OS: 69% vs 49%  
  
  Compared with CT in squamous[16]:  
  • RR: 58% vs 38%  
  • 1-year OS: 66% vs 48%  

Atezolizumab           | IV every 3 weeks over 1 hour  | • First-line therapy for nonsquamous NSCLC, regardless of PD-L1 expression and in the absence of EGFR or ALK aberrations, in combination with:  
  - Bevacizumab, paclitaxel, and carboplatin  
  - Carboplatin and nab-paclitaxel  
  - Single-agent therapy, regardless of PD-L1 expression, in patients with disease progression:  
    - On or after platinum-based CT, or  
    - On an FDA-approved therapy targeting an EGFR mutation or ALK rearrangement | Compared with bevacizumab + CT[23,24]:  
  • RR: 56% vs 41%  
  • 1-year PFS: 38% vs 20%  
  • 1-year OS: 67% vs 61%  
  
  Compared with CT:  
  • RR: 49.2% vs 31.9%  
  • 1-year PFS: 28.9% vs 14.2%  
  • 1-year OS: 39.3% vs 29.9%  

CT, chemotherapy; PFS, progression-free survival; RR, response rate; OS, overall survival.
• Other immune checkpoint inhibitors, immune checkpoint inhibitor combinations, and biomarkers of response are currently being investigated in late-phase clinical trials for first-line treatment of NSCLC
  - Nivolumab plus ipilimumab (CTLA-4–blocking antibody)[28-30]
    ○ Tumor mutational burden (TMB), an emerging biomarker of response to immune checkpoint inhibition,[31] was associated with improved response and PFS with nivolumab plus ipilimumab in patients with newly diagnosed NSCLC (TMB cutoff: ≥ 10 mutations/Mb of DNA)[29,30]
  - Durvalumab (PD-L1–blocking antibody) plus tremelimumab (CTLA-4–blocking antibody)[32]
  - Avelumab (PD-L1–blocking antibody)[33]

WHAT TO EXPECT WHILE RECEIVING AN IMMUNE CHECKPOINT INHIBITOR

Patient Monitoring During Treatment

• With each new treatment cycle:
  - Clinic visit with oncology care team
  - Labs: comprehensive metabolic panel, complete blood count, thyroid-stimulating hormone, other tests based on patient symptoms
  - Disease-directed imaging of chest with or without abdomen/pelvis

PATIENT CHECKLIST: WHEN TO CALL YOUR DOCTOR

Call your healthcare provider if you are experiencing any of the following symptoms[9-11]:

**Lung inflammation (pneumonitis)**
- [ ] New or worsening cough
- [ ] Chest pain
- [ ] Shortness of breath

**Intestinal inflammation (colitis)**
- [ ] Diarrhea or excessive number of bowel movements
- [ ] Blood or mucus in your stools or dark, tarry, sticky stools
- [ ] Abdominal pain or tenderness

**Liver problems (hepatitis)**
- [ ] Yellowing of skin or whites of your eyes
- [ ] Dark urine (tea colored)
- [ ] Nausea or vomiting
- [ ] Pain on the right side of your abdomen
- [ ] Bleeding or bruising more easily than normal

**Skin reactions**
- [ ] Skin rash, with or without itching
- [ ] Sores in your mouth
- [ ] Blistered or peeling skin
- [ ] Itching

**Nerve problems**
- [ ] Unusual weakness of legs, arms, or face
- [ ] Numbness or tingling in hands or feet

**Eye inflammation**
- [ ] Blurry vision, double vision, or other vision problem
- [ ] Eye pain or redness

**Kidney inflammation or failure**
- [ ] Decrease in volume of urine
- [ ] Blood in urine
- [ ] Swollen ankles
- [ ] Loss of appetite

**Pituitary gland inflammation (hypophysitis)**
- [ ] Persistent or unusual headache
- [ ] Extreme weakness
- [ ] Dizziness
- [ ] Fainting
- [ ] Vision changes
- [ ] Nausea
- [ ] Vomiting
- [ ] Severe fatigue

**Thyroid problems**
- [ ] Hyperthyroidism (fatigue, hand tremors, mood swings, rapid heartbeat)
- [ ] Hypothyroidism (changes in menstrual cycle, constipation, depression, dry hair/hair loss, fatigue)

**Other problems**
- [ ] Severe or persistent muscle or joint pains
- [ ] Severe muscle weakness

Immune-Related Side Effects and Their Management[34]

• It is important to talk to your healthcare team about potential immune-related toxicities associated with immune checkpoint inhibitor therapy, as a key factor in their successful management is early recognition and treatment
  - Ask your healthcare team for detailed information on potential side effects of immune checkpoint inhibition
    ○ Most are manageable when recognized and treated promptly
    ○ Potentially life-threatening toxicities may occur but are rare
  - It is important to consider any side effect as possibly related to your immunotherapy and notify your doctor immediately
    ○ Ask your doctor for detailed instructions for when and how to contact your healthcare team
    ○ See checklist below
    ○ Immunotherapy wallet card is also available from Oncology Nursing Society

• Management is generally based on severity of symptoms
  - **Mild (grade 1):** supportive care administered and drug withheld (optional)
  - **Moderate (grade 2):** drug withheld, restarting can be considered if toxicity resolves to grade ≤ 1; low-dose corticosteroids typically administered
  - **Severe (grade 3/4):** drug discontinued; high-dose corticosteroids administered with taper over ≥ 1 month once toxicity resolves to grade ≤ 1
OVERVIEW OF SHARED DECISION MAKING AND A PATIENT’S ROLE IN TREATMENT DECISIONS

What Is Shared Decision Making (SDM)?
SDM is a process in which patients and their caregiver(s) are involved as active partners with their healthcare provider in clarifying acceptable medical options and choosing a preferred course of clinical care. SDM is especially appropriate in settings where there are several competing “right” treatment options; for example, immunotherapy alone vs chemotherapy plus immunotherapy are both options for patients with advanced NSCLC and high PD-L1 expression.

6 Steps in Implementing SDM in Oncology

1. Patient and caregiver(s) invited by oncologist to participate in choosing optimal therapy.
2. Available treatment options presented to patient and caregiver(s) by oncologist.
3. Information on benefits and risks based on current medical evidence presented by oncologist with ample time for questions to ensure patient and caregiver understanding.
4. With the help of their oncologist, patient and caregiver(s) evaluate options based on their personal preferences, values, issues, and concerns.
5. Oncologist facilitates deliberation and decision making by patient and caregiver(s), allowing ample time for consideration and a follow-up visit to discuss any further questions or concerns.
6. Oncologist implements SDM, including ensuring patient and caregiver(s) understand their treatment decision and exploring possible issues with its implementation.

Questions to Ask Your Oncologist and Healthcare Team

The following information is designed to help guide you and your caregiver(s) on what to ask your oncology team during your visit. It is also a good idea for your or your caregiver(s) to take notes during the conversation.

- Communicate your goals, fears, and concerns; don't be afraid to tell your doctor what you want out of the treatment.
  - How will therapy affect my daily activities?
  - What are the short-term and long-term side effects of treatment?
  - What do I want the physician to know about me (religion, hobbies, diet, special needs)?

- The following are some examples of questions you can ask your oncologist:
  - Do I need any tests before I begin treatment and can I see the results?
  - What are my treatment options and why?
  - What are the benefits and risks of each of these treatments?
  - What is the goal of my treatment?
  - What is my outlook based on my cancer and my current health status?
  - Should I enroll in a clinical trial?
  - Should I get a second opinion?
  - Can I come back with further questions?
  - How much does therapy cost? Is my insurance going to cover treatment?
  - Are there financial and/or supportive resources available for me and my caregiver(s)?
  - Will any of my current medications or supplements affect my therapy?
  - Will this treatment affect my fertility?
  - When should I start treatment?
  - What are the possible side effects of treatment?
  - How can I prevent or treat side effects?
  - Who should I contact if I experience a side effect?
  - How will we know if the treatment is working or if my cancer is worsening?
  - What should we do if my cancer does not respond?
FINDING TRUSTWORTHY SOURCES OF INFORMATION ON THE INTERNET

Evaluating the Reliability of Internet Resources[37,38]

- Pay close attention to the source of any information you find and carefully consider the qualifications and motivation of the person or company providing the information.
  - Well-trained experts or very knowledgeable patients and caregivers connected to a nonprofit cancer organization should often be given more weight than less-expert people who are selling a product.
  - A nonprofit with a goal of educating patients should be recognized as having a different incentive than a company selling a product being promoted on a Web site.
  - Reliable and credible health-related Web sites will almost always have information of who is responsible for the information on the Web page, such as in an “About Us” link on the home page.
  - The letters at the end of the URL address can also provide you an idea of who is running the Web site (Table 2).

- If something seems unreliable, trust your instincts and try to find a second or even third Web site or source to check your findings.
  - There are no rules as to what can be written on Web sites; thus, it is important to know how to distinguish between scientific fact and a Web site writer’s opinion, especially regarding alternative therapies.
  - Note that evidence from clinical trials with human patients represent a far more reliable finding than a hypothesized scientific mechanism from the lab or animal models that suggest a treatment may be helpful.
  - In general, the more evidence you find, the more reliable the finding. Seek evidence beyond mere “case reports” or “testimonials” of a single person or a few people who happened to do well on products being sold on the Internet.
  - Discuss any unresolved questions with your oncology care team—remember that your healthcare providers are often your best source of information and can point you in the right direction and help to distinguish between options that offer realistic outcomes vs false hope being promoted to prey on patients desperate for alternative.

- Always be mindful of the truism that if something seems too good to be true, it almost certainly is.
  - There are no easy answers to difficult questions such as how to best treat cancer. Any alternative treatment or supplement should be discussed with your doctor before being used.
  - Be wary of people peddling conspiracy theories. If there were a miracle treatment for cancer, it would not be kept as a secret. Why would a company NOT offer such a therapy to people who would be motivated to pay for it?

<p>| Table 2. Using URLs to Identify Web Site Owners |</p>
<table>
<thead>
<tr>
<th>Internet Top Level Domain Name</th>
<th>Source of Web Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>.edu</td>
<td>Educational system (eg, college or university)</td>
</tr>
<tr>
<td>.org</td>
<td>Nonprofit organization</td>
</tr>
<tr>
<td>.gov</td>
<td>National or state governments</td>
</tr>
<tr>
<td>.com</td>
<td>Commercial (for profit) or private sector</td>
</tr>
</tbody>
</table>

Patient and Caregiver Resources

- Financial assistance for immunotherapy
  - Web sites: covermymeds.com, needymeds.org
  - Go to pharmaceutical manufacturers directly
- Reliable information and support resources

Selected Resources

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<thead>
<tr>
<th>Web Site</th>
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<tbody>
<tr>
<td>American Lung Association</td>
</tr>
<tr>
<td>Lung Cancer Alliance (eg, Phone Buddy Program)</td>
</tr>
<tr>
<td>Lungevity Foundation</td>
</tr>
<tr>
<td>National Institutes of Health</td>
</tr>
<tr>
<td>National Cancer Institute</td>
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<tr>
<td>Bonnie J. Addario Lung Cancer Foundation</td>
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<tr>
<td>American Cancer Society</td>
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<tr>
<td>Cancer Support Community</td>
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<tr>
<td>Patient Advocate Foundation</td>
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<tr>
<td>The LIVESTRONG Foundation</td>
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<tr>
<td>CancerCare</td>
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<tr>
<td>Global Resource for Advancing Cancer Education (GRACE)</td>
</tr>
<tr>
<td>CarePages</td>
</tr>
<tr>
<td>Inspire</td>
</tr>
<tr>
<td>Doctor-Approved Patient Information from ASCO</td>
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REFERENCES