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Empowering Clinicians to Optimize Patient Outcomes: *Addressing Global Challenges in the Use of Immunotherapy in NSCLC*

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Chapter 1: Addressing Challenges in Biomarker-Guided Selection of Immune Checkpoint inhibitor (ICI)-Based Regimens

Dr. Paz-Ares:
We are still facing challenges in optimizing the use of immune checkpoints in the first-line management of patients with metastatic non-small cell lung cancer. Overcoming these challenges is going to be the focus of our discussion today. In this first chapter, we are going to take a close look into how to incorporate predictive biomarkers in the clinical decision-making and how this can affect patient outcomes in the first-line setting in the case of metastatic non-small cell lung cancer.

This is CME on ReachMD, and I am Dr. Luis Paz-Ares.

Dr. Marrone:
And I'm Dr. Kristen Marrone.

Dr. Paz-Ares:
A recent international survey had been undertaken, focusing on US, on the big 5 cancers in Europe, to assess how our colleagues are actually using those biomarkers at a time of deciding in the management for metastatic non-small cell lung cancer patients. So could you actually bring to our audience how those findings, what they indicate about the global practice behavior today in our clinics?

Dr. Marrone:
Thank you, Dr. Paz-Ares. So I think the relevant interim findings from this AGILE survey show us a lot about the state of current molecular and immunologic testing in treatment approaches in the first-line treatment setting for our patients. So, for example, one of the first questions was regarding biomarkers that were routinely tested for in metastatic lung cancer, and overall, they found that PD-L1, EGFR, and ALK were all well representative in terms of being evaluated for, but ROS1, BRAF, KRAS, and HER2 were not. As I think we know now, this will miss a significant proportion of patients that are eligible for both molecularly selected therapies that would be available as both standard of care and potentially for clinical trial options. I think it also represents a potential missed opportunity to be thinking about subsequent lines of care as well.

Another question in this study evaluated when checkpoint inhibition is appropriate to prescribe in newly diagnosed patients. So about 70% of responders utilized using a PD-L1 of at least 1% and no autoimmune disease as sort of cutoffs for using this therapy. But 15% of respondents indicated that using a checkpoint inhibitor would be appropriate for patients with an actual biomarker.

I think this is an important point for us to clarify, as it depends on how we define an actual biomarker. I think we know now that for

patients with classical mutations in EGFR or ALK rearrangements, for example, they were either not included in our standard IO-based first-line trials, which is KEYNOTE-189, or were actually shown to have increased toxicity and worsened outcomes when receiving IO alone or prior to molecularly appropriate TKI [tyrosine kinase inhibitor]. However, I think for those patients whose tumors harbor mutations such as KRAS or HER2, we know that some of them could do quite well with IO-directed therapy, so it's important to also consider things such as co-mutations in genes such as STK11, KEAP1, as TMB [tumor mutational burden] status as well as potential other clinical indicators of response to IO therapy.

Another question asked about if PD-L1 IHC was ordered for all patients diagnosed with metastatic lung cancer. About two-thirds of respondents do that, and about 20% only test for PD-L1 if they are eligible for immunotherapy and tumors are found to not have an actual mutation. I personally favor testing for PD-L1 for all of my patients diagnosed with metastatic lung cancer because it helps me plan for therapeutic selection while I await NGS [next-generation sequencing] results, and it also gives me insight into potential clinical trials they may be eligible for. I think it also helps with talking with patients about potential effectiveness of therapies and the risks/benefits of some of the different options we have in the first-line metastatic setting.

Dr. Paz-Ares:
Okay, I think that you really went through the relevant topics here. So one of, maybe, my feedbacks here is that it is clear that for the oncogene addicted targets, it is clear that most of us are asking for at least the 3 or 4 more frequent ones. But still, there are some others that the frequency where the colleagues are actually testing is not very high. Let's say, RET fusions or MET mutations and so on.

Dr. Marrone:
Yeah, I think that's a great question. In general, as long as symptomatically the patient can wait, I do try to wait for those results to come back, and if I have to start therapy before I have those results back, I do usually start with chemotherapy alone, and then I layer in the immunotherapy with subsequent lines, as long as they do not come back with an actual mutation on their tumor testing.

Great. So, Dr. Paz-Ares, let's take a look now at findings from some recent clinical trials. Do you think they, in fact, demonstrate that patient outcomes are improved when we incorporate these biomarkers into our decision-making? And I think we can start with our trials that use checkpoint inhibition as monotherapy.

Dr. Paz-Ares:
Yeah, I fully – I think for those patients that are high in – high expression of PD-L1, such as the case of patients included in trials like the KEYNOTE-024 or 042, is the outcome is a lot improved by using pembrolizumab, for example, as compared to chemotherapy. Indeed, we have now data also on longtime survivorship, showing that some – let's say, more than 30% of the patients are actually 5-year survivors as compared to about half of the patients in patients that had received chemotherapy first. So all those data, including particularly the long-term follow-up data, are reinforcing the use of PD-L1 expression as a very important and relevant guide to help us to decide what is the best treatment option for our patients.

Dr. Marrone:
I totally agree with you. I think the exciting updated survival outcomes, especially from KEYNOTE-042, are really encouraging for our patients, and I think the idea that we can use IO therapy alone without chemotherapy really is a great quality of life option for our patients, and using information specific from their tumor to pick these treatments is really important.

Dr. Paz-Ares:
So, Dr. Marrone, which trials can you tell us about where those combinations have shown a benefit as compared to immunotherapy and monotherapy?

Dr. Marrone:
I would be happy to discuss these data. I think it's important, similarly to how you just discussed the last question, that we don't technically know exactly how chemotherapy plus immunotherapy compares directly to checkpoint monotherapy. We haven't seen a study looking at that, but I think, certainly, there's encouraging data about using triplet therapy with chemotherapy IO up front in multiple studies and sort of our clinical experience that suggests, similar to what Dr. Paz-Ares mentioned, that that's really sort of my default treatment option for patients who are fit enough to receive chemotherapy. So the studies that I think about when I talk about this with my patients are primarily KEYNOTE-189 and KEYNOTE-407. So those are our histologically defined, platinum doublet, pembrolizumab combination trials. And we can see from updated survival data, continued clinical benefit for our patients. At the most recent clinical updates, median overall survival were 22 and 17.1 months, respectively. And it should be noted that in KEYNOTE-189, improved overall survival was seen as PD-L1 expression increased.

IMpower150, which is the combination of carboplatin, paclitaxel, bevacizumab, and atezolizumab in non-squamous disease, also has continued to show improved overall survival benefit compared to non-IO therapy with a median overall survival of about 19.5 months.

Again, those exploratory analyses across PD-L1-defined subgroups showed improved benefit as PD-L1 expression increased.

CheckMate 227, which is our combination nivo/ipi study, which was the anti-CTLA4 antibody, most recently – was updated actually last month and showed sustained improvements compared to chemotherapy alone in both PD-L1-positive and PD-L1-negative disease. The hazard ratios updated were 0.76 and 0.64, respectively. Four-year overall survival rates with the combination therapy was 29% in the PD-L1-positive setting, and 24% in the PD-L1-negative setting.

CheckMate 9LA, which is the combination of everything – so platinum doublet with nivo and ipi – showed a median overall survival benefit of 15.6 months. Again, an interesting trend seen in PD-L1-negative disease, in that benefit was similar to PD-L1-positive disease, with hazard ratios of 0.62 and 0.66.

So I think that speaks to kind of what we need to learn going forward about how to use these combination approaches and how we integrate PD-L1 and things like TMB into making these decisions.

Dr. Paz-Ares:
Yeah, I think you're totally right. I think for those patients that are low expressers or negative expressers, I think combination treatment is the way to go.

Dr. Marrone:
All right, so our next question is, Dr. Paz-Ares, why don't we switch direction and look specifically at some current and possibly emerging predictive biomarkers that are being used? What do you think our audience really needs to know?

Dr. Paz-Ares:
Well, I think the more important issue is that, first of all, we have to be sure that our patients do not have a tumor with a genomic aberration that is dictating treatment with a targeted therapy.

The second important thing, as we have mentioned here, is look at, if my patients are wild-type for those genomic aberrations, I would tend to look at the PD-L1 expression. But if possible, I tend to look at some other biomarkers if I have the opportunity to have them, like TMB or some simple genomic aberrations. They help me to make decisions sometimes.

Still, I have to say we cannot forget about some clinical factors. Let's say, if I am having a patient with a tumor that is high expressers, that does not mean for every single patient I'm going to use pembrolizumab or cemiplimab or atezolizumab as monotherapy. There will be some cases where I tend to use chemo-IO. A good example would be patients that really are very symptomatic, so they do need a quick, fast response. I tend to use chemo-IO on those patients. Another good opportunity would be a patient which is high expression but in the range of 50%-60%. The patient also is a woman. On those patients, maybe I would tend to use chemo-IO as immunotherapy on its own. A single agent is not as beneficial for women as compared to men, or at least these are some of the data. Having some genomic aberrations that are not predictive of benefit from immunotherapy, such as, let's say, LKB1 mutation or KEAP1 mutations, may help me to decide against monotherapy in that case as well. Of course, always taking into account the patient's convenience, the patient expectations on the treatment as well, and comorbidities and safety profile.

Dr. Marrone:
Great. I totally agree with everything you're saying, and I use all of the important sort of clinical and tumor molecular information that you described every day in clinic.

I think my sort of big takeaway from our conversations right now is that you're exactly right, that it's important for each institution and oncology team to recognize how best to get the right information for each patient to make the right treatment decision.

I think that there was a lot of interesting data recently discussed at ASCO, thinking about how to optimize single-agent immunotherapy for our patients whose tumors have high-expressing PD-L1 and also for our older patients. I think more data will be forthcoming as well at World Lung this year, and it's important for us to incorporate all of this exciting data into our clinical practice.

Dr. Paz-Ares:
In Chapter 2, we are going to use some patient cases to illustrate what we just learned.

Dr. Marrone:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Kristen Marrone, and here with me today is Dr. Luis Paz-Ares. We're discussing how incorporating predictive biomarkers into clinical decision making can optimize first line patient outcomes in metastatic non-small cell lung cancer.

Chapter 2: Demonstrating Application of Biomarker Use into Clinical Practice in the Management of First-Line Metastatic NSCLC

Dr. Marrone:
Welcome back. In the first chapter, we took a close look at how incorporating predictive biomarkers into clinical decision-making can optimize first-line patient outcomes in non-small cell lung cancer. Here in Chapter 2, we're using patient cases to apply what we learned in Chapter 1. I'm Dr. Kristen Marrone.

Dr. Paz-Ares:
Hello, I'm Luis Paz-Ares.

Dr. Marrone:
Dr. Paz-Ares, why don't we begin with a case discussion for a patient whose PD-L1 status is between 1% and 49%?

Dr. Paz-Ares:
This is a 68-year-old man. Prior smoker with some chronic bronchitis. The patient is in good shape, but is being recently diagnosed of stage IV squamous cell carcinoma of the right upper lobe. The patient had metastatic disease to the pleura and is somehow symptomatic, particularly in terms of chest pain and some increase in dyspnea. At the time of deciding which treatment should I use for my patient, there are a number of possibilities. In that very specific patient, the PD-L1 expression was 20%, and the patient had had a panel of NGS without relevant genomic aberrations. TMB actually being 10 mutations per megabase, very much on the average for those patients.

When we discussed with my patient what would be the treatment opportunities, first we discussed about single-agent checkpoint inhibition with drugs such as pembrolizumab, following the KEYNOTE-042 trials. That was actually, to be honest, not my recommendation. I tend not to use monotherapy for those patients that are having, let's say, expression of PD-L1 on their tumors lower than 50% unless the patient has some contraindication to receive chemotherapy, and I don't think this is the case. So the 2 main opportunities for best choices for this patient would be a combination of chemoimmunotherapy, such as the regimen of the 407 trial with chemotherapy, plus pembrolizumab, or could be an alternative with double immunotherapy – ipi/nivo with or without chemotherapy, 2 cycles. In that very particular patient, we decided to go with chemoimmunotherapy following the 407 trial. I don't think at the current stage we have data suggesting chemo-IO is any better or any worse as compared to chemo-IO/IO, but that patient was somehow more concerned about the potential side effects, particularly immune-related, which of course is increasing when you're using dual immunotherapy as compared to the use of only pembrolizumab in combination with chemotherapy.

I don't know, what do you think? What would be your taking on that very patient, Dr. Marrone?

Dr. Marrone:
I feel similarly that in that setting, with how they are feeling and what that PD-L1 expression is, is that I would go to chemo-IO as my first preference in terms of treatment option.

Dr. Paz-Ares:
Okay, Kristen. So thank you very much, and let's move on to a patient whose PD-L1 expression is more than 50%.

Dr. Marrone:
Yeah, so I actually just saw a 67-year-old woman last week with this presentation. So she had a 50-pack-year smoking history and had recently been diagnosed with COVID. She had a CT scan for that, and she was actually found to have a 5-cm mass in her right lung with mediastinal and axillary lymphadenopathy, several small hepatic metastases. She was asymptomatic. Her breathing was actually improving after her COVID diagnosis. She underwent a biopsy of her liver and was found to have TTF-1+ adenocarcinoma. So brain MRI was negative. Her labs were all completely within normal limits, including her liver function test, and then the testing came back with a PD-L1 of 90%, a TMB was about 11 mutations per megabase, and the NGS actually showed a KRAS G12C mutation and a P53 co-mutation.

So similarly to how you approach speaking with your patients, we sort of talked through the different options of treatment, and I sort of explained that in this scenario, where she is overall asymptomatic with a relatively low burden of disease and really was focused on maintaining her quality of life and continuing to work full-time, we talked about the KEYNOTE-042 regimen of single-agent pembrolizumab with a really great 5-year overall survival rate of about 22%. And in that scenario, we decided to proceed with that treatment option.

I think similarly to your case, I should point out though, in some instances, I consider the KEYNOTE-189 regimen, so adding chemotherapy to this to ensure sort of optimal disease control. I think in this scenario, if this patient had had either a larger or more symptomatic burden of disease, I would have added chemotherapy to improve our time to response. Or if the tumor NGS were to show a co-mutation that would suggest less benefit with single-agent IO, such as we mentioned earlier, STK11 or KEAP1, I would also add chemotherapy here, even in the setting of high PD-L1 expression, to try to obtain improved response to therapy. I think using doublet

immune checkpoint inhibition for patients whose tumor's TMB might suggest a highly immunogenic tumor that are quite fit and could tolerate the increased toxicity of ipilimumab is an option. Another clinical scenario I would consider CheckMate 227 for would be those patients whose tumors progress on durvalumab during therapy for locally advanced non-small lung cancer who are, again, fit and interested in potential long-term disease control, although recognizing that that chance is lower than for those patients who have not received prior IO therapy.

Dr. Paz-Ares:
And how important is for you the gender? Do you tend to make any difference or, you know, maybe some of the trials showed that women tend to benefit less from PD-1 blockade when given as monotherapy. Is that something that you take into account?

Dr. Marrone:
That's a great question. I think that a lot goes into that, as well, in terms of thinking about the molecular profiling of those patients. When I think about my female lung cancer patients, when they have a significant smoking history and their NGS sort of plays out multiple mutations, I feel more comfortable with making a decision about single-agent IO. But otherwise, I think you're right. We have to really take into account that data that has shown single-agent IO might not be as effective for women.

All right, Dr. Paz-Ares, we can't forget those patients whose PD-L1 status is presented in clinical trials as greater than or equal to 1%, all comers who are PD-L1 positive, and those whose PD-L1 status is less than 1%. Rather than examine specific cases, can you talk about how we might approach treating these patients in general?

Dr. Paz-Ares:
Okay. I mean, concerning patients whose tumor cell PD-L1 more than 1%, I mean, as you mentioned, I tend to go with single-agent immunotherapy for those cases with high expression – more than 50% – and tend to do chemo-IO for patients that are with expression in 1%-49% of the cells. Of course, as we mentioned, I will take into account some other considerations. This is just the general rule. At the end, some 30% of the patients whose expression is more than 50% of the cells are actually being treated in my clinic with chemo-IO as compared to IO alone. And we have mentioned some of those cases, maybe women, never-smokers, maybe particularly patients that are very symptomatic or patients with high tumor burden, and so on. On the contrary, typically, patients with expression of PD-L1 in 1%-49% of the cells, I more often use chemo-IO – the 189 or the KEYNOTE-407 type of regimes, unless the patient is having clear contraindications for chemotherapy. On those cases, I may think about using a immunotherapy single agent, particularly if the patient is reluctant to have chemotherapy.

For those patients that are PD-L1 negatives, I tend to use combination treatments. Chemo-IO is a good possibility – 189 or 407 type of regimes. But dual immunotherapy is also an opportunity, particularly for those patients that are having squamous cell carcinoma histology. On those patients, I tend to discuss the pros and cons, the long-term data which are pretty favorable, particularly with dual immunotherapy, but also the side effects.

Dr. Marrone:
So unfortunately, that's all the time we have today, so I want to thank our audience for listening in and thank you, Dr. Luis Paz-Ares, for joining me and for sharing all of your valuable insights. It was great speaking with you today.

Dr. Paz-Ares:
Thank you, Kristen. It's been great to be with you in the discussion today. Thank you, everyone, for being here with us.

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