Plotting the course: optimising treatment strategies in patients with advanced adenocarcinoma

Pieter E Postmus

Thank you for the invitation to participate in this interesting symposium as well.

I'm going to do the remaining part of, let's say, non-squamous, which is quite a big field, for 15 minutes, so it's impossible to discuss everything on that.

Disclosures

These are my disclosures, which are not very relevant in this situation.

Learning Objectives

These are the learning objectives for you.

Question 1

I start with a question, but I'm not sure whether the right answer is there, but you may choose: should every patient be treated with an immunotherapy agent as second-line treatment, if he or she has adenocarcinoma? Three answers: regardless of PD-L1 status; only in patients who present with PD-L1-positive tumours; only in patients with PD-L1-positive tumours but no mutation in *EGFR* or *ALK*.

I think in retrospect, making this question the right answer is not there – number three is getting closest, but nivolumab, you don't need to do testing for PD-L1, although in the recommendation by the EMA it is stated that it might be worthwhile doing it, for the simple reason that in the phase 2 study the curves are crossing, which means that patients who have zero expression of PD-L1 might have a somewhat higher risk of being harmed by the therapy – if you go back to the text of the EMA, it's there. For pembrolizumab, it is very clear, it's only in PD-L1-positive patients, 1% or more.

The view on lung cancer is changing…

The view on lung cancer is changing, and I'm not sure whether the years mentioned here are the right years, because in 1990 we knew already that there was small cell and non-small cell, and not in 2000 that separation came up, but anyhow, what it shows is that lung cancer is becoming not a single disease but it is becoming a disease with multiple faces and multiple approaches by that as well. Part of that has already been discussed in this part with the testing, and there might be much more testing later on for specific targets to be found in the near future.

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Even guidelines have difficulty in keeping up to date…

Saying that, that makes it difficult for guidelines to keep up-to-date, and I'm not sure which guideline you use. I prefer the ESMO one, instead of the NCCN one, because that one might be even more up-to-date, but I'm not sure whether it is completely balanced in opinion.

Case discussion: WS, born 1945

Let me illustrate this with a case discussion: it's a patient born in 1945, healthy smoker, 40 pack-years, a CT/PET was done and found a mass that was dried up, and the lymph node was positive as well, the SUV was 20 and in the adrenal gland there was also an uptake, with an SUV of 16. A biopsy was done from the right upper lobe and proved that there was a metastasis in the adrenal, we did a biopsy of that as well, and we did according to the guidelines as already expressed by Professor Aerts molecular testing for EGFR and ALK. What we also did, we tested for PD-L1 expression, which was 65%

Case discussion: WS, born 1945 (continued)

This is the chest CT, a number of slices from it: big mass, some lymph nodes in the mediastinum, I didn't show the PET, but it illustrates a case you might have in your own practice as well.

Question 2

The question then is, what kind of treatment you would recommend in this situation? You have the choice between a carboplatin-based doublet, or a cisplatin plus pemetrexed, or carboplatin plus one of the forms of paclitaxel with nevacizumab, PD-1 or PD-L1 checkpoint inhibitors, or a combination of PD-1 or PD-L1 checkpoint inhibitors and chemotherapy, so please vote.

ESMO Guidelines: stage IV non-squamous cell carcinoma (3 slides)

Interesting to see what we find in the end: I would agree on the number 4, so that's what we did with this patient as well. If you look at the guidelines – and this has already been highlighted by the previous speaker – you can see here that there are molecular tests and it's only specified for ALK and EGFR, and all the others are grouped together in no *EGFR*/*ALK* mutation; what's really missing is there is no test for PD-L1. I looked at the update of the ESMO Guidelines which were published on 28 June, and still it's not in there, so I think the guidelines need to be updated again, to add this to it.

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ESMO Guidelines: stage IV non-squamous cell carcinoma (no driver mutations)

So, what kind of chemotherapy is there available in this situation? You have a number of options, which are shown here, in this column, it's readable I think from the room as well: platinum-based, with pemetrexed, gemcitabine, docetaxel or paclitaxel, or with or without bevacizumab – as I mentioned in the question – for, as it's stated, younger patients with a good performance status. I'm not sure whether the evidence for the age is that strong, that you would deny a patient of 75 who is fit, not to go in this part – I would do it, but this is what the guideline says. Poor performance status, I can understand, you are a little bit more reluctant to give this type of combination chemotherapy.

Then there is the maintenance treatment for pemetrexed – either switch or continuation, depending on what you started with.

The reality…

In reality, 80% of patients have no treatable oncogenic alteration like *EGFR* or *ALK*, so for these patients a different therapy is needed. They are in need of systemic treatment. The efficacy of chemotherapy we know pretty well, and we have seen impressive activity of immunotherapy in pretreated patients; the impressive part of it is mainly due to the tail of the curve, that patients are living longer; it's not the response rate that is better than the standard chemotherapy, but it's still not very high, with about 20%

PD-L1 expression associated with a favourable outcome with pembrolizumab

Looking for PD-L1, this is one of the examples of how you do it – this is from a paper by Garon in the *New England Journal of Medicine*, related to pembrolizumab, and you see this is the level of expression of PD-L1, the number of tests around – we're not going to do a detailed analysis of that. Just as an example, this is a strongly expressing cancer, and the patient we are discussing had a strongly expressing cancer.

KEYNOTE-024: study design

This patient could have been treated in a trial which was crucial and was presented last year at ESMO, which is KEYNOTE-024. That trial randomised patients with a PD-L1 expression level of 50% or more into pembrolizumab fixed dose every 3 weeks, up to 2 years, or dealer's choice chemotherapy. There was the possibility for crossover for those who were on chemotherapy starting, were progressing, to go on immunotherapy as well.

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KEYNOTE-024: PD-L1 screening

Just to give you an idea how many patients in your practice will be candidates for this type of therapy, this study selected for screening about 2000 cases, and ended up for about 500 to be put on the study, which makes it 25–30% of the whole population – not the majority, but still a considerable part.

KEYNOTE-024: PFS and OS (ITT population)

If you look at the curves presented last year by Martin Reck, then you can see here, PFS, a nice spread with a hazard ratio of 0.50, and for overall survival, a nice spread as well, with a hazard ratio of 0.60, so very enthusiastic audience in the room in Copenhagen, and this led to approval of this drug for first-line therapy.

KEYNOTE-024: response (ITT population)

You can see also the response rate is higher, it's 45%, compared to standard chemotherapy, only 28%.

KEYNOTE-024: PFS in key subgroups (ITT population)

If you break it down in subgroups, then the majority of markers have a role, except the ones that have never smoked, and this might be the group that has an *EGFR*/*ALK* mutation, so that is not sure from this forest plot.

KEYNOTE-024: exposure and AE summary (as-treated population)

Looking at toxicity – and look at this, time of treatment is 7 months median, which is double from the chemotherapy, 3.5 months, and despite that, grade 3 to 5 adverse events is only 27% versus 53, and "leading to discontinuation", only 5 versus 6 in the chemotherapy, so overall this seems to be a reasonably well-tolerated treatment – I'm not saying it's non-toxic, but compared to chemotherapy, it seems to be very well doable for patients, that's my own experience as well.

KEYNOTE-024: updated OS analysis in patients with advanced NSCLC

This is the updated curve, which was kindly supplied by Julie Brahmer at ASCO, we asked her and got permission to show it here. This still has a very nice hazard ratio, 0.63 – this is overall survival, with a much longer period, so at 12 months, 1 year, two-thirds of the

patients are already at that point – that is still confirming what the initial conclusion from Martin Reck was, in Copenhagen.

Case: WS, born 1945 (continued) (2 slides)

So, looking at this patient, had a very nice response after two cycles of pembrolizumab, and that is continuing, and maybe he will progress, and then the question comes, what kind of therapy should we give in that situation? The guidelines do not specify that, but you might make your choice.

Question 3

This is a kind of dealer's choice for you, what would you give in this situation? Two-thirds go for a platinum doublet, less than 10% go for docetaxel, a little bit more than ten go for the combination of nintedanib and docetaxel, and 11% go for pemetrexed, single agent.

Case discussion: BU, born 1955

OK, we go to another case: this is a patient born in 1955, adenocarcinoma with a pleural effusion, which was cytology-positive there, and molecular testing showed no ALK, no EGFR and PD-L1 was zero. The patient was treated with cisplatin and pemetrexed, and responded nicely, was put on maintenance therapy with pemetrexed for another eight cycles, and then the mass in the left lower lobe as shown here is growing.

Question 4

What would be the next step for you – what would you do now? Would you go for another biopsy, to re-evaluate for PD-L1? For RET, for ROS1, for BRAF, for T790M, or would you do something else? One-third would do something else, which I am curious to know what that is, and that might come in the discussion later. Close to a third would go for PD-L1, despite the fact that was initially negative, and then people would go for T790 and BRAF and ROS. I didn't mention ALK, but that could have been added to the list. No one is going for RET. I'm not sure what is the best answer, but I would go for PD-L1 testing again.

ESMO Guidelines: stage IV non-squamous cell carcinoma

The ESMO Guidelines state in the situation of second-line therapy, which is a situation that this patient is really in, that after maintenance treatment with pemetrexed you have a choice for pemetrexed, docetaxel, nivolumab, and the guidelines say only for those who have no mutation in *EGFR* or translocation in *ALK*, pembrolizumab for more than 1% expression of PD-L1, the licence of pembrolizumab does not exclude *EGFR*-mutated or

ALK-translocated patients, so that group might be treated with pembrolizumab. I'm not sure what the licence of nivolumab says about EGFR and ALK, and maybe Joachim knows that, we'll come back to that in the discussion.

Then there is the possibility of combining docetaxel with either ramucirumab or nintedanib, and this is still stating that erlotinib is a feasible option, and I would never do that any more, so I think that should be taken off the guidelines.

Issues around second-line treatment (2 slides)

There are a number of issues around second-line treatment. If there are no targetable mutations found, what should you do? Is there access in your area and your country for immunotherapy? If so, is the marker analysis needed? For instance, in the UK, in England – Scotland is different, it's part of the UK as well, but Scotland you have nivolumab anyhow, you don't have to test – in England you only have pembrolizumab, so you have to test for PD-L1 expression, otherwise you're not allowed to give pembrolizumab for second-line.

In that situation, I quite often do a repeat biopsy for the patient, even if the initial biopsy didn't show any PD-L1 expression, for the simple reason, as already mentioned, a tumour has a lot of heterogeneity – if you take it from a different area it could very well be that the expression is there, and certainly you only need it for a very low level, only 1%, so we have quite some successes in that situation. The reproducibility of no expression of PD-L1 I guess is pretty low if you do a big series – I've not seen that published in the literature, but that is my impression from my clinical practice.

If you have no access to immunotherapy, or if there is no PD-L1 expression in a country where only pembrolizumab is allowed, then my first choice would be docetaxel and nintedanib, because that is what is allowed in the UK, ramucirumab is not on the market there; but another option could be docetaxel and ramucirumab, in the countries where that is available.

Anti-angiogenic agents as second-line therapy in advanced adenocarcinoma: nintedanib

I'll just show you the curves where the conclusions concerning nintedanib and ramucirumab come from: this is the LUME-Lung 1 study, where it was shown that nintedanib added to docetaxel is better than docetaxel alone, and if you do a further analysis in that paper – and that has been done – you can see that especially those who are progressing

early after chemotherapy are the ones that benefit most from the combination of nintedanib and docetaxel. We might mention this as well in the panel discussion later on.

Anti-angiogenic agents as second-line therapy in advanced NSCLC: ramucirumab

For ramucirumab, comparable hazard ratios for PFS, 0.76, and for overall survival, 0.86, without any further details on which group might benefit most.

Summary

In summary, to come to the end of my presentation, targeted therapy is an option for approximately 10–15% of the patients, as discussed by the previous speaker; immunotherapy, if available in your country, is first choice for second-line therapy, depending on PD-L1 expression – if it is for pembrolizumab, if it is for nivolumab, you don't need it.

For non-pretreated patients, pembrolizumab is first choice if the level of expression is 50% or higher for PD-L1. Then for those who have no expression of PD-L1, standard chemotherapy is still first choice, and my preference then is nintedanib and docetaxel.

I think that was my last slide – thank you for your attention.

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