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# Case 2: In a Patient With PD-L1 1–49%, Should I Use Single Agent IO or Combination IO?

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**Dr. Aggarwal:**
Hello and welcome. I'm Dr. Charu Aggarwal. I'm the Leslye Heisler Associate Professor for Lung Cancer Excellence at the Abramson Cancer Center at the University of Pennsylvania. Today I will talk to you about practical advice and management for patients with metastatic non-small cell lung cancer with PD-L1 expression in the 1 to 49% range without actionable driver mutations and how we should treat these. Should we treat them with single-agent immunotherapy or combination immunotherapy?

So let's get started with a case. I saw a 70-year-old female, had a fall and went to the ER. Brain MRI was performed that revealed multiple brain metastases, and a CAT scan was done at the same time that showed the right upper lobe lung mass, mediastinal lymphadenopathy, as well as liver metastases. A PET/CT scan confirmed metastatic disease. Biopsy revealed or no carcinoma with a PD-L1 level of 2%. Molecular sequencing was performed TP53 was mutant. There were no other actionable alterations. She underwent stereotactic radiation, or Gamma Knife treatment, for her brain metastases.

So the question really becomes, for this patient in the absence of any immediately actionable alteration, so the PD-L1 level of 2% with an adenocarcinoma, what should this patient receive? Should we manage this patient with chemotherapy alone? Immunotherapy alone? Chemo plus immunotherapy? Or should we really think about chemo plus immunotherapy doublet, so-called quadruplet regimen?

So firstly, I think we should just set the stage, and just state a fact that in 2023, chemotherapy alone is not standard of care unless and until there is a huge contraindication of immunotherapy such as a solid organ transplant, such as a cardiac transplant, or other significant immunotherapy contraindication. A number of trials have shown superiority of immunotherapy as well as chemoimmunotherapy in this situation. And this should be considered substandard care, too, that is to deliver chemotherapy alone.

But that opens up a very difficult proposition because now we have so many options. And I think that's why we wanted to discuss this a little bit more in detail today. When you look at category 1 recommendations for patients with advanced or metastatic lung cancer with the PD-L1 of 1 to 49%, you can see there are more options than we can count on one hand. These are for adenocarcinoma on the left, and squamous cell carcinoma on the right. I will not read all of these out, but fair to say that many of these are chemoimmunotherapy or triplet combinations with different PD-1 and PD-L1 inhibitors, and a few of them are also looking at quadruplet combinations. And I'll go through a few of those.

So when we look across the trials, this is a nice chart summarizing the PD-L1 parameters, the population, the response rate, as well as the duration of response, and overall outcomes. Starting with CheckMate 227, that looked at dual immunotherapy with nivolumab and ipilimumab. I will remind everyone that this is currently indicated and approved for PD-L1 greater than 1%. You can see a median overall survival of 17.1 months. When we look at quadruplet ipi/nivo, as well as chemotherapy, you can again see we are seeing overall survival for about 15.8 months. And then as we go across the board towards the right, for the next 4 or 5 columns, you'll see chemoimmunotherapy with using a platinum doublet and either pembrolizumab in the KEYNOTE-021, 189, and 407 trials, IMpower150

looking at atezolizumab plus chemotherapy, and then EMPOWER-Lung 3 looking at cemiplimab plus chemotherapy. We see here, overall survival is again in the ballpark of about 2 to 3 years. And then finally POSEIDON, which is again quadruplet chemoimmunotherapy using durvalumab and tremelimumab, you can see a median overall survival of 14 months. All hazard ratios looking very good at about point 0.5 to 0.75, again establishing chemoimmunotherapy or quadruplet chemoimmunotherapy as the standard against chemotherapy alone.

KEYNOTE-189 was really one of the landmark trials to establish chemoimmunotherapy. We now have 5-year outcomes from this trial. It just goes to show how long we've been using these drugs. On the left, you can see overall survival median is about 22 months. On the right, if we look at the 1 to 49% category, median overall survival is about 22 months here as well. KEYNOTE-407, looking at same sort of concept in a squamous non-small cell lung cancer. Here, you can see overall squamous cell cancer Prognosis is slightly worse than adenocarcinoma, but we see median overall survival of 20.6 months. And on the right, you can see PFS of about 11.8 months. Again, I think this is very, very meaningful for our patients.

What about CheckMate 9LA? I talked to you about a quadruplet regimen a little bit ago, a few slides ago, when we highlighted the overall survival. But when you look at this, you know, again significant improvement. This is a fishtail curve compared to chemotherapy hazard ratio of about 0.61. And then when we specifically look at this PD-L1 1 to 49% population, overall response rate with this combination is up to 39% with a median duration of response of about 10 months.

Same is the case for cemiplimab plus chemotherapy. These are results from EMPOWER-Lung 3 trial. I think isn't looking also very good, similar to what we expect from KEYNOTE-189 with a hazard ratio of 0.65. And then durvalumab plus/minus tremelimumab in combination with chemotherapy, FDA approved as of last year. Again, I think the combination looking pretty good in terms of the quadruplet on the right. and there may be some differential activity in molecularly-driven subsets of patients.

So dual immunotherapy in this setting is an option. You know, we talked about chemoimmunotherapy. Of course, KEYNOTE 189, EMPOWER-Lung 3, and IMpower150 have all looked at triplet. Well, what about dual immunotherapy? Just immunotherapy alone without the chemotherapy? CheckMate 227 was this very large trial that evaluated several different populations of patients. But when we focus on patients with PD-L1 greater than 1%, those that received nivo plus ipi did have a superior overall survival compared to nivo, or chemo, you can see 17.1 months on the left, and then you can see overall survival on the right as well. This is pretty far out in terms of median follow-up and about 5-year survival for about 24% for these patients with the use of nivolumab and ipilimumab.

But is there a difference in terms of. for this population that has 1 to 49%, should they be treated with chemo IO? Or IO alone? You will note that I didn't really show you much data with immunotherapy alone, because most of the data with immunotherapy alone is in the population that is greater than or equal to 50%. However, one trial called KEYNOTE-042, did include patients with greater than 1% into the immunotherapy-alone arm. And the FDA wanted to do a large analysis to see amongst these group of patients that PD-L1 1 to 49%, are there differences in overall survival and progression-free survival when treated with chemoimmunotherapy versus immunotherapy alone? They looked at several of these trials that are listed on the right. These are all randomized clinical trials that the FDA had data for. And as you can see, they had a total of 2,100 patients across these trials. The patients were well balanced between chemotherapy, IO alone, and chemo IO alone, reading from right to left. And then basically what they found was that chemoimmunotherapy for this population, PD-L1 1 to 49%, was better. Median overall survival pooled from all these trials was 21.4 months.

And I think this is an important takeaway point, we can expect our patients to live about 2 years when they come in with a PD-L1 1 to 49% in the absence of a driver mutation if we treat them with chemoimmunotherapy, versus immunotherapy alone is only 14 months. The forest plot is shown here. And you can see overall chemoimmunotherapy looked better across most categories.

So in summary, I showed you a lot of data. This is a space that has multiple approvals, multiple category 1 recommendations. I will say that one thing sticks out that there is no clear role for single-agent immunotherapy in this setting. This has been shown based on the FDA analysis that I just shared with you, as well as our personal experience where we don't find a lot of response rate or prolongation of overall survival with the use of this therapy. Immunotherapy and chemotherapy as a triplet regimen is a well-established strategy. There are several different clinical trials looking at different combination partners well established. Quadruplet regiments can also be used. I showed you data on two such regimens, CheckMate 9LA, as well as POSEIDON, which can both be used.

So in summary, for our 70-year-old female with metastatic disease to the brain, TP53 mutant, no other driver mutations, with a PD-L1 level of 2%, underwent brain radiation, what should she receive? And to put this data in context, I'd like to transition to our peer discussion and welcome Dr. Joshua Reuss. Welcome.

**Dr. Reuss:**
Thank you, Dr. Aggarwal. My name is Joshua Reuss. I'm a Thoracic Medical Oncologist and Assistant Professor of Medicine at Georgetown Lombardi Cancer Center and Georgetown University School of Medicine. And I'm happy to be here for this important

discussion.

**Dr. Aggarwal:**
That's great. So with seven category 1 recommended regimens, Josh, how do you individualize your choice between chemoimmunotherapy combinations? We have just so many.

**Dr. Reuss:**
Yeah, no. And it's great to have so many options. But I think it is important, you know, we do know that the frontline treatment, that's where you want to choose the regimen that's most likely to be efficacious for your patients. And so it's important to have a decision-making tree, you know, that allows you to do that and to have that discussion with your patients.

In my practice, I think one important aspect of this is histology. I do think that for the PD-L1 1 to 49%, by and large, the IO plus chemo regimens in adenocarcinoma are very effective and that's usually my go-to in that setting. Squamous, a little bit more variability for me. I think what I'm getting to the PD-L1 low status, that's when I'll oftentimes grab a dual IO-based regimen, or dual IO plus chemo.

**Dr. Aggarwal:**
Yeah, that mirrors my approach as well. And I will say that I tend to use chemotherapy, perhaps more of the triplet combinations in a situation such as this where we have a TP53 mutation, we don't have any other significant mutations in terms of IO resistance. And, you know, most of these patients are pretty symptomatic. You know, some of these patients present with brain metastases, I think that's a different question. But you know, given this situation, I would have probably use chemoimmunotherapy alone.

Do you tend to use dual immunotherapies such as the CheckMate 227 approach for your patients? Talk to us about that.

**Dr. Reuss:**
Yea, so I agree, for your patient I would have probably grabbed the chemo IO regimen and worked in brain SRS in there as well. I don't know if there's really enough data to say that we can hold on CNS radiotherapy in the setting of brain metastases in patients who do not have a driver mutation. You know, when will I typically grab for a dual IO regimen with or without chemo? I think there are other factors that could play a role there, perhaps KEAP1/STK11 mutations, alterations that at least in some retrospective data suggest that single-agent IO or IO chemotherapy may not work as well as we'd like it to. You know, I think those are probably the main scenarios where I will consider adding in a dual IO approach or again, if I have a patient with squamous histology and PD-L1 low or negative, I think there is some good subgroup data to support the addition of a CTLA4 inhibitor in those patients.

**Dr. Aggarwal:**
Yeah, absolutely. And I think with so many options, it's really important for us to just sit down with our patients and discuss. You know, I think it's so important to incorporate molecular markers into our treatment algorithms and sequencing of choices, because, you know, if this patient had a KRAS G12C mutation, there may be implications in terms of what the patient receives first line, followed by second-line therapy. Not that they are clear to us right now, but I think clinical trials will help us determine also the appropriate sequencing for these patients with different molecular subsets in the future.

So with that, I will summarize that for patients with PD-L1 1 to 49%, it's important to remember that chemotherapy alone is no longer an option. Immunotherapy alone actually may not lead to the best outcomes for our patients, even though there may be approvals for this. We tend to prioritize use of chemoimmunotherapy either in a triplet or in quadruplet fashion for these patients. Dual immunotherapy using both PD-L1 and CTLA4 blockade remains an option. However, we should carefully discuss with our patients, as well as determine which situations may be best depending on how fast we want to achieve a response rate and what the patient's symptom burden may be.

With that, I'd like to thank you, Josh, for joining us and really leading a stimulating conversation on management of these patients with PD-L1 1 to 49%. Thank you.

**Dr. Reuss:**
Thank you, Charu.

**Announcer:**
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