Advanced NSCLC: what are the options?

An independent satellite symposium held in conjunction with the 17th European Congress: Perspectives in Lung Cancer. Prague, Czech Republic

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Chaired by Giorgio Scagliotti and Pieter Postmus

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Dear Colleagues

Thank you for attending the satellite symposium ‘Advanced NSCLC: what are the options?’ at the Perspectives in Lung Cancer (PILC) congress.

PILC provides a unique environment for a focused dialogue among experts in lung cancer. It is within this environment that we provided a highly interactive learning experience for international healthcare professionals (HCPs) that care for patients with advanced NSCLC. The symposium adopted a case-focused approach with the aim of aiding attendees in confirming their current practices and optimising their patient care.

To this aim, delegates were encouraged to use the audience response technology to foster dialogue between the Faculty and symposium attendees. Via this technology, attendees were able to vote on which treatment decisions they would have made during the interactive case studies. These decisions were used to stimulate discussion about what is current best practice for advanced NSCLC patients.

The symposium concluded with a Faculty panel discussion on the current and future best practice for individualised care. There was a debate on the emerging therapies for the advanced and metastatic NSCLC patient and how clinicians can best operate within these new treatment paradigms and the resulting increased complexity in patient management. The therapy landscape for advanced NSCLC and, accordingly, the patient pathway through it, has greatly increased in complexity in recent years, so this discussion provided a unique opportunity for attendees to discuss with the expert Faculty on how best to use the latest developments in therapy in their daily practice.

We hope that you found the symposium engaging and informative and, for others, we hope this Scientific Summary provides a useful tool in understanding current best practice in NSCLC and its treatment.

Yours faithfully,

Pieter Postmus & Giorgio Scagliotti

Symposium Co-Chairs
Faculty biographies

Giorgio V. Scagliotti
Symposium Chair
Professor of Oncology,
University of Torino,
Torino, Italy

Giorgio Scagliotti is currently Professor of Oncology at the University of Torino. He earned his medical degree and completed his postgraduate training in Respiratory Medicine, Internal Medicine and Medical Oncology at the University of Torino. He is currently Chief of the Medical Oncology Division at the S. Luigi Hospital, Orbassano (Torino) and Head of the Department of Oncology at the University of Torino.

Professor Scagliotti is a member of several scientific societies, including the Italian Society of Respiratory Medicine, the European Respiratory Society, the American Society of Clinical Oncology (ASCO), and the International Association for the Study of Lung Cancer (IASLC). From 2003–2007 he was an Executive Board member of the IASLC.

He is also Associate Editor for *Journal of Thoracic Oncology*, International Editor for *Clinical Lung Cancer* and the author or co-author of more than 280 publications in peer-reviewed journals. Alongside this, he is the International Editor of the 4th Edition of ‘Lung Cancer: Principles and Practice’ and co-editor of the IASCL textbook ‘Multidisciplinary Approach to Thoracic Oncology’.

Pieter E. Postmus
Symposium Chair
Professor of Thoracic Oncology, Liverpool University, Liverpool, UK

Pieter Postmus was born in 1951 and obtained his MD at the University of Groningen in 1976. He trained as a pulmonologist in the University Hospital of Groningen from 1977–1981 and has worked in the field of thoracic oncology since 1978.

He defended his doctorate thesis “New approaches in small cell lung cancer” in 1985 and became Associate Professor in the Department of Pulmonary Diseases at the University Hospital of Groningen from 1989–1992.

Professor Postmus was Head Of Department and Professor of Pulmonary Diseases from 1992–2014 at the VU University Medical Center in Amsterdam. He was also a board member of IASLC from 2003–2011 and President of the World Conference on Lung Cancer (WCLC) 2011, held in Amsterdam.

Since March 2015 he has been Professor of Thoracic Oncology in Liverpool. His research in thoracic oncology focuses on early detection, endobronchial therapy, staging procedures, testing and introducing new drugs and new combinations, and methods to communicate with and inform patients and relatives.
Silvia Novello graduated in Medicine from the University of Turin in 1995. She then did a postgraduate course in Respiratory Medicine. In 2006 she achieved a PhD in Human Oncology and went on to do another postgraduate course in Medical Oncology.

In the past she has worked at S. Luigi Hospital, Clinic of Respiratory Diseases, Turin; the Institut Gustave Roussy, Villejuif and the Thoracic Oncology Division, University of Turin. Now, she is Assistant Professor of Respiratory Medicine at the University of Turin, in the Department of Clinical and Biological Sciences, where her main area of expertise is the aspects of basic research and applied clinical research concerning bronchogenic carcinoma.

Professor Novello has been involved in trials and studies in different lung cancer and pleural mesothelioma clinical stages including: supportive care; the treatment of lung cancer in elderly patients; the role of cytokines in thoracic malignancies (lung cancer, pleural mesothelioma); the role of oncogenes, anti-oncogenes, growth factors and their receptors in lung cancer (pathogenesis, prognosis); women and lung cancer; pharmacogenomics and lung cancer; and applied clinical research aspects regarding interstitial lung disease.

Professor Novello is a Member of ASCO, the ‘Innovators in Lung Cancer’ and IASLC, and has been on the IASLC Board of Directors Member since July 2011. She is also a member of Member of the National Lung Cancer Partnership Scientific Committee, the IASLC Young Investigators Awards Scientific Committee, and President of the European Association – Women Against Lung Cancer In Europe.

Fabrice Barlesi is Professor of Medicine and Head of the Multidisciplinary Oncology and Therapeutic Innovations department at Aix Marseille University, France. He also coordinates the Centre of Early Phase Cancer Trials of Marseille dedicated to phase I trials in oncology. Professor Barlesi’s main clinical interests in the field of lung cancer lie in angiogenesis, bioguided therapies and immuno-oncology as a part of Marseilles Immunopôle.

Erik Thunnissen is consultant pathologist and staff member in the Department of Pathology, VU University Medical Center, Amsterdam, with a focus on pulmonary pathology. Dr Thunnissen is a long standing member of the IASLC pathology committee, leader of reproducibility studies of the WHO classification for lung cancer, and has taken responsibility for pulmonary molecular external quality assessment programmes in the Netherlands and for the European Society of Pathology.
Mapping better outcomes in advanced NSCLC: new treatment options in squamous NSCLC

Dr Erik Thunnissen
Department of Pathology, VUmc, Amsterdam, the Netherlands

The symposium opened with an overview of the key genetic biomarkers currently used for predictive testing in NSCLC. Table 1 indicates whether tumour samples are best assessed using immunohistochemistry (IHC) to measure protein expression, fluorescent in situ hybridisation (FISH) to detect gene amplification, or sequencing of the mutation itself. The table also lists the treatments associated with the gene markers.

Rebiopsy demonstrates EGFR tyrosine kinase inhibitor resistor mutations

Multiple mutations and alterations have been detected in NSCLC samples examined after the development of resistance to an EGFR tyrosine kinase inhibitor (TKI), Dr Erik Thunnissen explained.

For instance, a rebiopsy study of 37 patients showed their tumours had retained their original EGFR mutation but gained a raft of different mutations, including amplification of MET or HER2.

And approximately 60% of patients with EGFR TKI resistance will acquire the EGFR T790M mutation in exon 20, he stated. Using sensitive techniques to reanalyse initial biopsy tissue has shown the T790M mutation is present at this time in a small number of patients, less common than other EGFR mutations, but usually it is not present at diagnosis.

Third-generation EGFR TKIs are designed to tackle patients with recurrence after treatment with a first-generation EGFR TKI, including tumours with the T790M resistance mutation.

Figure 1 shows that a very high fraction of patients with the T790M mutation who are given rociletinib will achieve at least a partial response. A similar finding was also reported for AZD9291 (osimertinib) but the speaker noted that the response to this third-generation EGFR TKI is lower in patients who also have the EGFR C797S mutation.

Rebiopsy after resistance reveals additional ALK alterations

Rebiopsy may also shed light on the mechanism of resistance in patients with an ALK rearrangement who progress after treatment with the ALK inhibitor crizotinib.

For example, around a third of patients who develop resistance to crizotinib will show an additional mutation in the ALK kinase domain, such as L1196M, while other patients develop cKIT amplification or KRAS mutations that may also lead to resistance.

Table 1: Overview of genetic markers and their associated laboratory methods used for predictive testing in NSCLC.

<table>
<thead>
<tr>
<th>Genetic Marker</th>
<th>IHC</th>
<th>FISH</th>
<th>mut/indel/transl</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>erlotinib, gefitinib, afatinib</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>ALK</td>
<td>crizotinib</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>C-MET</td>
<td>met mab</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>ROS1</td>
<td>crizotinib</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>BRAF</td>
<td>sora/vemurafenib</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>ever/temsirolimus</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HER2</td>
<td>trastuzumab/ lapatinib/ dacitublinib</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>EGFR IHC</td>
<td>cetuximab</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>PTEN</td>
<td>ever/temsirolimus</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>NRAS</td>
<td>vemurafenib</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>cKIT</td>
<td>imatinib/sunitinib</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>KRAS</td>
<td>selumetinib, docetaxel</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>DDR2</td>
<td>dasatinib</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>FGFR1</td>
<td>ponatinib</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Courtesy of Dr Thunnissen
This rebiopsy information may also allow redirection of treatment, with trial findings indicating that crizotinib-resistant patients may benefit from treatment with the second-generation ALK inhibitor alectinib.

It is clear that there may be more than one resistance mechanism within a tumour, as demonstrated by the “very interesting” case study of a patient with ALK-rearranged, metastatic NSCLC who developed the ALK C1156Y resistance mutation during treatment with crizotinib. Analysis revealed the emergence of a second mutation during treatment with the third-generation inhibitor lorlatinib that resulted in resensitisation to crizotinib.

Why rebiopsy?

Rebiopsy is overlooked when it does not form a routine part of the clinical care of patients with NSCLC, when the anatomical location makes biopsy difficult, or when there is a sense of risk associated with the procedure.

However, Thunnissen noted that it may be “more in the mind of some physicians that it’s difficult to take a biopsy” and that if you explain the reason for rebiopsy, “frequently the patient is willing to undergo another procedure.”

While recognising that, at present, there are a limited number of drugs that patients can be redirected to on rebiopsy results, he emphasized that “if there is a drug available, it’s very favourable to the patient, at least for a short while.”

Rebiopsy in NSCLC is recommended when the previous tissue sample is too small for adequate tumour characterisation, such as genetic testing of predictive mutations.

In addition, rebiopsy may be indicated if a patient experiences relapse more than 6 months after a complete response, if the recurrent disease behaves in a different way to that expected from the primary tumour, or if there is disease at a new site, such as in the liver.

Finally, a rebiopsy may be beneficial if a new molecular treatment enters clinical trials that may be relevant to the patient, Thunnissen said.

Trial results from a recent paper by Ramirez et al highlighted the raft of molecular alterations that occur under the selective pressure of treatment.

Figure 1: Best Response to Rociletinib. Each bar represents an individual patient, and the amplitude and direction of each bar represent the percent change in tumour burden during treatment as compared with baseline. Tumour burden was measured as the sum of the longest diameters of the target lesions, according to RECIST, v1.1. The dashed line at 20% represents the boundary for determination of progressive disease, and the dashed line at –30% represents the boundary for determination of partial response. FB denotes free base, and HBr hydrogen bromide salt.
These results give “the impression of how difficult it is to predict what the recurrence mechanism will be, so you can only know by biopsy,” Thunnissen commented.

However, liquid biopsy may be a good alternative to rebiopsy when a safe site cannot be found. And rebiopsy is also not recommended when the result is unlikely to change treatment, the presenter said.

Liquid biopsy – handle with care

Liquid biopsy uses highly sensitive techniques to examine plasma for biomarkers, with the possibility of monitoring patients every 2 weeks to look for evolution of the biomarkers over time. “That’s very useful” and an “advantage” over rebiopsy, Thunnissen said.

However, he noted the need for careful handling of plasma samples, as there is only a very limited amount of cell free (cf)DNA available, less than 2 ng/mL, and this level begins to reduce within 30 minutes. Moreover, if the sample is not centrifuged immediately, cfDNA from the degradation of white blood cells becomes detectable.

“So take care to handle the blood specimen immediately after venous puncture”, he advised.

Analysis of circulating tumour cells is also feasible but the process is “quite cumbersome” and unlikely to enter daily practice, and in the future platelet analysis may be possible, Thunnissen added.

cfDNA predicts NSCLC diagnosis, EGFR mutation status

Research has demonstrated that cfDNA is a significant indicator of the presence of NSCLC\textsuperscript{10} and several different highly sensitive techniques have been developed, including quantitative polymerase chain reaction, Picogreen, Nanodrop and Qubit.

cfDNA has also been demonstrated to significantly predict EGFR mutation status, with mutations detected in 13.7% of tumours and 10.5% of plasma samples. Plasma analysis was 66% sensitive for detection of EGFR mutations in NSCLC trial participants\textsuperscript{11}.

And the objective response rate to the EGFR TKI gefitinib was 77% for patients who were positive for mutations in both tumour and plasma samples compared with 60% for those who only tested positive in their tissue specimen.

However, Thunnissen cautioned that while a positive cfDNA result above 2% may be reliable, the results are not convincing at lower levels.

“So from this study, you can conclude that if there is no tumour tissue – [which is the case for approximately] 20–25% of NSCLC patients with metastases – then you can go for tumour biopsy”, Thunnissen said. “You can take another standpoint about using liquid biopsy but that is for another discussion.”

Pooled data from older studies conducted in Eastern Asian patients gives cfDNA a sensitivity for EGFR mutations of 67.4% and a specificity of 93.3%\textsuperscript{12}. But forest plot analysis in Figure 2 shows that the spread of individual study sensitivity values occur both along the mean and off target, prompting Thunnissen to question the time taken to process patient samples.

“If you have low sensitivity, it may be that the blood was not centrifuged on time”, he suggested.

State of the art

State of the art comparison of biopsy/rebiopsy and liquid biopsy techniques highlights that liquid biopsy is now performed in some laboratories, using commercial techniques. This is usually done where there is a known mutation.

One drawback of liquid biopsy analysis is that tumour specimens are taken from a specific location, whereas blood samples may include information that could come from more than one tumour site, Thunnissen observed.

And setting tumour biopsy at 100% sensitivity and specificity, liquid biopsy is less likely to give an answer to the question of mutation, with lower rates, at around 70% and 94–99%, respectively.

However, monitoring response is better achieved with liquid biopsy and may show early relapse, he said.

Conclusions

“So the conclusions of this study... are that rebiopsy is indicated in a patient with recurrence after TKI treatment for guidance of subsequent therapy, for change of
tumour behaviour, or tumour relapse or metastases”, Thunnissen summarised.

“If rebiopsy is not possible – liquid biopsy is an alternative with a rapid initial work-up”, but he noted that this requires methods with a high analytical sensitivity.

“And for EGFR mutations, also the T790M, you can apply now for daily practice and also for monitoring treatment response and detecting early relapse.”

References

8. Jekunen AP. J Oncol 2015; 809835

**Figure 2: Forest plot of sensitivity and specificity of cDNA. The pooled sensitivity was 0.691 (95% CI: 0.569–0.790).**

Professor Fabrice Barlesi presented the case of a female nonsmoker, born in 1949, who had been diagnosed in 2007 with a right-sided, hormone receptor (HR)-positive, HER2-negative breast adenocarcinoma. The patient received adjuvant chemotherapy, radiotherapy and hormone therapy.

The woman was subsequently diagnosed in 2010 with left pleural effusion and computed tomography (CT) revealed a tumour close to the pericardium but without evidence of tumour in the bronchus or cytological aspiration. Left thoracentesis revealed malignant cells and left thoracoscopy showed tumour involvement in the parietal pleura and visceral pleura.

The patient was treated with talc poudrage and pleural biopsy revealed a HR-negative adenocarcinoma, positive for TTF-1, and genotyping showed the tumour to be wild-type for EGFR and K-RAS. Approximately 20% of the cells were malignant and the patient was diagnosed with stage IV lung adenocarcinoma.

Four cycles of cisplatin and pemetrexed chemotherapy achieved stable disease by RECIST criteria but left pleural effusion remained. After a further four cycles of pemetrexed maintenance therapy, the patient showed tumour progression at the same site and pleural effusion.

A second left thoracoscopy in 2011 revealed pleural adhesions with few malignant cells in the pleural fluid, although pleural biopsy demonstrated only talc granuloma. The patient received talc poudrage for pleural effusion.

Members of the audience were asked to vote on what would have been their treatment decision at this time and had a broad range of answers, with 39% of physicians choosing a standard second-line chemotherapy for the patient, 29% thoracoscopy for updated genotyping, 20% thoracoscopy for updated histology, and 13% the EGFR TKI erlotinib.

Barlesi agreed that there is “no firm answer” for this case and explained that as the patient was reluctant to undergo a third invasive treatment, he chose to treat with erlotinib 150 mg/day. The decision was made “mainly because of the clinical criteria: because she was a woman, with an adenocarcinoma, she was a nonsmoker”, and thus, the clinical probability was that she might be sensitive to erlotinib even though preliminary genotyping suggested otherwise.

The patient had a “very dramatic response” and the left pleural effusion disappeared after TKI therapy and talc poudrage. However, there was disease progression after 16 months of treatment, with solitary lesions in the brain and liver.

Although the patient remained EGFR-negative, Barlesi noted that such patients may have prolonged survival of over 6 months while using EGFR TKI therapy. “Probably we are missing some of the predictive factors for the efficacy of TKI”, the speaker observed.

The audience response to the second question – what would be your decision at this time? – was evenly split between radiosurgery, liver biopsy and continuation with erlotinib, chosen by 26%, 33% and 29%, respectively. Just 7% and 5% of physicians chose neurosurgery and radiofrequency ablation of the liver lesion, respectively.

Radiosurgery is the preferred option given the size of the brain lesion, the speaker explained, and liver biopsy is “really important” to genotype the disease, but with two sites of progression, he argued against continuing with erlotinib.

Liver biopsy confirmed adenocarcinoma with 95% malignant cells and wild-type status for EGFR, K-RAS,
**B-RAF, PI3KCA and HER2**. The patient had a positive IHC result for EML4–ALK rearrangement but just 12% of cells were positive by FISH.

“By definition, the ALK rearrangement is… demonstrated by more than 15% of cells rearranged”, Barlesi said, adding that it was unlikely that the patient was ALK rearranged as data indicates that such patients do not respond to EGFR TKI therapy².

Indeed, his own recent research demonstrates that among over 17,000 patients, just 10 had both aberrations³, making it “very rare to have a double mutation”.

Nevertheless, the answer to the audience poll on what to do next was overwhelmingly in support of crizotinib therapy, at 65%, with small numbers of physicians opting for platinum- or docetaxel-based chemotherapy, continuing erlotinib, or entering an immune checkpoint inhibitor trial.

Despite not having a clear indication for crizotinib, the patient began treatment with the ALK inhibitor and she had another “dramatic response” to the treatment but experienced liver progression after 12 months.

Rebiopsy of the liver revealed the same genotype profile with ALK rearrangement and the patient was put forward for a ceritinib trial. After initial clinical benefit she experienced rapid liver progression and cardiac tamponade at 2 months.

Noting that phase I results suggest that it is “very rare” to progress on ceritinib even after crizotinib⁴, Barlesi asked which useful biomarker might have been missed from their genotyping.

The speaker stated that cMET amplification “was important to assess in this patient, especially because… if you look at the differential activity of crizotinib and ceritinib, crizotinib is a good cMET inhibitor and ceritinib does not act on the cMET pathway”. And he hypothesised that that might be why she responded to crizotinib after TKI therapy.

The patient’s renal impairment ruled out a trial of alectinib or brigatinib and she was not eligible to participate in an expedited access programme for alectinib.

The patient achieved stable disease after four cycles of nivolumab but had progressive disease after eight cycles and is now undergoing standard chemotherapy.

**Table 2: Overview of patient biopsy and rebiopsy results.**

<table>
<thead>
<tr>
<th>Site</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2015</th>
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<tbody>
<tr>
<td>Pleura</td>
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<td>Liver</td>
<td>Liver</td>
<td>Liver</td>
</tr>
<tr>
<td>EGFR</td>
<td>WT</td>
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</tr>
<tr>
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<td>WT</td>
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</tr>
<tr>
<td>B-RAF</td>
<td>ND</td>
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<tr>
<td>PI3KCA</td>
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<tr>
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<td>WT</td>
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<td>WT</td>
</tr>
<tr>
<td>ALK</td>
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<td>N/A</td>
<td>FISH +/-</td>
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<td>IHC-/-</td>
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<td>Useful?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>?</td>
</tr>
</tbody>
</table>

**Conclusions from this ‘exceptional case’**

Summarising the patient’s results from five different biopsies in Table 2, Barlesi said that “at all the times the rebiopsy was useful to help us decide the strategy for this patient” but acknowledged that the patient was an “an exceptional case”. He hypothesised that tumour heterogeneity or an unknown molecular change might have played a role and this may be aided in the future by systematic rebiopsy or cfDNA monitoring.

“The systematic rebiopsy is, to my opinion, a standard that should be included in our routine but we have to decide what kind of patient population should be systemically rebiopsied and when we have to do this rebiopsy, and what is the objective beyond rebiopsy”, he concluded.

Recognising that biopsy is not always possible, the speaker added: “[W]e know we have some complications for all these invasive techniques and this is maybe one of the problems of precision medicine that will be changed with the advancement of the liquid biopsy.”

**References**

NSCLC case study of a young, female nonsmoker

Professor Silvia Novello described the case of a 40-year-old woman with no history of smoking or passive smoking who visited her doctor after a single episode of non-dental haemoptysis and a lingular lesion on X-ray.

Most (62%) of the audience believed that the next step in patient management should be CT imaging or perhaps positron emission tomography (PET, 26%), with fewer physicians suggesting antibiotics and steroid therapy followed by repeat X-ray or immediate resection.

Novello suggested that the guiding factor on this poll was the presence of haemoptysis rather than the patient’s age, gender or smoking status.

CT with contrast media demonstrated a lesion with adenopathy and she agreed with the majority (58%) of the audience who recommended fibrobronchoscopy as the next step, noting that there was a connection between the bronchus and the lesion.

The use of CT-guided biopsy might depend on whether the medical centre has radiologists who are “very aggressive” or “lead the multidisciplinary team”, Novello commented, adding that the third option of mediastinoscopy while awaiting CT–PET results “is not wrong” while moving to a surgical diagnostic work-up.

PET confirmed lung lesions, adenopathy and lesions at other sites including the brain, while fibrobronchoscopy and biopsy/brushing confirmed adenocarcinoma but there was not enough material to test for EGFR or ALK status.

When asked what the next step would be, 45 days after the initial X-ray, more than half of the audience recommended Novello’s actual action of starting platinum-based doublet chemotherapy while waiting for the results of a rebiopsy, with a plan to change treatment as necessary. A quarter suggested rebiopsy at first relapse and a fifth suggested holding off treatment until rebiopsy results. Just 5% of physicians felt no need to check the patient’s mutation status.

Ultrasound-guided liver biopsy revealed an exon 18 EGFR mutation and the patient was prescribed an EGFR TKI on the basis of her characteristics from June 2011 until January 2012 – she achieved stable disease and treatment was well tolerated.

But in January 2012, CT imaging revealed new bone and spleen lesions, and progressive liver and brain metastases, despite the patient having a good Eastern Cooperative Oncology Group performance status.

Describing the patient as “committed to treatment”, and in the absence of liquid biopsy, Novello agreed with the 47% of the audience who recommended discussing rebiopsy with the patient at this point.

She doubted that a localised approach to treatment, chosen by a third of the audience, would be a “good choice” in this particular clinical case, suggesting that the combination of several sites of progression and the exon 18 mutation indicated that the patient would be unlikely to achieve more than stable disease.

CT-guided biopsy confirmed the tumour remained an adenocarcinoma with an EGFR exon 18 mutation but all other genetic biomarkers were negative. The patient received second-line panencephalic radiotherapy and achieved a response after four cycles of cisplatin plus pemetrexed.
Panel discussion

A panel discussion of the satellite symposium presentation, co-chaired by Professors Giorgio Scagliotti and Pieter Postmus, with Erik Thunnissen, Fabrice Barlesi and Silvia Novello.

ALK FISH criteria – how well defined?

The panel opened the discussion with a question regarding the strictness of criteria of ALK FISH analysis, with Professor Pieter Postmus asking how well this 15% threshold is defined.

Dr Erik Thunnissen explained that a recent German study indicated that a FISH result of 10–14% is associated with a more than 1% risk of a false-negative result, while a 15–20% FISH result has a greater than 1% risk of a false-positive finding.

“So ALK FISH, in essence, has limitations around the threshold”, Thunnissen said, but “higher than 20% is generally rearranged”. He continued that there are two validated IHC approaches and a strong positive on these is sufficient to guide treatment, whereas a weak positive should also be evaluated with FISH.

Professor Fabrice Barlesi emphasized, as a clinician, the need to keep in mind the high likelihood of a molecular aberration in adenocarcinomas in women and nonsmokers, recommending repeated analyses where necessary “in order to provide the patients with the best treatment”.

EGFR T790M mutation – when to shift treatment?

A question from the audience addressed how best to interpret the results for the EGFR T790M mutation when using very sensitive techniques.

Thunnissen replied that large cases series are required to provide the “real experience” with this biomarker but that some clinical centres are now using a T790M-positive blood sample as an indicator for treatment.

Barlesi commented that very sensitive T790M techniques may detect the biomarker in just 1% of cells but this level might be “without impact on the outcome of first-line EGFR TKI treatment”. The speaker emphasized the need to compare analytical techniques and determine the evolution of the biomarker over treatment, in the hope of allowing cfDNA to become a good tool to direct a change in treatment.

Postmus mooted whether a patient with a T790M mutation might be better beginning treatment with a third-generation EGFR TKI than a first-generation agent; Barlesi replied that trials are ongoing to answer this “good question” but stated that “as a clinician, I prefer to have two or three different solutions, it’s better than one.”

The liquid biopsy learning curve

Professor Giorgio Scagliotti asked the panel about the wider clinical utility of liquid biopsy and Professor Silvia Novello observed that liquid biopsy is being launched while we are still in the “learning curve” of tumour rebiopsy, and that the techniques are still being used in parallel with tissue analysis.

She cautioned against switching to a different regimen within a few months of beginning a treatment on the basis of liquid biopsy results, “because we have the real demonstration that this patient could be treated properly and for a long period of time with a sequence of treatments”.

Second-line NSCLC therapy decisions and tumour morphology

Describing second-line treatment of oncogene addicted and non-addicted tumours as the "most exciting field" at the moment, Scagliotti asked how best to navigate through the different molecular targeted treatment options on NSCLC progression.

Barlesi noted the absence of clear guidelines for second-line treatment and hoped to find answers in the future using next-generation sequencing (NGS) techniques and
ongoing clinical research, while Novello commented that, as there are more data than drugs, and no real biomarkers in the clinic for these agents, we need to look for other ways to guide treatment at this time.

We may have insight on these issues in the future from the results of the National Lung Matrix Trial in the UK, which is allocating patients’ treatments on the basis of biopsy biomarkers, said Postmus.

Scagliotti emphasized the current difficulty in clinical practice in choosing between second-line options for non-oncogene addicted tumours, such as immunotherapy and anti-angiogenic agents, or between ALK inhibitors in the oncogene addicted tumour patients.

Thunnissen was asked how influential factors such as tumour microenvironment, immune cell infiltrates and micro blood vessel density are when providing a pathology report to a clinician. He replied that these factors are not currently used for diagnosis, nor prognosis, but should be explored.

We have not previously made clinical decisions on the basis of immune infiltrates, Scagliotti commented, adding that the presence of these cells is surely needed for an immunomodulatory agent or checkpoint inhibitor to work.

Thunnissen explained that if you look for infiltrates, you will find lymphocytes and PD-L1-positive immune cells, such as lymphocytes and macrophages. “Sometimes they are even between the tumour cells”, he said, noting that this characteristic might indicate a better prognosis, but concluded that these features must be explored further before we can use them as a predictive marker.

Conclusions

Scagliotti closed the panel discussion by thanking the panel for their “informative” clinical cases and pathology lecture, concluding that the symposium “will help every one of us to make the best choices for our patients.”

Reference

Advances in the ‘challenging’ field of second-line NSCLC treatment

A conversation between Professors Giorgio Scagliotti and Pieter Postmus

Professor Giorgio Scagliotti continued the discussion on the “challenging” second-line setting for oncogene addicted and non-oncogene addicted NSCLC, describing it as an “exciting field in the past 10 years” through the development of three generations of EGFR TKIs and two generations of ALK inhibitors.

Professor Pieter Postmus noted that while it is accepted that patients should be treated with a TKI as soon as they are diagnosed with a sensitising EGFR mutation, the question is now what to do when the tumour is growing.

He reiterated the need to retype progressing tumours to look for markers that might point to a different treatment, such as a T790M mutation that would direct the patient to a third-generation EGFR TKI.

Scagliotti highlighted the recent development of crizotinib targeting the exon 14 MET mutation as an example of the one by one addition of new treatments for NSCLC patients.

And the sequential use of front-line and third-generation EGFR TKIs in patients who develop T790M mutation will “change the natural history” of the disease by adding almost 2 years of life without progression, he said.

Postmus observed that whether a third-generation EGFR TKI could be used as a front-line treatment is still an “unsolved question”. He queried how the tissue and mutation status of tumours treated with a third-generation agent will look like, what the impact is on the T790M mutation, and whether treatment might resensitise tumours to first-generation EGFR TKIs. So far the evidence is “only anecdotal and not yet fully established”, Postmus said.

Scagliotti also raised the issue of tumour heterogeneity, noting that lung cancer is a polyclonal disease and that not enough is known about tumour dynamics and evolution, or the pressure of targeted therapies.

Acknowledging the emerging role of immuno-oncology agents in phase II and III clinical trials, especially in the field of squamous cell carcinoma, Scagliotti asked Postmus his opinion on second-line treatment for NSCLC.

Postmus said that the trials of anti-PD-1 and PD-L1 monoclonal antibodies indicate that the well mutated cancers respond less to treatment and the reason for this is not well known.

“Is it because they are not expressing PD-1/PD-L1?” he asked. “Or is there less immunogenicity of these cancers?” Alternatively, these tumours may be less affected by the immune system or have a different environment, he added, noting that some researchers question whether patients with mutated tumours are good candidates for trials of these agents.

In addition, PD-L1 expression has an impact on the outcome of squamous and nonsquamous patients undergoing single agent checkpoint inhibitor treatment. Postmus observed that “there is a tendency that the better they express, the higher the chance they will respond, and the longer that they will respond, apparently, as well.”

However, he cautioned that it is hard to draw a final conclusion from the different checkpoint inhibitor trials published in high-ranked journals because each company uses a different platform for determining sufficient PD-1 expression, with thresholds of 20% or 50% or even 1%.

In addition, the “enormous degree” of tumour heterogeneity means that some areas might highly express PD-L1 whereas other areas of the tumour, perhaps even areas of the biopsy sample, express nothing, Postmus said, questioning the “real truth” for these tumours with regard to this category of drugs.

Discussing tumours that are PD-L1-negative, with “clear evidence of an inferior level of activity of the immuno-oncology”, Scagliotti said that this opens “alternative treatment strategies”:

“[I]t’s a matter of fact that the inhibition of angiogenesis...
is a potential way of treating patients in the second line”, he said, emphasizing his belief in the potential for combinations of anti-angiogenic and chemotherapy agents in second-line treatment.

**Next-generation sequencing and NSCLC**

Postmus observed that NGS is a “very promising approach” that may provide different clues to the use of immunotherapy than those found using IHC.

For instance, NGS on resected tissues may be able to define patient populations with regard to expression of PD-L1, with the possibility of identifying correlations between tissue changes and later stage disease. For instance, the potential to define a patient subgroup that will benefit from checkpoint inhibitors by identifying DNA or genetic changes associated with the biomarker.

It might be “simplistic thinking”, Postmus acknowledged, but it shows the need to carry out such research and also to determine the impact of treatment on cancer. And this brings to the fore, the role of rebiopsy to allow adequate NGS and IHC testing to find such correlations, he added.

Watch the full video here