Decision making for systemic treatment of non-small-cell lung cancer

Non-small-cell lung cancers (NSCLC) covers a heterogeneous group of diseases, accounting for around 80% of all lung cancers, which were previously lumped together because there was no apparent reason to use different therapeutic approaches for the various histologies. This has now changed, and choosing the best treatment option for NSCLC patients is increasingly complex.

Research over the past few years has demonstrated differential activity of chemotherapy depending on the morphology and histology of NSCLC.

There has been considerable focus on adenocarcinoma of the lung, because of its increasing frequency and the realisation that the response of one of the newer class of agents – epidermal growth factor receptor tyrosine kinase inhibitors – is associated with adenocarcinoma histology.

Evidence is accumulating from pharmacogenomic studies to suggest that improved results might be obtained in the future by selecting chemotherapeutic agents based on the molecular properties of the tumour.

A few years ago, the 75-year-old man diagnosed with stage IIIB NSCLC whose case is reported here, would have been treated as an 'average' NSCLC patient. Today, as the case clearly illustrates, a wide variety of questions need to be addressed before deciding on the best management plan.

European School of Oncology
e-grandround

The European School of Oncology now presents weekly e-grandrounds which offer participants the opportunity to discuss a range of cutting-edge issues, from controversial areas and the latest scientific developments to challenging clinical cases, with leading European experts in the field. One of these will be selected for publication in each issue of *Cancer World*.

In this issue, Rolf Stahel, professor of medicine at the University of Zürich, Switzerland, reviews new developments in decision making for the systemic treatment of non-small-cell lung cancer. He reviews the data on which treatment decisions are based, and suggests that clinicians are making increasingly sophisticated decisions based on greater knowledge of individual tumour types.

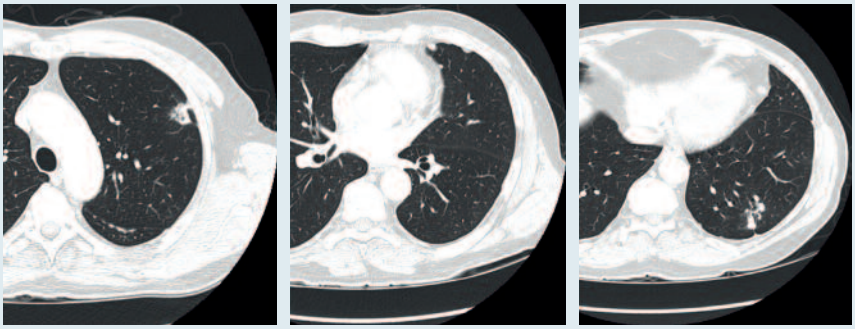
The recorded version of this and other e-grandrounds, together with 15 minutes of discussion, is available at www.e-eso.net/home.do

Case Report (part 1)

The patient is a 75-year-old man, who is retired after having had many jobs, including working as a driver, a petrol-station attendant and a sexton. He plays trombone for the Salvation Army. He presented with benign prostatic hyperplasia, for which he underwent transurethral prostatectomy. One year after this surgery, a CT scan of the chest showed a small solitary lesion in the left lower lobe. Three months later, this was confirmed by a follow-up CT scan, which showed 1.5 cm lesions in the left upper and left lower lobes, and additional small pleural-based lesions.

The patient was sent for thoracic surgery, where a wedge resection was performed and a diagnosis was made of non-small-cell lung cancer with carcinomatosis of the pleura. The cancer was considered unresectable and the patient was referred for palliative chemotherapy. At this stage, the patient was asymptomatic, and had normal haematology and chemistry.

So, we are dealing with a stage IIIB ('wet') non-small-cell lung cancer in a 75-year-old, asymptomatic patient with good performance status and no comorbidities.



CT scan shows lung lesions in the left upper and left lower lobes

How do we proceed with this patient?

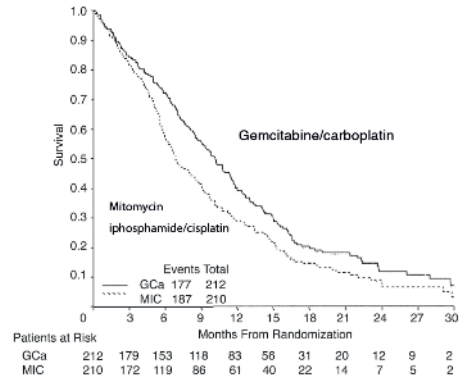
The question now is: what next?

- Would you order some more investigations?
- Do you think in a patient of this age with no symptoms there is a need for systemic therapy, either now or later?
- If yes, what would be your choice of systemic therapy?

Let us assume that you consider chemotherapy is indicated. Is there a best first-line combination chemotherapy for the 'average patient'? The evidence supporting this approach is that all randomised trials using a platinum combination with gemcitabine, docetaxel, paclitaxel or vinorelbine have shown similar results.

It is an ongoing debate as to whether to use carboplatin or cisplatin. How would you make your choice? Would you make your selection based on results of a meta-analysis, as individual trials give similar results? Would you select a treatment based on expected side-effects? Or would you select a treatment based on local feasibility or cost considerations? Some may think about using non-platinum chemotherapy regimens.

COMPARING PLATIN COMBINATIONS



Carboplatin/gemcitabine is clearly the better option

Source: RM Rudd, *J Clin Oncol* 2005

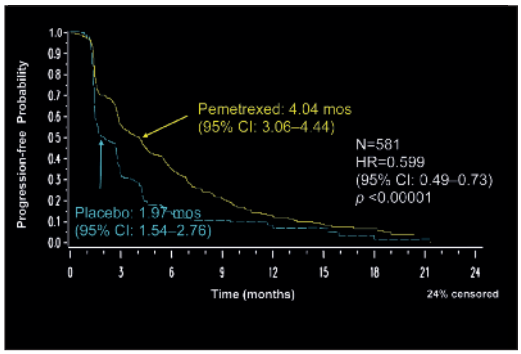
Does it matter which platinum combination is used?

I want to show that it does matter which platinum combination you choose. While it has been well demonstrated, for example in the study by Schiller (*NEJM* 2001), and in other studies, that the four different combination regimens give similar results, it has also been demonstrated that some combinations are inferior to others. A UK study clearly demonstrated that gemcitabine/carboplatin gave superior results compared to mitomycin/iphosphamide/cisplatin – a combination very much used in the country at that time.

Does it matter which platinum drug is used?

Several meta-analyses have compared cisplatin- to carboplatin-based combinations. A meta-analysis by Ardizzoni and colleagues (*J Natl Cancer Inst*, 2007) showed a slight advantage for cisplatin-based combinations. Breaking down the meta-analysis according to whether cisplatin or carboplatin was combined with an earlier or a third-generation combination drug, it seems clear that cisplatin does a lot better than carboplatin when used in combination with newer combination drugs.

THE VALUE OF MAINTENANCE THERAPY



Pemetrexed maintenance therapy following standard chemotherapy showed a clear improvement in progression-free survival

Source: T Ciuleanu, ASCO 2008

However, it is important to point out that this meta-analysis showed a clear advantage with a cisplatin combination for stage III disease, but no obvious advantage in stage IV disease.

Overall, the data from this study can help in selecting the chemotherapy regimen for the 'average patient'.

Comparing side-effects

A randomised, phase III, non-inferiority study comparing first-line treatment with cisplatin/pemetrexed versus cisplatin/gemcitabine in 1,725 patients showed identical results for progression-free survival and overall survival in the average patient with non-small-cell lung cancer (Scagliotti, *JCO* 2008).

Earlier studies showed that the combination of cisplatin/gemcitabine had less clinical toxicity, including less febrile neutropenia than, for example, certain taxane combinations. Scagliotti's study showed that using cisplatin/pemetrexed rather than cisplatin/gemcitabine led to further reductions in side-effects, with lower rates of febrile neutropenia and alopecia of any grade (Scagliotti, World Conference on Lung Cancer 2007). Considerations of side-effects suggest therefore that the cisplatin/pemetrexed combination might be the better option.

Elderly patients should receive the same chemotherapy as younger patients. However, performance stage 2 (PS2) and comorbidity issues are very different. In these patients, a combination of carboplatin with another agent, or occasionally a single agent, may be best. There is a clear need for a clinical trial in the PS2 population to better define the treatment.

What is the optimal duration of chemotherapy?

Current recommendations call for four to six cycles of treatment in patients with NSCLC, followed by observation only. This is now being challenged. A recent meta-analysis compared continuous treatment with gemcitabine or vinorelbine for a longer term versus a shorter term, looking at maintenance treatment or no maintenance treatment after completion of standard chemotherapy. There seemed to be a clear improvement in progression-free survival with maintenance treatment (Soon, World Conference on Lung Cancer 2007). However, there are no results for overall survival.

A study reported at ASCO last year (Ciuleanu, ASCO 2008) looked at the use of pemetrexed after standard treatment with four cycles of a cisplatin-based combination compared to placebo plus best supportive care in patients with no progressive disease. The first results showed a dramatic difference in progression-free survival in patients where maintenance therapy with pemetrexed was added to standard chemotherapy. These results are intriguing, and it will be very interesting to see a breakdown according to tumour histology. However, we cannot say that this is the new standard until we have seen the follow-up data on survival and histology.

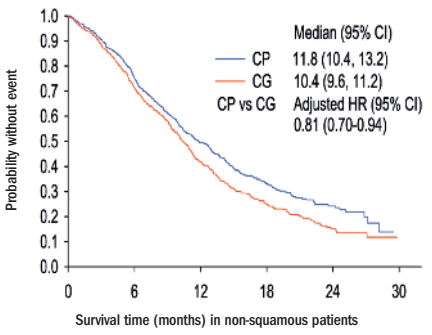
Can we select the best chemotherapy for an individual patient?

There are some important issues to consider in personalising chemotherapy in NSCLC:

- NSCLC is not a single disease, but a group of morphologically and molecularly different diseases.
- The first evidence of differential activity of chemotherapy based on morphology was obtained with the combination therapy of cisplatin and pemetrexed.
- There is accumulating evidence from pharmacogenomic studies which suggests that improved results might be obtained in the future by selecting chemotherapeutic agents based on the molecular properties of the tumour.

Scagliotti's study showing identical

PATIENT SELECTION BY HISTOLOGY



An analysis by NSCLC histology showed that the combination using pemetrexed gives better survival than gemcitabine in non-squamous carcinomas (adenocarcinoma and large-cell lung cancer)

Source: GV Scagliotti, *JCO* 2008

results for the 'average patient' (Scagliotti, *JCO* 2008) looks very different when analysed by morphological subgroup. A predefined subgroup analysis by histology showed an advantage of the cisplatin/pemetrexed combination over cisplatin/gemcitabine for patients with adenocarcinoma of the lung. On the other hand, a similar advantage was seen with cisplatin/gemcitabine for large-cell carcinoma, although the number of patients was lower and the difference did not reach statistical significance.

Some people would say that this is very interesting but needs confirmation. But the validity of these data is strongly supported by a previous study (the Hanna trial, *JCO* 2004), which compared second-line pemetrexed versus docetaxel, and found a similar differential effect with pemetrexed in adenocarcinoma. In my opinion, I think we do have a selective treatment for patients with adenocarcinoma of the lung.

Adenocarcinoma of the lung

Adenocarcinoma of the lung has received particular attention for a number of reasons:

- It has increased in frequency, with adenocarcinoma now being the most common type of lung cancer in many regions.
- The results of studies with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have shown that a response is associated with adenocarcinoma histology. Furthermore, adenocarcinoma histology is associated with the presence of activating EGFR mutations.
- Advanced adenocarcinoma has been the focus of phase III trials with bevacizumab.
- Pemetrexed shows differential activity in advanced disease.

Therefore, when you receive a pathology diagnosis of NSCLC, you should always go back to the pathologist and ask what type of lung cancer the patient has.

Molecular markers

In vitro data have suggested that high expression of ERCC1 (excision repair cross-complementation group 1 protein) is associated with relative resistance to cisplatin. This enzyme is part of a DNA repair complex. It is very plausible that if a cell has a high DNA repair capacity, it would be relatively resistant to cisplatin.

A study from the Spanish Lung Cancer Group (Cobo, *JCO* 2007) investigated this concept prospectively. Patients with NSCLC (at that time we did not distinguish between histologies) were randomised to a control group receiving cisplatin/docetaxel as first-line treatment, or to a test group.

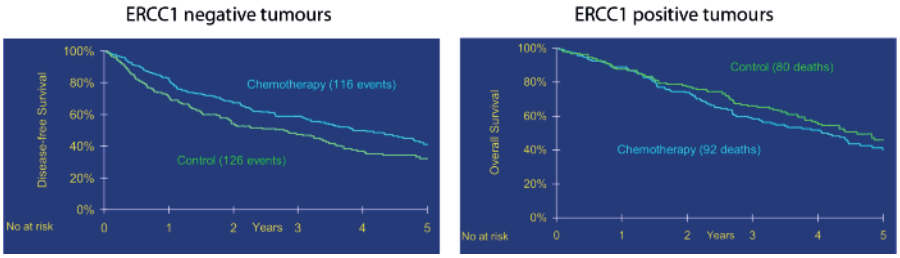
The test group's tumours were tested for ERCC1, and those with high ERCC1 expression, who were likely to be resistant to cisplatin, received docetaxel and gemcitabine as chemotherapy. Patients with low ERCC1 were treated with cisplatin and docetaxel.

The study proved the underlying principle. There was a response rate of 51% in patients whose treatment was guided by their tumour biology, compared to 39% in patients who did not have selective treatment.

The International Adjuvant Lung Cancer (IALT) study of adjuvant chemotherapy in patients with resected NSCLC showed a survival benefit of 4.1% at five years with adjuvant chemotherapy (Arriagada, *NEJM* 2004). More than 800 tumours were collected from patients who participated in this study, which were then examined for their molecular properties, including ERCC1. Very interestingly, the results showed that patients whose tumour had a high level of ERCC1 appeared not to benefit from adjuvant chemotherapy, while those with ERCC1-negative tumours did benefit (Olaussen, *NEJM* 2006). So there are now two studies suggesting that ERCC1 might be a useful marker for the selection of treatment in the future.

The enzyme RRM1 is important in the synthesis of DNA, controlling a rate-limiting step. Gemcitabine inhibits this enzyme, so again it seems very plausible that a high level of RRM1 might be associated with relative resistance to gemcitabine combinations. A study by Bepler (*JCO* 2006) confirmed this concept, showing an inverse relationship between RRM1 expression and tumour shrinkage.

OVERALL SURVIVAL CURVES ACCORDING TO ERCC1 EXPRESSION



Survival curves for 800 patients with completely resected NSCLC given adjuvant chemotherapy show that patients with low ERCC1 expression benefit, while those with high ERCC1 expression do not

Source: KA Olaussen NEJM 2006

The Spanish Lung Cancer Group is continuing its investigation of customised treatment by looking at BRCA1 expression. The BREC (**BR**CA1 **E**xpression **C**ustomisation) study randomised patients to different treatment options according to their BRCA1 expression. There is good evidence from the laboratory that BRCA1 expression confers resistance to paclitaxel and vinorelbine, but sensitivity to cisplatin.

Most of the studies testing whether adding a targeted agent to combination chemotherapy improves outcomes in unselected patients with advanced NSCLC have shown negative results. This has been very disappointing, but we have learned that it is necessary to select patients likely to benefit from specific treatments, rather than giving treatment on an arbitrary basis to 'average' patients.

RCTs OF FIRST-LINE CHEMOTHERAPY +/– TARGETED THERAPIES IN UNSELECTED PATIENTS

TARGET	AGENT	CHEMOTHERAPY	OUTCOME
EGFR	Gefitinib, Erlotinib	PC/GP	No benefit
	Erlotinib	PC/GP	No benefit
	Cetuximab	PC	No benefit
VEGFR2	Sorafenib	CP	No benefit
MMPs	AG3340; BMS275291	PC	No benefit
FT (ras)	Ilonafarnib	PC	No benefit
PKCα	ISIS 3521	PC/GP	No benefit
RXR	Bexarotene	PC	No benefit
mTOR	Sirolimus	Various	No benefit

EGFR = epidermal growth factor receptor, VEGF = vascular endothelial growth factor, MMP = matrix metalloproteinase, FT = farnesyl transferase, PKC = protein kinase C, RXR = retinoid X receptor, mTOR = mammalian target of rapamycin, PC = paclitaxel/carboplatin, GC = gemcitabine/cisplatin

Targeted therapy for selected patients

Phase III trials with bevacizumab were targeted to patients with adenocarcinoma who had good performance status and little comorbidity. This group was selected because of concerns over the toxicity, which therefore did not constitute 'positive' targeting based on markers of response, but it still gave a targeted patient group. With cetuximab, the FLEX trial included patients who were positive for EGFR immunohistochemistry, and gave positive results.

A trial by the US Eastern Cooperative Oncology Group (ECOG), looking at the addition of bevacizumab to chemotherapy with docetaxel and carboplatin, showed a strikingly positive result, with an improved response rate and a two-month increase in survival (Sandler, *NEJM* 2006). A similar trial performed in Europe, the AVAiL trial, added bevacizumab to the combination of cisplatin/gemcitabine, which is the most commonly used combination in Europe. The trial met its endpoint, with an increase in progression-free survival in patients who had bevacizumab added to chemotherapy, and there was a similar increase in response rate to that in the Sandler study. Disappointingly, however, a late report showed no benefit in overall survival.

The question now is: how do we deal with the addition of bevacizumab for adenocarcinoma of the lung in clinical practice?

Soria (ESMO 2008) carried out a very interesting *post hoc* analysis comparing patients in the IALT trial who received second-line chemotherapy or EGFR therapy with those who did not. Two-thirds of the patients received second-line treatment, while one-third did not. The addition of bevacizumab appeared to have a survival benefit in patients not given second-line treatment. This benefit was completely absent in patients who did receive second-line treatment.

The findings indicate that it will become difficult to study the addition of targeted treatments with good second-line treatment increasingly available. They also raise questions as to whether the most appropriate endpoint for future studies should be overall survival or progression-free survival.

EGFR receptors and downstream signalling

Up to 50% of patients with adenocarcinoma of the lung harbour somatic mutations of six genes that code for proteins in the EGFR signalling pathway. This pathway is important in non-small-cell lung cancer, and much research has been done looking at antibodies and TKIs directed against EGFR.

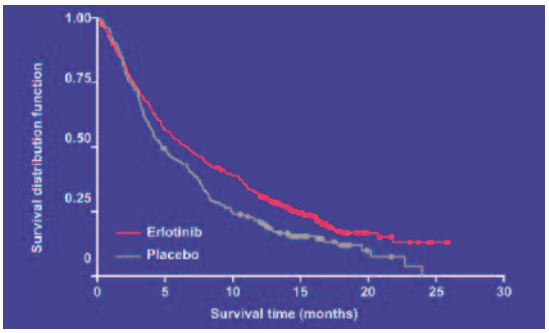
The FLEX study randomised patients to chemotherapy with or without cetuximab (Pirker, ASCO 2008). The overall trial results demonstrated a significant survival benefit when cetuximab was added to chemotherapy. However, looking at the results in more detail revealed no survival benefit with cetuximab in patients of Asian ethnicity. The survival benefit was restricted to patients of Caucasian ethnicity. The median overall survival differed strikingly between the two ethnicities: 9.6 months for Caucasian patients compared to 19.5 months for Asian patients. These were clearly different patient populations, with a higher rate of adenocarcinoma and non-smokers in the Asian population. This suggests that we are treating different diseases as well as different ethnicities.

A randomised study of erlotinib versus placebo after failure of first- or second-line chemotherapy in a NSCLC trial showed positive results, with a survival benefit in a large group of patients. There was particular benefit in patients who were non-smokers, those with adenocarcinoma and those of Asian ethnicity. This treatment has entered into clinical practice very rapidly.

The question now arises: how do we select patients for erlotinib treatment?

While some favour clinical parameters for patient selection, the debate on which patients should be offered targeted treatments has changed with the availability of molecular analysis. Most, or all, of the patients who show a high response to EGFR TKIs have EGFR mutations, frequently with a deletion in exon 19 or a mutation in exon 21. Almost 90% of patients with an exon 19 deletion show a response, as do 70%–80% of those with a mutation in exon 21. There are also mutations that do not confer sensitivity, such as T790M.

BENEFITS OF SECOND-LINE ERLOTINIB



Median survival was 42.5% longer in patients given erlotinib vs placebo after failure of first- or second-line chemotherapy

Source: Shepherd, *NEJM* 2005

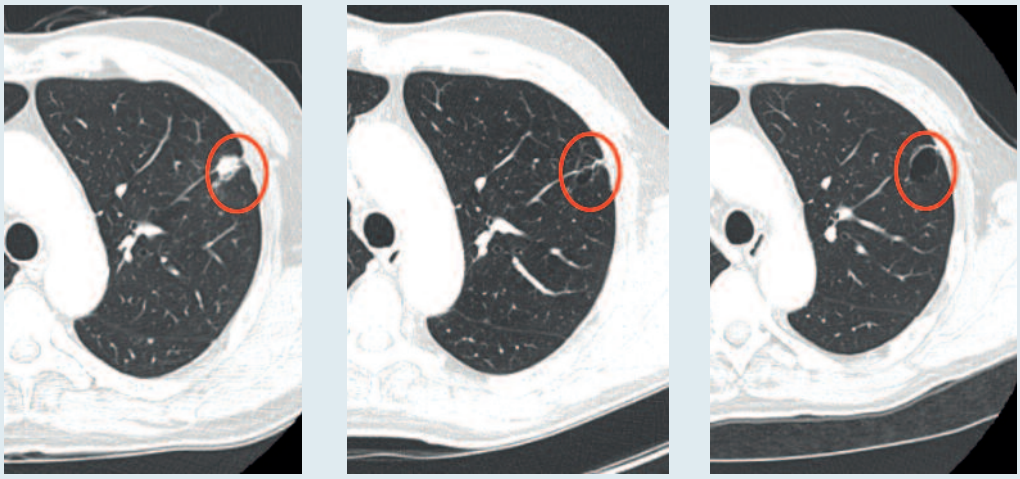
Case Report (part 2)

Going back to our case study, the patient had an adenocarcinoma, and when asked his smoking history, said he had never smoked. EGFR mutation analysis, which is now done for all our patients, showed a deletion in exon 19, and so the patient was entered into a trial with erlotinib/bevacizumab as first-line combination treatment, with cisplatin/gemcitabine on progression.

The CT scans below show the dramatic response that occurred within six weeks. The lesion in the left upper lobe completely disappeared, and what was visible after six weeks and after one year was just like a cystic structure in the left upper lobe. The patient has been continued on that treatment.

However, the left lower lobe showed a persistent density. We debated as to whether this was a scar or residual disease, and whether it should be removed. Together with the surgeon and patient, it was decided to perform another resection of the lesion to remove it and determine its histology. Histology showed a viable adenocarcinoma, with a deletion in exon 19, and no new mutation associated with resistance to erlotinib. The patient has since continued on treatment, and remained in remission for over two years.

Why did we take this lesion out? We were afraid that the patient might go on to develop the T790M mutation, which has been described to occur in 50% of patients who develop resistance to erlotinib (Kosaka, *Clin Cancer Res* 2006).



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CT scans show a dramatic response of the lesion in the patient's left upper lobe

Selecting patients for first-line treatment with erlotinib or gefitinib

A study from Asia has had tremendous impact (Mok, ESMO 2008). The study included patients with adenocarcinoma of the lung and was enriched for EGFR mutations because it included only former light smokers and people who had never smoked at all. They were randomised to first-line treatment with chemotherapy or gefitinib. Results showed a clear difference in tumour response in mutation-positive patients, favouring treatment with gefitinib and vice versa.

Other tumour types

Much attention has been focused on adenocarcinoma of the lung, but there has been some development in other tumour types in targeting the insulin-like growth factor-1 receptor (IGFR1). There are now antibodies to IGFR1 and there is good preclinical evidence of their efficacy in cancer. A randomised phase II study that compared treatment with an antibody to IGFR1 plus chemotherapy versus chemotherapy alone showed an increased response rate (52% vs 33%). Several phase III studies in non-adenocarcinoma NSCLC patients on this topic are ongoing (Karp, ASCO 2007).

Conclusion

A diagnosis of non-small-cell lung cancer is no longer acceptable as the only basis for treatment decisions. It is important to recognise that adenocarcinoma of the lung is not a uniform disease. It is desirable to know the EGFR status, at least, before making treatment decisions in patients with advanced disease. Pemetrexed/cisplatin is superior to gemcitabine/cisplatin in non-squamous-cell carcinoma and the opposite is likely to be true in squamous-cell carcinomas. Maintenance chemotherapy prolongs time to relapse.

The addition of bevacizumab to platin-based chemotherapy improves response and time to progression, but does not consistently improve survival in patients with adenocarcinoma. This might be due to the effect of second-line therapy. The addition of cetuximab to cisplatin/vinorelbine in NSCLC patients testing positive for EGFR on immunohistochemistry improves survival in non-Asian patients. For patients with adenocarcinomas with an activating EGFR mutation, erlotinib or gefitinib are first-line options.

In the adjuvant situation, ERCC1 status may contribute to decision making. While some targeted approaches, such as VEGF antibodies, appear to be broadly applicable, newer approaches, such as MET or ALK inhibitors, will mandate a molecular selection of patients for clinical trials.

Enriqueta Felip (EF), of the department of oncology at the Vall d'Hebron Hospital, Barcelona, Spain, hosted a question and answer session with Rolf Stahel (RS).

EF. *What molecular markers do you recommend in non-small-cell lung cancer patients in clinical practice outside clinical trials? Do you think we should determine EGFR mutations on a routine basis?*

RS. I know that not everyone can do it, but I recommend testing for EGFR mutations, FISH status and immunohistochemistry for patients who have adenocarcinomas. Immunohistochemistry is helpful when thinking about using cetuximab, and mutation status for erlotinib and gefitinib. Our hospital routinely performs EGFR mutation analysis.

EF. *You commented on the Spanish Lung Cancer Group GILT trial (Cobo, JCO 2007). One problem in this study was that, with predictive markers in advanced disease, the tumour tissue is usually small to scarce. What is your opinion of the relevance of blood sample examinations?*

RS. I am convinced that, within a few years time, measurement of EGFR mutations in blood serum DNA will be introduced into the clinic. It is not yet there, and is investigational, but I think it will find its place.

EF. *You commented on ERCC1 in the adjuvant setting. Do you use ERCC1 expression to determine adjuvant treatment in patients with stage II or stage I disease?*

RS. I do not ask routinely for staining from histopathology, but I will ask for it for individual patients when I am ambivalent about whether to select an adjuvant treatment.

EF. *What is your opinion of the influence of EGFR activating mutations on the efficacy of EGFR targeting monoclonal antibodies?*

RS. This is a very personal opinion, and not based on data. I do not think mutation status influences the efficacy of an antibody. However, we will see what the analysis of the FLEX trial, and other trials collecting tumour samples, shows on this issue.