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BULLETIN:

SITC GUIDELINES FOR LUNG CANCER IMMUNOTHERAPY

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The Society for Immunotherapy of Cancer (SITC) hosted a webcast on Cancer Immunotherapy Guidelines for Non-Small Cell Lung Cancer (NSCLC) on September 13, 2018, with at least 84 people participating. It was a thorough review and timely given the number of checkpoint inhibitors that have been approved by the FDA since 2015:

- Bristol-Myers Squibb's Opdivo (nivolumab) for second-line squamous NSCLC *and* non-squamous NSCLC.
- Merck's Keytruda (pembrolizumab) for second-line NSCLC in patients with PD-L1 expression ≥50%.
- Merck's Keytruda (pembrolizumab) for first-line NSCLC in patients with PD-L1 expression ≥1%.
- Roche/Genentech's Tecentriq (atezolizumab) for second-line NSCLC.
- Merck's Keytruda (pembrolizumab) + pemetrexed and carboplatin for first-line NSCLC.
- AstraZeneca's Imfinzi (durvalumab) for Stage III NSCLC after chemoradiation.

This means the chioces in NSCLC are:

- First line: Keytruda if patients have PD-L1 expression >1%, or Keytruda + chemotherapy.
- Second line: Opdivo, Tecentriq, or Keytruda (in patients with PD-L1 expression ≥50%).
- Stage III after chemoradiation: Imfinzi.

Patrick Forde, MBBCh, a medical oncologist from Johns Hopkins University, reviewed the first-line pembrolizumab trials: KEYNOTE-042, KEYNOTE-024, KEYNOTE-189, and KEYNOTE-407. Among the comments he made:

- "Generally, we don't start with pembrolizumab alone."
- On the efficacy of anti-PD-1/L1 in EGFR-mutated or ALK+ patients, he said ALK+ patients were excluded [from anti-PD-1/L1 treatment] because they didn't seem to have the same benefit, adding, "That doesn't mean patients with EGFR mutations or other driver mutations don't benefit at all. When nivolumab was added as last line, there was some response, but there was another study where they didn't respond."
- "It is a bit controversial on how long to continue an anti-PD-1…Generally, it is until progression or unacceptable toxicity, but at two years sometimes we discuss a possible holiday from anti-PD-1 therapy."
- "The second-line [guidelines] may not be as relevant because most patients get a PD-1 first line, but three are approved for use second line. Pembrolizumab depends on PD-L1 status but not the others."

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Scott Gettinger, MD, a medical oncologist from Yale Cancer Center, reviewed the data on Stage III NSCLC. Among his comments were:

- "In the Phase III PACIFIC trial, durvalumab after chemoradiotherapy showed a significant improvement in overall survival (from 5 to 16 months)…There was a concern about pneumonitis, but…it was very well tolerated. This has become established as the standard in the U.S. We heard more recently that the overall survival co-primary endpoints have been met. **The data will be at the World Congress on Lung Cancer [September 23-26, 2018, in Toronto**]."
- "The IMPOWER130 trial [of atezolizumab + chemotherapy (carboplatin + nab-paclitaxel)] in (metastatic) non-squamous NSCLC was reported as positive, but we await publication of the data."
- "We have data that tumor mutational burden (TMB) is a marker. However, not all patients with PD-L1+ respond and some PD-L1-negative patients respond, so there is ongoing research for markers. Patients with higher TMB are more likely to benefit from PD-1 blockade."
- The guidelines subcommittee:
  - ✓ Unanimously agreed that PD-L1 tests should be performed for all newly diagnosed metastatic patients, including those tested for EGFR/ALK/ROS1 mutations, and 100% of the subcommittee members had experience with this.
  - ✓ 100% of the panel reported waiting for PD-L1 testing before initiating first-line treatment.
  - ✓ 72% of the panel did not retest PD-L1-negative patients after disease progression on first-line therapy.
  - ✓ Recognize that TMB testing may be necessary for appropriate treatment decisions *in the near future.*

Summary of First-Line Immunotherapies for Advanced NSCLC

Drug	Trial	PFS	OS	ORR
Pembrolizumab (PD-L1 >50%)	KEYNOTE-024	10.3 months	30 months	44.8%
Pembrolizumab (PD-L1 >1%)	KEYNOTE-042	5.4 months	16.7 months	27.3%
Atezolizumab + chemotherapy	IMPower150 (non-squamous)	8.3 months	19.2 months	63.5%
Pembrolizumab + chemotherapy	KEYNOTE-189 (non-squamous)	8.8 months	21.3 months	47.6%
Pembrolizumab + chemotherapy	KEYNOTE-407 (squamous)	6.4 months	15.9 months	58.4%
Nivolumab + ipilimumab	CHECKMATE-227	7.2 months	23 months	45.3%

Julie Brahmer, MD, a medical oncologist and director of the Thoracic Oncology Program at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, discussed the toxicity of immunotherapy. Among her comments:

- "We are always concerned about pneumonitis in lung patients, but it is not common, occurring in 1%-5% of patients, but generally it is easy to manage."
- Adding pembrolizumab to chemotherapy doesn't seem to be additive in terms of toxicity.
- "When you combine two checkpoint inhibitors that work differently, like nivolumab and ipilimumab [Bristol-Myers Squibb's Yervoy], the immune-related side effects or treatment-emergent adverse events are a bit more common…but compared to chemotherapy, there is not much difference …But if you look back comparing combination to single-agent nivolumab, it does have more Grade 3/4 immune-related side effects. Rash is a bit more common, and diarrhea."
- The guidelines for management of immune-related adverse events in NSCLC were developed in collaboration with radiologists, pulmonologists, dermatologists, rheumatologists, and endocrinologists.
  - ✓ 93% of panel members routinely use thyroid function studies, 93% use liver function tests, 96% use blood urea nitrogen (BUN) and creatinine tests, 71% do whole body imaging.

- ✓ All patients with radiographic and/or clinical evidence of pneumonitis should see a pulmonary specialist. With Grade 2 pneumonitis, immunotherapy should be withheld and steroids given. With Grade 3/4 pneumonitis, immunotherapy should be permanently discontinued. "If patients improve on steroids and you taper the steroids, you can consider restarting the immunotherapy."

- "I personally have a few rheumatologists and pulmonologists on speed dial in case I have a question on immune-related adverse events, particularly those refractory to steroids. These folks are a great resource."

Single-Agent Toxicities in 2/3-Line NSCLC				
Toxicity grade	**Atezolizumab**	**Nivolumab second line**	**Nivolumab third line**	**Pembrolizumab**
Grade 3-5	15%	8%	11%	13%-16%
Discontinuations due to related adverse events	5%	6%	6%	4%-5%
Pneumonitis	1%	5%	3%	4%-5%

Asked how often the guidelines are updated, Dr. Brahmer said that normally yearly would be fine, but so much data has been coming out that it is currently every six months, adding, "We'll see if that trend continues."

Asked if TMB is measured on tumor cells or in other cells, Dr. Gettinger said, "Right now, it is on tumor cells…Roche initially suggested there might be some benefit with measuring expression on immune cells, regardless of expression on tumor cells, but currently that is not used to make decisions."

Asked about the differences in PD-L1 assays, Dr. Forde said, "Several of the assays appeared to perform similarly. The Roche test seemed to be somewhat of an outlier…Many of us rely on the companion diagnostic for pembrolizumab." Dr. Gettinger said, "We use one that was not evaluated in trials…It comes down to cost."

Asked when immunotherapy is used alone, not in combination with chemotherapy, Dr. Gettinger said, "Right now, you can go either way. In my practice, I generally use pembrolizumab alone. It might be reasonable to do triple therapy, but generally I use pembrolizumab alone." Dr. Forde said that is his approach as well.

Asked if there has been an effort to harmonize these guidelines with the NCCN (National Comprehensive Cancer Network) guidelines, Dr. Brahmer said, "I think attempts to harmonize would be helpful. I don't think there are many differences, though the NCCN guidelines are a bit more nimble and use some earlier phase data to help support the use of some of the other combinations much earlier on …Trying to harmonize, especially for combinations that are FDA approved would be helpful." Roy Herbst, MD, PhD, chief of medical oncology at Yale Cancer Center and moderator of this webcast, added, "That is my experience, too. NCCN does change more quickly. I think there is room to look at both."

Asked if there are patients to whom they wouldn't give immunotherapy:

- Dr. Brahmer said it is important to assess the general health of the patients as well as any history of autoimmune disease that requires active treatment or a history of organ transplant since some patients may be at risk of transplant rejection, adding, "But from a fitness standpoint, the majority of patients allowed in the trials had no symptoms and were fully active or had minimal symptoms. Patients with a lot of symptoms who spent a majority of their time in bed because of symptoms were not included in the trials…So, people with a lot of symptoms or a lot of other health issues that are causing quite a bit of side effects is where the question about the safety of this treatment lies…And that is when you need to talk about the pros and cons of receiving immunotherapy or immuno-therapy + chemotherapy. The question would be: Are you well enough to tolerate the treatment?"

- Dr. Gettinger added, "Over the last 10 years we have become much more lenient on who we will treat. At one point I would have been reluctant to treat active psoriasis or rheumatoid arthritis, but it really comes down to risk:benefit…We had a multiple sclerosis patient recently…These drugs can be life-saving…It is a discussion I am having more and more frequently as I see patients with baseline autoimmune problems."

Asked what the next big study is that will change practice:

- Dr. Gettinger: "We need something to overcome primary resistance because the majority of our patients have primary resistance to monotherapy. We need to find a way to overcome that – maybe getting immune cells into the tumor. PD-L1 can be induced in a tumor, hindering further regression of the tumor…So, I think it may need more than chemotherapy to overcome resistance…One thing I am interested in is TILs. **There will be an abstract at WCLC** on taking them out of the body, expanding them, and re-introducing them. I have some hope with that."
- Dr. Brahmer: "The question is are we at a plateau now and there will be a long wait, or will we see rapid improvement? That comes with precision medicine…Potentially, other biomarkers are down the road…or testing a patient's blood to decide when to add a treatment. But moving this to an earlier stage will occur over the next 5 years either in the neoadjuvant or adjuvant setting."
- Dr. Forde: "I think primary resistance is a major problem…and even acquired resistance…We are seeing responses in trials of 10%-15%…More than 60% of patients relapse after surgery for resectable NSCLC."
- Dr. Herbst added: "Let's not forget small cell lung cancer."

Asked what they've seen when treatment is discontinued after two years of immunotherapy, Dr. Brahmer said, "There is a group of patients who have long-term control of their disease after stopping treatment after 2 years…Even out to 5 years there are patients who have disease control even three years off therapy. We have yet to figure out who those patients are. Still, for the majority of patients, at some point their tumors will start growing again." Dr. Gettinger added, "I hope there will be a percentage, but I don't know what that percentage is, whose disease will not recur or become clinically meaningful, and we are trying to figure out who those patients are …Some stop after two months with no return of disease. We are trying to figure out how to predict long-term response …My experience is most patients who take a break and the disease comes back, ~50% will re-respond, but it will be relatively short-lived."