The road less travelled:
what options are available for patients with advanced squamous cell carcinoma?

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Good afternoon. I would like to thank the organisers, Excerpta Medica, for inviting me to talk here. The title was given to me – "The road less travelled"; I'm not sure if this is a really good travel when you have 1.8 million lung cancer cases every year globally, and 30% are patients with squamous cell carcinoma, so I think it's a road that is quite often travelled, but that's how it is.

Disclosures

Let's now come to my conflicts of interest: I have received speaker's fees from Eli Lilly.

Learning Objective

What should you learn? You should learn how to manage treatment with patients with advanced squamous non-small cell lung cancer, so we will focus on first-line. I will give an elderly case, and then I will finish with a case on second-line treatment.

Case discussion A

A typical case for me: a former smoker, 65-year-old, and he developed a cough for 3 months, reasonably good performance status, and was diagnosed with stage IV squamous cell carcinoma.

Case A (continued) (2 slides)

You see the CT scan, a lesion in the right lung, you see a lesion in the thorax [...] you also see a lesion in the vertebra, so we have stage IV non-small cell lung cancer, and I have to tell you, we do also EGFR, an analysis in bio-immunohistochemistry. Weichel in Vienna used this score and he had high expression of EGFR in his tumour; and we did PD-L1 testing, it's 5%.

Question 1

So, the question now comes up: stage IV squamous cell carcinoma, high EGFR expression, 5% PD-L1, no driver mutation – what is the treatment? You can read it, and please vote.

So, you see cisplatin and gemcitabine, it's an option, no doubt about this. 7% said add necitumumab. Hopefully at the end I will try to convince you that the patient who has high expression in terms of EGFR, that you might at least seriously consider adding

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necitumumab to treatment. Of course, I don't know, I don't usually give bevacizumab, but I would not say it's a mistake. Few people still believe if you have 5% expression; it's enough to be a very expensive treatment in the first-line setting. OK, I can agree. Some others have decided other treatments.

Of course, it's very modern now to talk of oligometastatic disease, so we decided to give systemic treatment, so some people could say let's see this in oligometastatic disease and choose a different strategy.

Metastatic NSCLC: ESMO clinical practice guidelines for diagnosis, treatment and follow-up

What do the guidelines say? Guidelines are there, but when you treat lung cancer for nearly 30 years you know how to treat this patient, so let's look at squamous non-small cell. PD-L, of course you will do PD-L expression if you have more than 50%, you can use pembrolizumab as first-line treatment in these patients; but the patient had 5%, so pembrolizumab is not an option for this patient. No driver mutation, good performance status, less than 70 years, so in the guidelines it says platinum-based doublet, so those who said cisplatin/gemcitabine are in accordance with the guidelines.

Cisplatin/gemcitabine + necitumumab: SQUIRE

Overall survival (n = 1,093)

I would say give to patients also more benefit from adding necitumumab, if he has immunohistochemistry-positive disease, and that's based on the randomised phase 3 trial which compares chemo versus chemo plus necitumumab, in the SQUIRE trial. There was no selection based on EGFR expression. The hazard ratio was 0.84.

Cisplatin/gemcitabine ± necitumumab: SQUIRE

Overall survival (n = 935: subpopulation of patients with EGFR protein expression)

The next step of course was to look at, can you get a more relevant outcome, more meaningful benefit when you do EGFR immunohistochemistry analysis? That was done, 935 patients, the vast majority had some type of expression – if you do expression in advanced non-small-cell lung cancer up to 85% will have some degree of EGFR expression in the tumours. When you look into the population EGFR positivity, you end up with a hazard ratio of 0.79, so there's a 21% risk reduction in death. I would say a 21% risk reduction in death, that's nearly what you achieve going from best supportive care to chemo – we all accept chemo, so if you accept chemo probably you should also consider seriously adding the small monoclonal antibody because the benefit is also 20% risk reduction.

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So, based on this, we decided to treat the patient with chemo, cisplatin/gemcitabine, plus necitumumab, and necitumumab is given at 800mg on day 1 and day 8, and cisplatin/gemcitabine according to standard doses. The patient had a good partial response to the treatment, and is now in observation.

Case discussion B

Let's now come to elderly patients. Approximately one-third of patients will be above 30 at the time of inital diagnosis, so this is an important issue, and we are getting older and older, so we will see more of these patients in the future. I'll show you the case of a 70-year old female, she told me she was never a smoker. I'm not quite sure whether she told me the truth: she looked a little like a former smoker, she had vascular diseases, coronary artery diease, but that's what she claims, no smoking history. She had dyspnoea at exercise during the last months, was a reasonably good performance of ECOG-1, and we performed a CT scan.

Case B (continued) (2 slides)

The CT scan is shown here. You have a lesion in the right lung, you have a lesion in the left lung. It would be an interesting discussion – is this a metastasis, or is this a second primary? There is some pulmonologists here, but whatever it is, the patient had mediastinal lymph node involvement, that you can see here on the left side of the mediastinum, the uptake, and she had also a hot spot in the neck, so it was not supraclavicular, it was cervical lymph node. Based on this, it was for sure stage IV squamous cell carcinoma of the lung, and probably the other lesion on the left side also looks more like a secondary primary, but whatever, she has metastasis.

We did bronchoscopy, bronchoscopy revealed squamous cell carcinoma, and there's no doubt, stage IV, particularly based on the cervical lymph node, potentially also because of the contra in the lung, and no driver mutation, so never a smoker, no driver mutation; and 73 year-old. ECOG status, 0/1.

Question 2

So, elderly: which type of treatment would you recommend? Please vote.

There are certainly experts in the meeting: I can fully agree on this pembrolizumab, I'm not 100% sure whether we did it or we did not do it, so we did not mention it. The data on elderly, with immune checkpoint inhibitors, I would call it soft, so I'm not sure, whether if you are above 70 there is really demonstration that you benefit. Some people said they would give it, so it's fine. The majority said doublet carboplatin in combination with gemcitabine or

vinorelbine, some said single agent, some are very much influenced by a French study which indicated superiority of carboplatin and paclitaxel over one of the single agents.

Lung cancer therapy in elderly patients: factors to be considered

What you have to consider in the elderly, as all those who are treating lung cancer see, it was always not that easy, it's not much more complicated today than it was 20 years ago, in my opinion, you just have more treatment options. Lung cancer was also a heterogeneous disease and you always had to consider various factors, patient-related factors. You had to consider tumour-related factors, and of course, it's a question of cost-effectiveness, value of the treatment and also access to the treatment.

If we go to the patient-related factors, age is of importance, it's not the major factor, but it makes a difference whether you are 71 or 85, life expectancy. Gender might play a role, performance status is important, and then of course, comorbidity organ functions and geriatric syndromes, which can be present. The older you are, the more you suffer from geriatric syndromes, and they have an impact. They might impact on functional status, and of course in the elderly you can also say convenience of administration is of importance – should they come weekly, should they come every 2 weeks, whatever. Of course, you have to consider that if a patient takes a lot of drugs, there might be drug interactions, and patient preference is important, of course.

Of course, then you have tumour-related factors: histological and molecular characteristics, of course we have stage IV, but it also depends in the elderly, is the tumour growing? If you have an indolent tumour you might also consider a "wait and see" strategy, in my opinion.

First-line chemotherapy in elderly patients with advanced NSCLC phase 3 trials

What are the data? I'll just show you the randomised data. Of course, you can do subgroup analysis of large trials that have included also patients beyond 70, and elderly usually is defined as beyond 70. Vinorelbine was shown to be superior to best supportive care, then we have two trials comparing single agent with double non-platinum-based agent – one trial was positive supporting the doublet, one was negative. Then we had the French trial demonstrating the superiority of carboplatin plus paclitaxel over vinorelbine or gemcitabine.

Recently Dr Gridelli presented his data from the MILES 3 and 4 study, where he looked into cisplatin-based chemotherapy. Of course, you have dose adapt, but he couldn't show a survival benefit for a cisplatin-based protocol over a single agent, of course the study

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didn't demonstrate. Of course, you could say the study was underpowered, and there still might be some kind of benefit, it's not so easy to decide, but these are the randomised studies.

First-line chemotherapy in elderly patients with advanced NSCLC phase 3 trials

We decided to give chemotherapy. Because of the data from the French we did a doublet, but we selected carboplatin plus gemcitabine. Carbotaxol in the elderly is neurotoxic, so I am not so sure whether this is a very good combination. So, we decided to combine gemcitabine with carboplatin, but after two cycles, due to haematotoxicity (leucopenia and in particular anaemia), I had to switch to single agent, gemcitabine.

She received four cycles of treatment – I usually give four – she had symptom relief, had radiological response, but she had increased toxicity, particularly leucopenia and anaemia.

Case B (continued)

Here you can see the CT scan. You can believe me if you see the left before and right after the chemo, that Dyspnoea improved. She had improvement in this disease, but what have we learned? This comes with increased toxicity.

Predicting chemotherapy toxicity in elderly patients

There's a lot of research ongoing in the elderly – I'll just refer to one of the studies, by Dr Hurria. They looked into, can you predict toxicity in elderly patients? They have done a study that included 29% of patients in their study and looked at whether they could predict toxicity grades 3 to 5.

They developed a model that was based on the following factors. Age – of course, the older, the more careful; then hearing, so if you have a hearing impairment, it's a sign that you are not in such good condition; and of course, haemoglobin levels. To start with, low haemoglobin levels means you run into the problem of haematotoxic anaemia, like I did.

Then of course, falls in the last 6 months – as long as you are young, you never fall, but if you are getting older you realise sometimes you are not so sure in walking and you fall, you realise falls are an important sign of how well you are performing in daily practice. Of course, we consider creatinine clearance, creatine function, then you see how the patient walks in, whether he can walk, or whether he needs support. Of course, other factors – social activity – are important.

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The main toxicities they were able to predict were leucopenia and haematotoxicity, but also fatigue, infection and dehydration. When they used the performance data – on the right side, on the bottom – there was no difference between good and poor performance, they just took predicted outcome of this toxicity, but they developed a scale with low, medium and high risk, so you can use this, but I'm not so sure we really need it, because you judge from your clinical experience, you take into account pulmonary function, kidney function and of course how he is performing.

Chemotherapy in elderly patients with advanced NSCLC

Chemotherapy in the elderly, it's individualised, it's based on evidence, but I'm 100% sure that the older, or the ones who are more experienced in the field of lung cancer or medicine in general, know it's personal experience, it's judgement. I do believe medicine is more like an art than just an evidence.

Then of course patient preference is of relevance, performance status, comorbidity, organ function, geriatric syndromes, social support, and so on. Chemotherapy for first-line, fit patients doublet or single; if you are vulnerable, consider single agent, but be careful; frail, no chemo. Expect toxicity and enhance your supportive care.

Case discussion C

Let's come now to the last patient, who was a heavy smoker, 50-year old, had pain in the left shoulder, and there was a lesion in the upper left lung, a lesion in the right adrenal gland. We did a biopsy of the lung, it was squamous cell carcinoma of the left lung and was PD-L1 negative, stage IV, and received chemotherapy plus thoracic radiotherapy.

Case C (continued)

We did a very aggressive approach because of the good performance status and the young age, but after the treatment, after finishing chemo and radiotherapy, at the restaging he progressed in the adrenal glands and lymph nodes in the abdomen, and the primary tumour was pretty much similar.

Question 3

So, what would you treat in a patient who rapidly progresses after chemo? Radiotherapy and radiotherapy, which treatment would you recommend? Please vote.

So, you have docetaxel and we decided to add ramucirumab in the data, and there are people who said take immune checkpoint inhibitors, of course, and we also have data on afatinib.

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Metastatic NSCLC: ESMO clinical practice guidelines for diagnosis, treatment and follow-up

Let's see, what do the guidelines say? We have stage IV disease, front-line treatment progressing and good performance status, so you have the option of immunotherapy – we had the discussion, nivolumab or pembrolizumab. Nivolumab is approved independent of PD-L1 level, pembrolizumab is 1 or more. You still have the option of docetaxel, you can add in squamous ramucirumab, you can also consider erlotinib or afatinib.

Recent advances in pretreated patients with advanced squamous NSCLC

Let's come now to why we decided to give the patient docetaxel and ramucirumab. These are the trials: we have the REVEL trial, we have the afatinib trial and we have the immune checkpoint inhibitors.

Docetaxel ± ramucirumab (10 mg/kg): REVEL

Let's come to the REVEL: that was docetaxel plus or minus ramucirumab, 10mg/kg every 3 weeks – you have a benefit hazard ratio of 0.86, that's significant, you can question the clinical meaningfulness. However, if you look at the patients who are fast progressing, within let's say 6–8 months, their hazard ratio is going down, so it's like nintedanib, you have a benefit. That was the reason we decided to give docetaxel plus or minus ramucirumab. Of course, we can't give them pembro, it was negative, and nivolumab, I would argue, if you are below 10, there is no proven benefit. You have also to consider other factors, so that's how we treated.

Afatinib versus erlotinib in squamous cell carcinoma of the lung: LUX-Lung 8

What are the other options? We have the LUX-Lung, erlotinib versus afatinib, superiority of afatinib.

Nivolumab versus docetaxel in advanced NSCLC: overall survival

We have nivolumab, you have seen this trial so many times, you have squamous, 60% risk reduction.

Pembrolizumab (2 or 10 mg/kg) versus docetaxel in advanced NSCLC: overall survival

You have pembrolizumab versus docetaxel, we have a benefit, in particular if you have a high expression.

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Conclusions

So, let's conclude. Necitumumab added to first-line chemotherapy with cisplatin plus gemcitabine improves the survival of patients with advanced squamous cell histology – I consider this as a treatment option.

Elderly patients also benefit from chemotherapy, but they have to have well-tolerated protocols and you have to enhance your supportive care measures.

Ramucirumab added to docetaxel improves also overall survival, particularly in patients who are fast-progressing after first-line chemotherapy, so you have another treatment option. The beauty is you have a lot of treatment options, you choose the option that you believe is the most appropriate for the patient, there are many factors that guide treatment.

Benefits of stopping smoking: UK Million Women Study

Since it's a lung cancer symposium, I finish with the most important slide of the whole ESMO, and that is here. Smoking causes about one-third of cancers, lung cancer is due to smoking on a global level in 70% of the cases, in our area in 85% of the cases, and that's what is the impact of stopping smoking.

Thank you very much.

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