Cambridge Oncology

Module 2 e-learning case 1

Cancer biology and targeted therapies

Introduction

- This is an interactive e-learning case which explores the themes in your ‘cancer biology and targeted therapies’ module in relation to a patient.
- This case will take you less than 30 minutes to complete.

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MK is a 61 year old Caucasian female. For the last 3 months she has observed fatigue, a cough with pink tinged sputum and right sided shoulder pain. She denies any weight loss, loss of appetite or other constitutional symptoms. She is normally fit and active.

She used to smoke 5 cigarettes per day for about 20 years but stopped smoking 15 years ago.

In her past medical history she has mild exercise induced asthma but has never been to hospital for breathing problems. She has been diagnosed with mild osteoarthritis of both hips

She is married with 3 children, and used to work as a primary school teacher.

She went to visit her family in South Africa 6 months ago

Her grand-daughter come to see her. She is training to be a doctor and convinces her she must go and see her GP

The GP sees her and comes up with a differential diagnosis. What would you consider on your differential?

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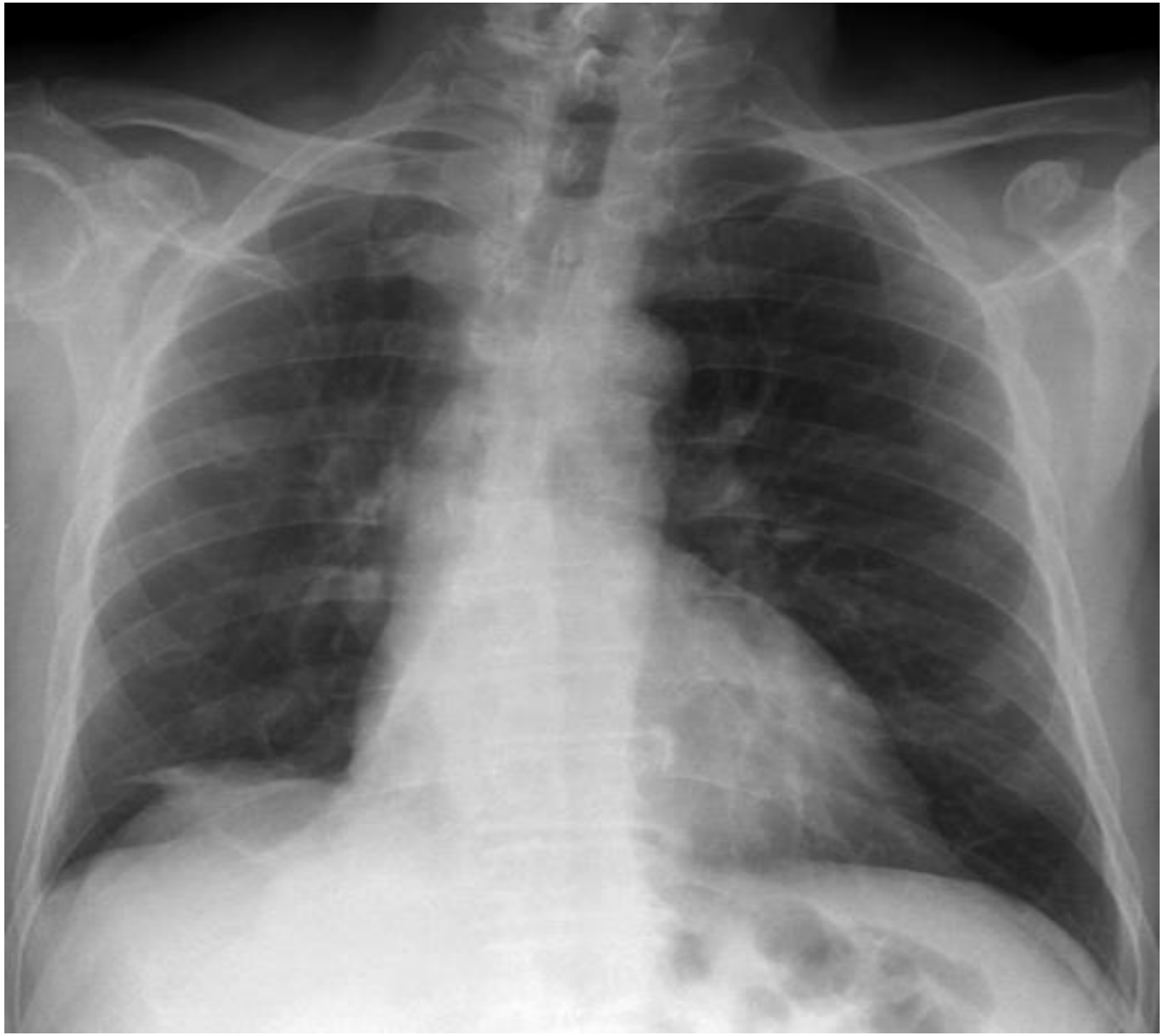
The GP sees her and comes up with a differential diagnosis. What would you consider on your differential?

- TB
- Pneumonia
- COPD
- Non-Hodgkin's lymphoma
- Primary mediastinal B-cell lymphoma
- Lung malignancy (small cell or non-small cell)

She is sent for a chest radiograph later the same day. Can you describe any abnormal findings?



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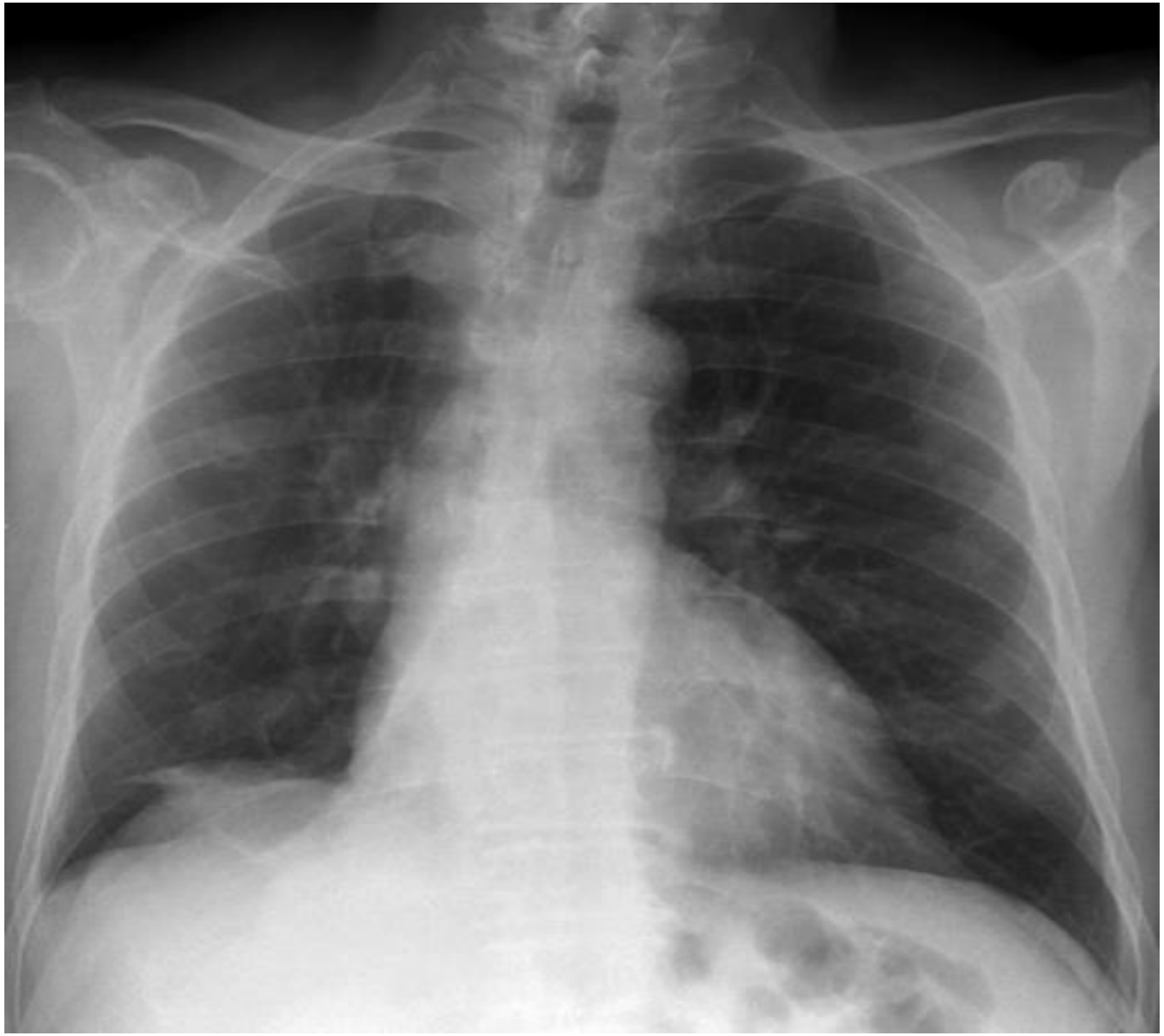
She is sent for a chest radiograph later the same day. Can you describe any abnormal findings?

There is an area of increased opacification at the right lung base consistent with consolidation or collapse

The radiology report triggers a 2 week wait referral to the local lung MDT and she is assessed in a multidisciplinary clinic.



At the lung clinic, she has the following investigations

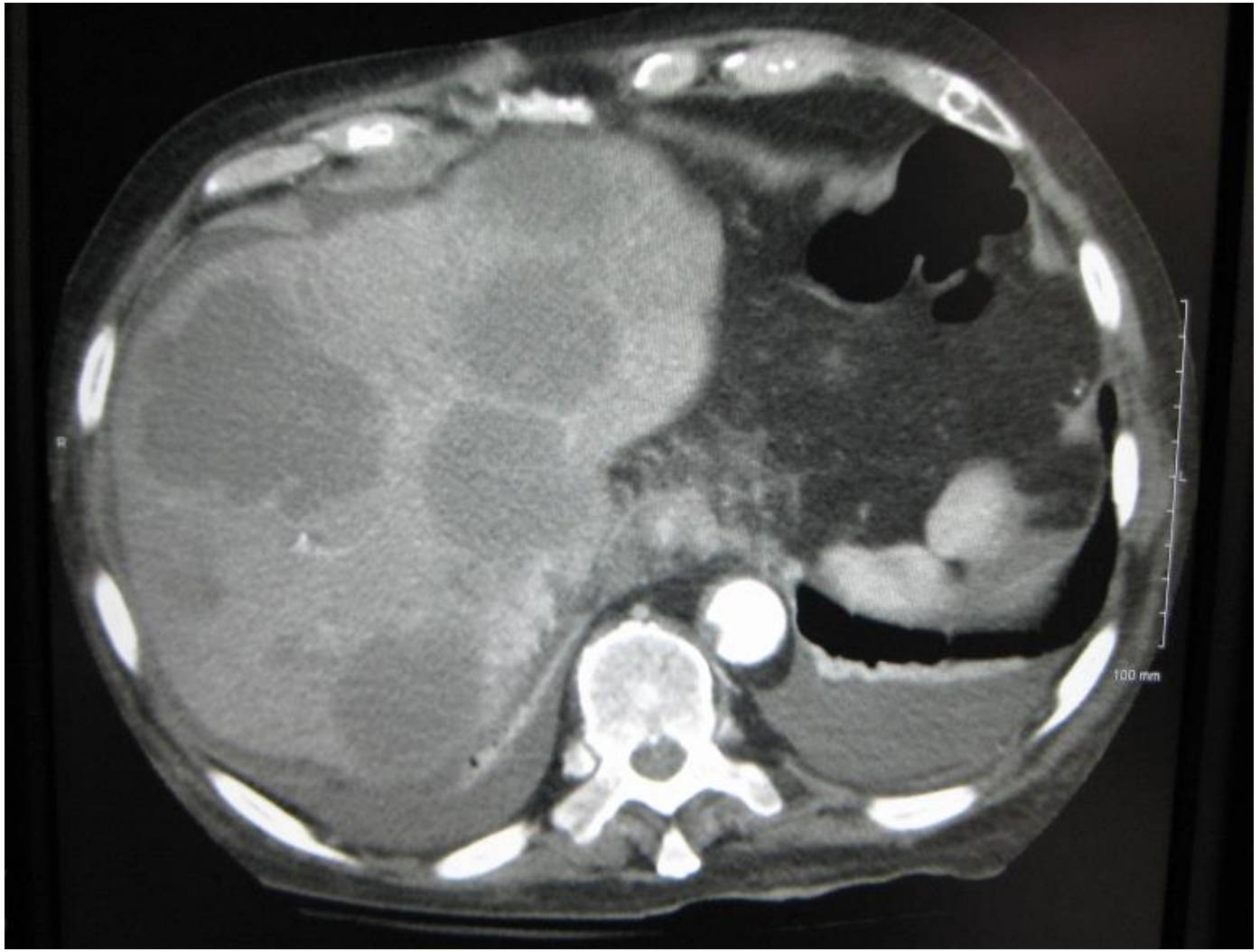
Full blood count – normal apart from mild anaemia (HB 104 g/l) and prolonged PT 15.4

Biochemistry – ALT 160 Bilirubin 22

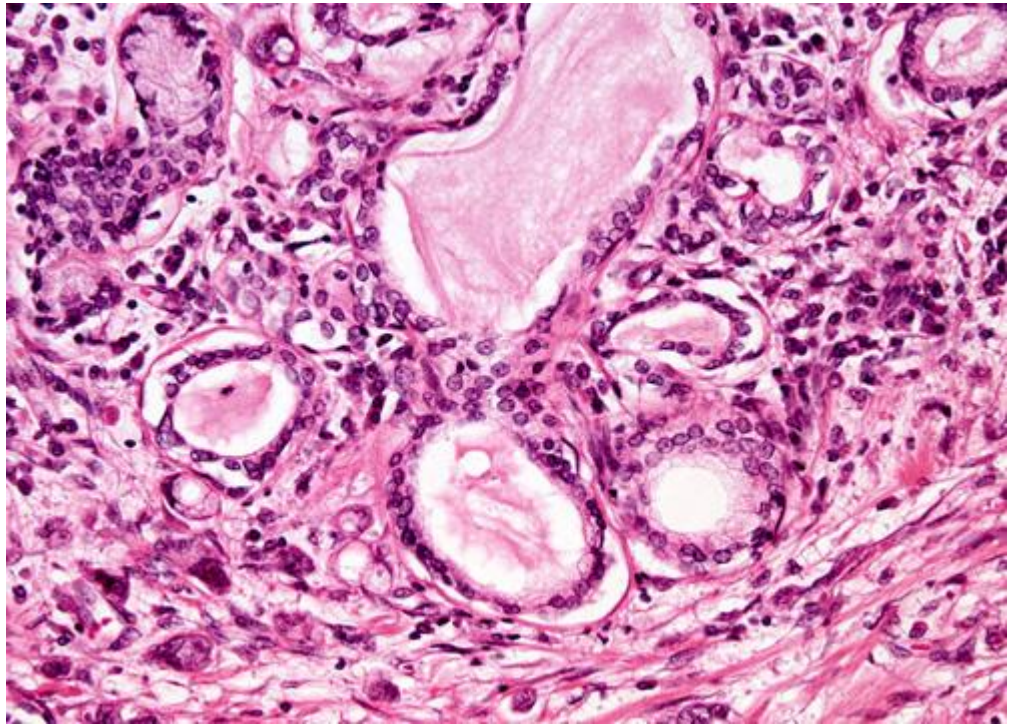
CT Chest and upper abdomen reveals 2.0 cm X 2.2 cm lesion in R lower lobe with associated lung collapse and contralateral mediastinal node involvement.

This is the CT scan of her liver…

What would you do next?



She proceeds to an ultrasound guided biopsy of one of the liver lesions.



The biopsy shows evidence of metastatic adenocarcinoma forming poorly differentiated glandular structures

Immunohistochemistry showed the following

CK7 positive

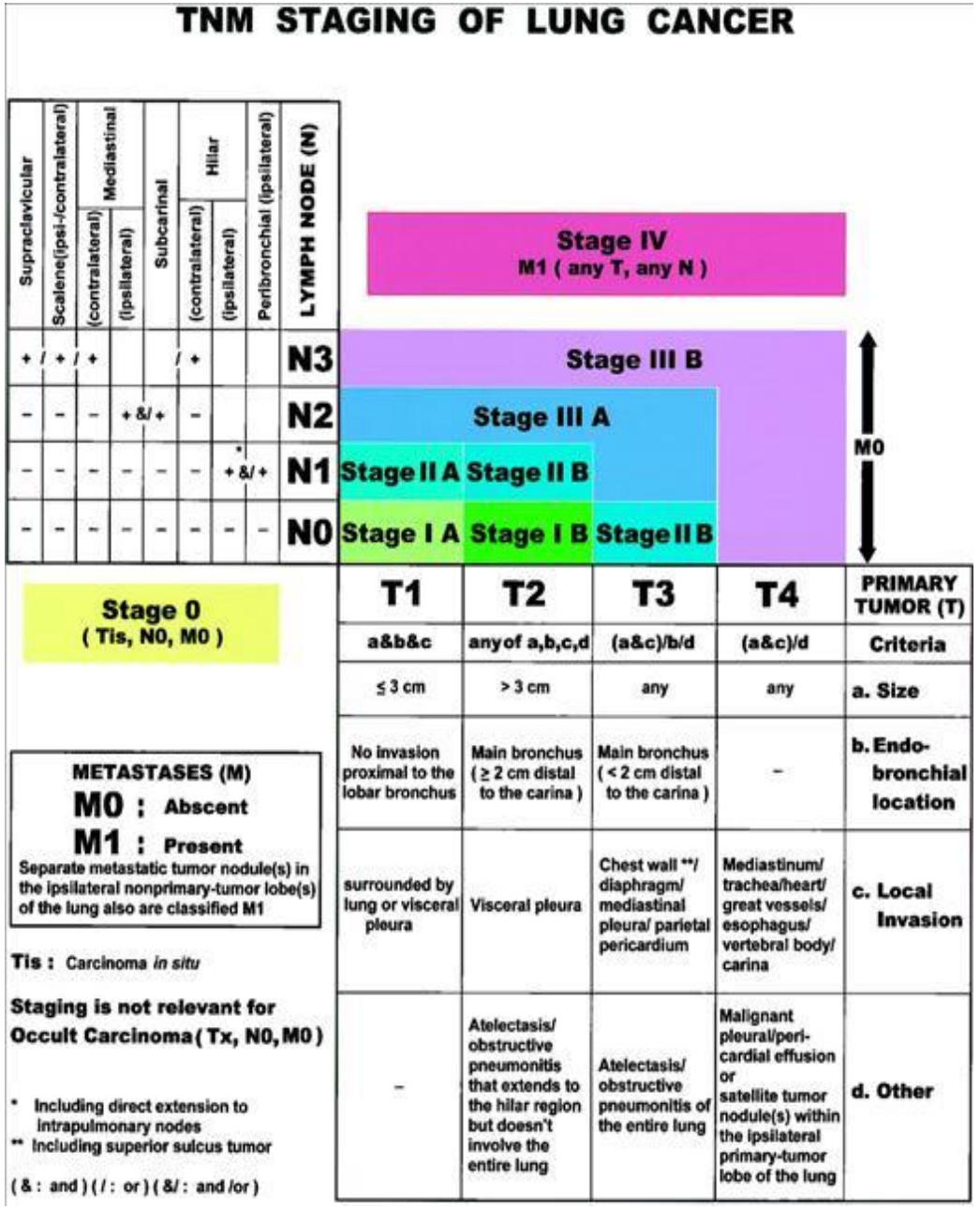
CK20 negative

TTF1 positive

What is the most likely underlying diagnosis?

Is it consistent with non-small cell lung cancer (adenocarcinoma)

From the information we have so far can you stage the patient?



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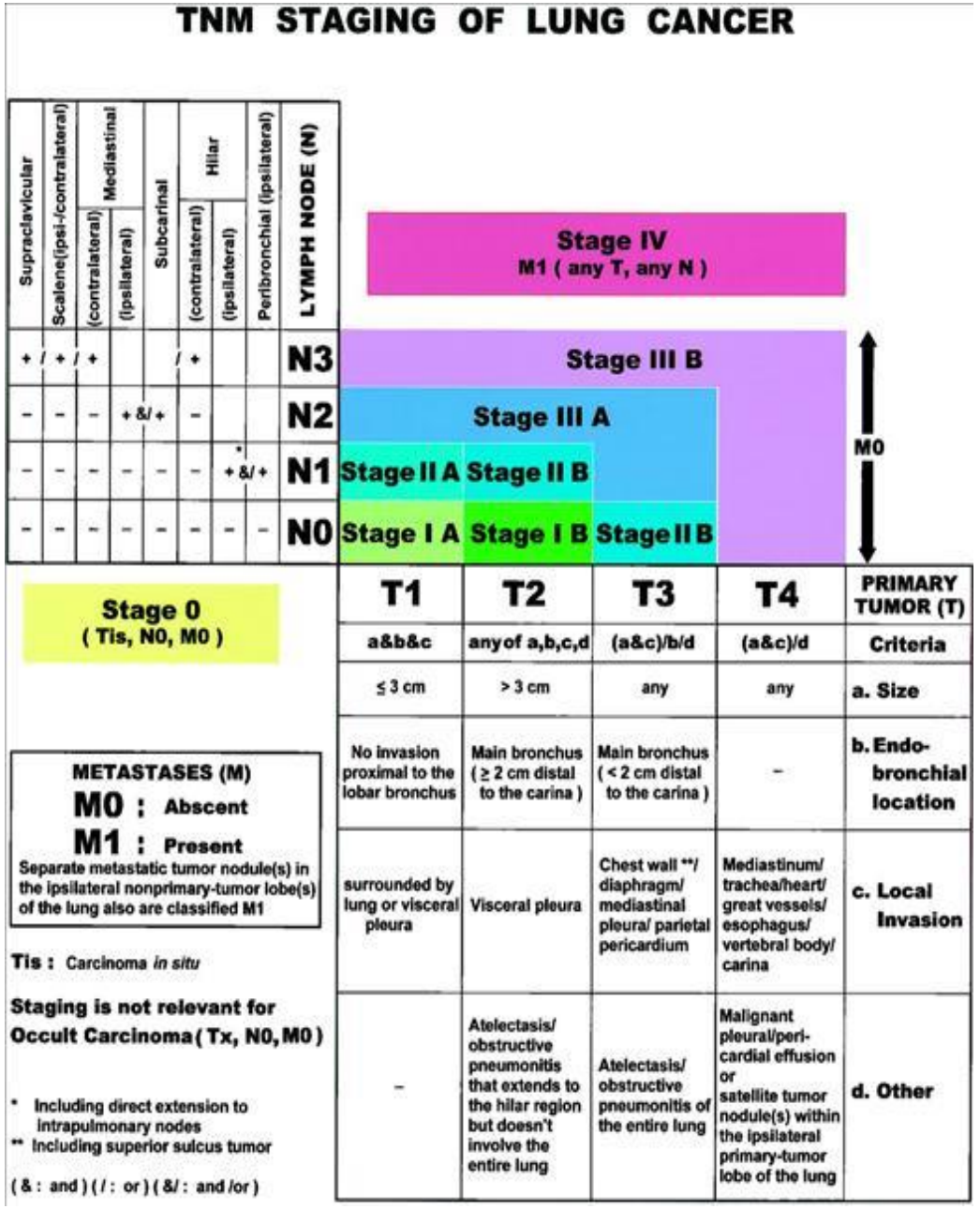
Is it consistent with non-small cell lung cancer (adenocarcinoma)

From the information we have so far can you stage the patient?

Staging is pT1N3M1, which is stage 4 lung cancer

So the picture we have so far tells us about the clinical stage of the cancer, but it does not help us target therapy to this patient's tumour

What additional tests would you ask to be performed on the tumour sample?



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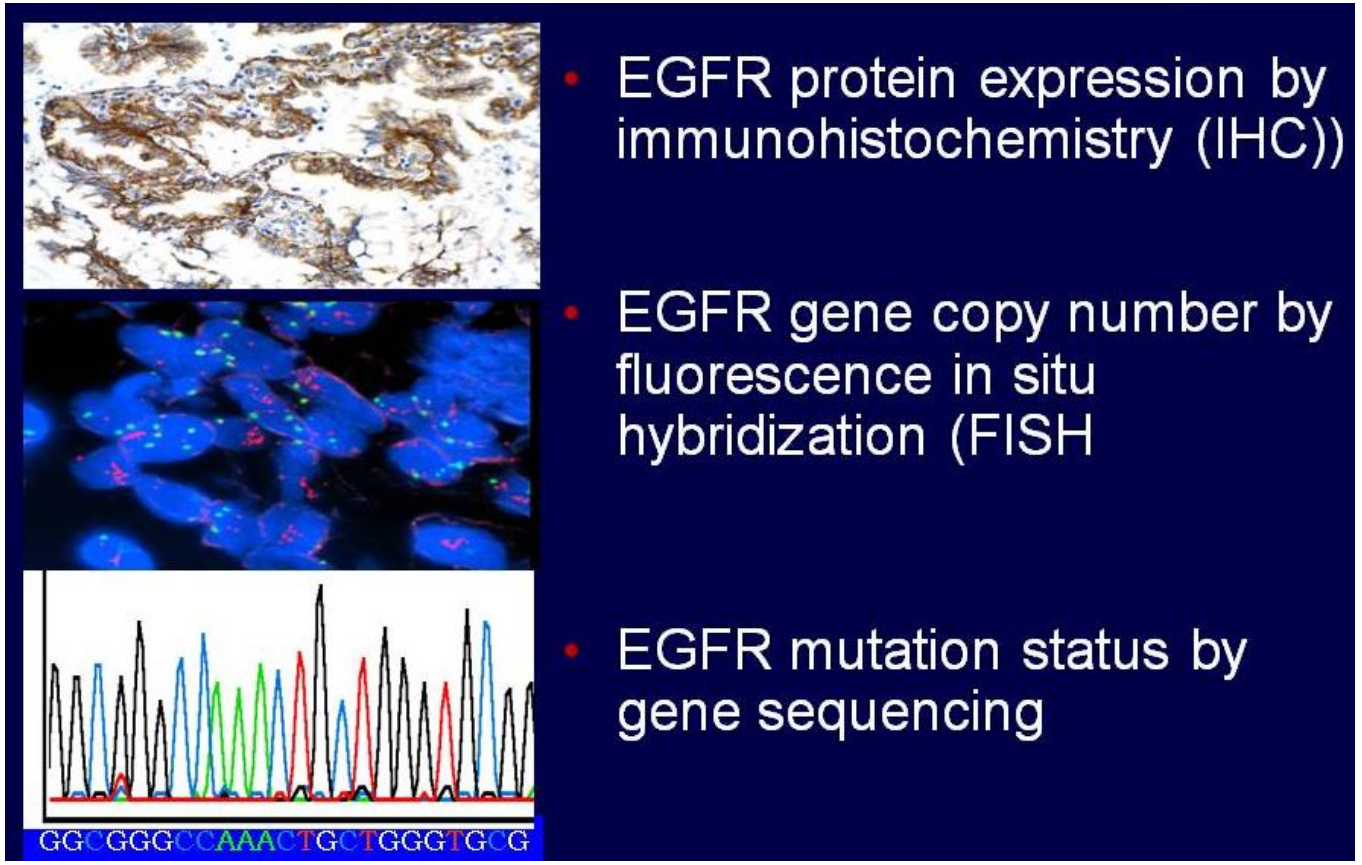
Molecular profiling of the tumour, looking for EGFR and ALK mutations that can guide therapy

These investigations were in fact automatically requested by the pathologist, because she had attended the MDT meeting and knew that this patient would be offered systemic therapy, the nature of which would depend on the molecular profile of the tumour



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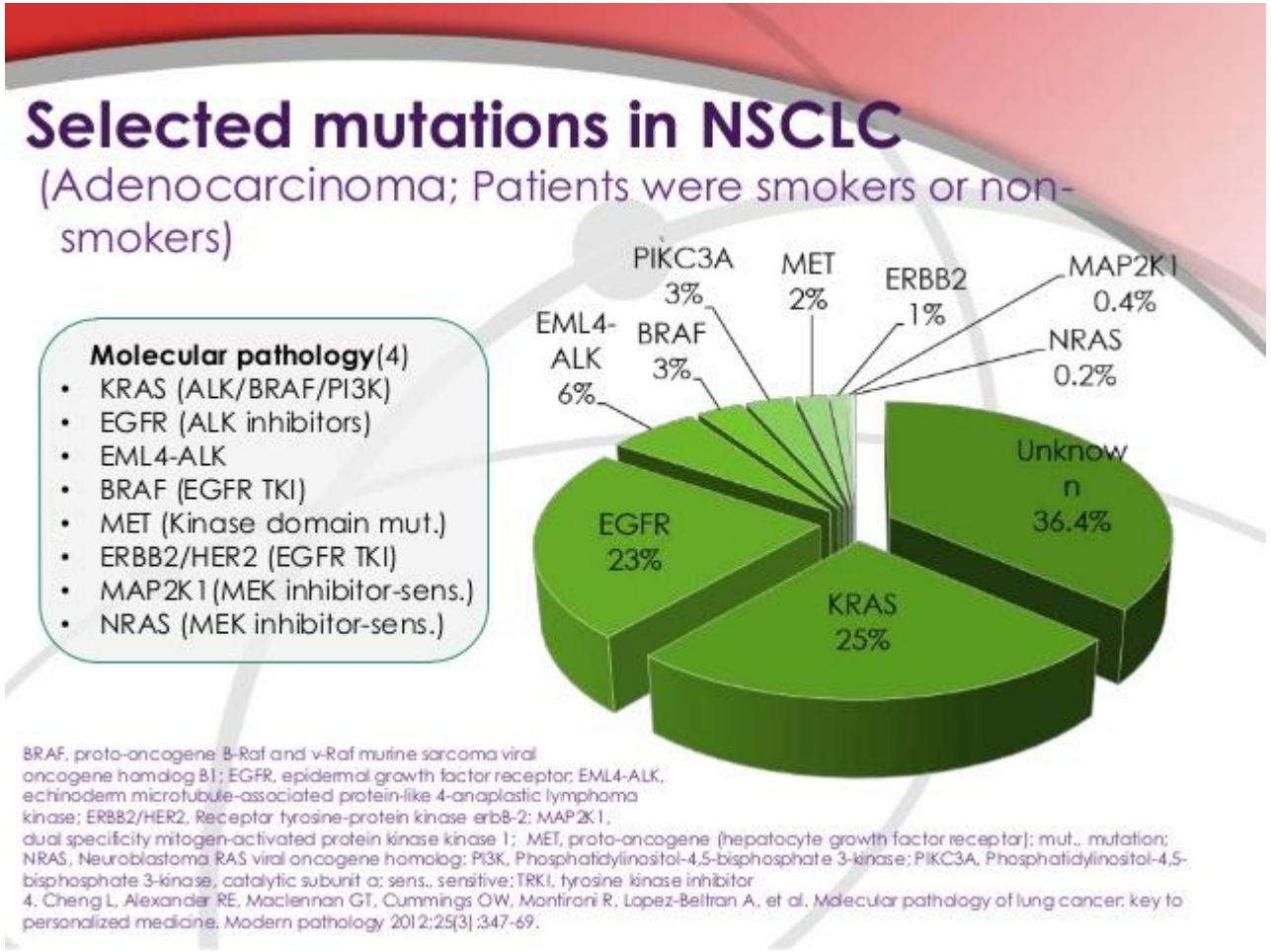
She has to stay in hospital for a few days after her biopsy due to bleeding complications but makes a full recovery.

She comes to the oncology clinic and the molecular pathology results are back:

Tumour is positive for EGFR point mutation DEL19R

What are her treatment options?



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She has to stay in hospital for a few days after her biopsy due to bleeding complications but makes a full recovery.

She comes to the oncology clinic and the molecular pathology results are back:

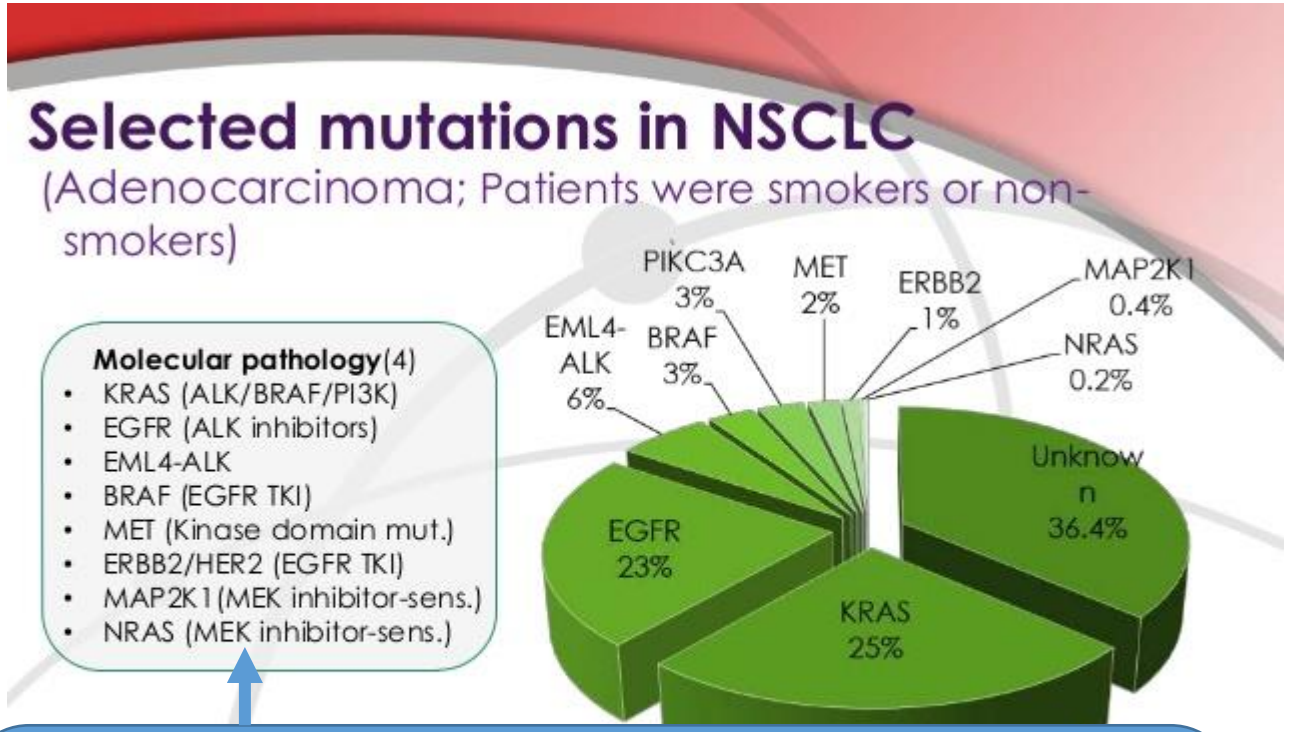
Tumour is positive for EGFR point mutation DEL19R

What are her treatment options?

Conventional chemotherapy

Targeted EGFR inhibitor

Best supportive care



Predictive assays : These molecular pathology tests are looking for mutations in druggable cancer pathways, and are predictive of response to a specific therapy.

Mutation status may also predict clinical outcome independent of treatment, in which case they are also **prognostic assays**

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The consultant is away on leave and you are asked to see the patient. You enlist the help of Professor Google Serge who finds this:

Overall survival of patients with advanced NSCLC with common EGFR mutations (Del19/L858R) treated with afatinib versus chemotherapy: analysis of pooled data from LUX-Lung 3 and LUX-Lung 6

Study design

- Stage IIIB/IV adenocarcinoma of the lung
- Presence of EGFR mutation in the tumour tissue*
- No prior treatment with chemotherapy for advanced/ metastatic disease or EGFR inhibitors
- ECOG PS 0 or 1

Randomization

2:1

Stratification by EGFR mutation type: Del19/L858R/other and by race (LUX-Lung 3 only): Asian/non-Asian

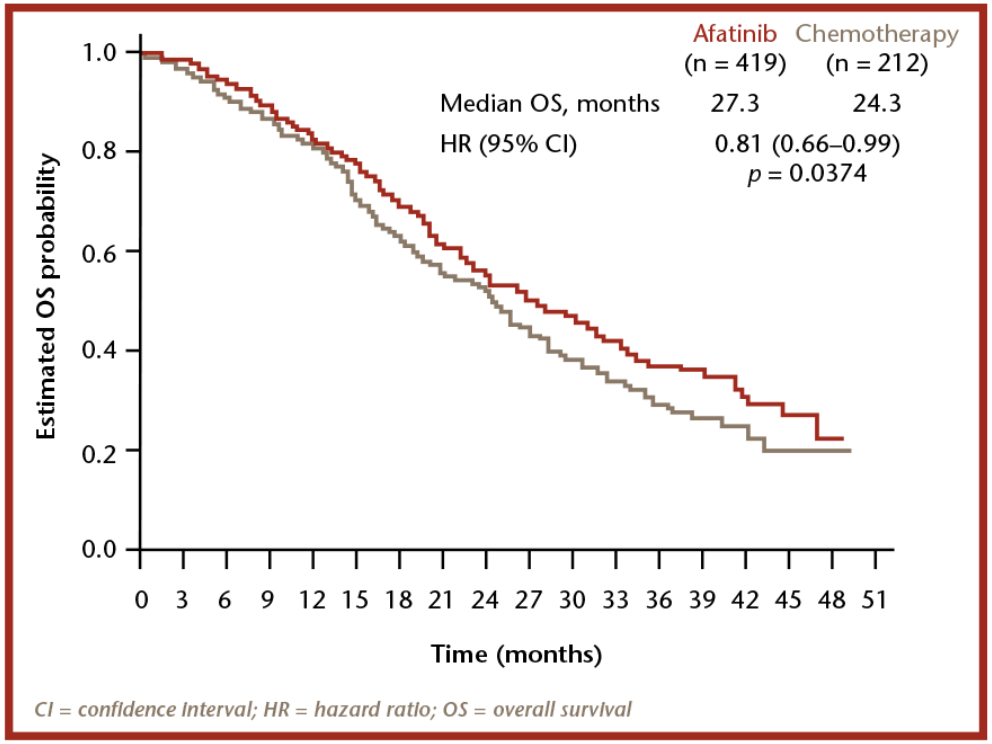
Afatinib 40 mg orally once daily	LUX-Lung 3[1]: Cisplatin + pemetrexed up to 6 cycles
	LUX-Lung 6[2]: Cisplatin + gemcitabine up to 6 cycles

Primary endpoint: PFS (independent review)
Secondary endpoints: ORR, DCR, OS, PRO, safety

**EGFR29: 19 deletions in exon 19, 3 insertions in exon 20, L858R, L861Q, T790M, G719S, G719A, and G719C (or G719X), S768I.*
[1]Sequist et al. J Clin Oncol 2013;31:3327–34.
[2]Wu et al. Lancet Oncol 2014;15:213–22.

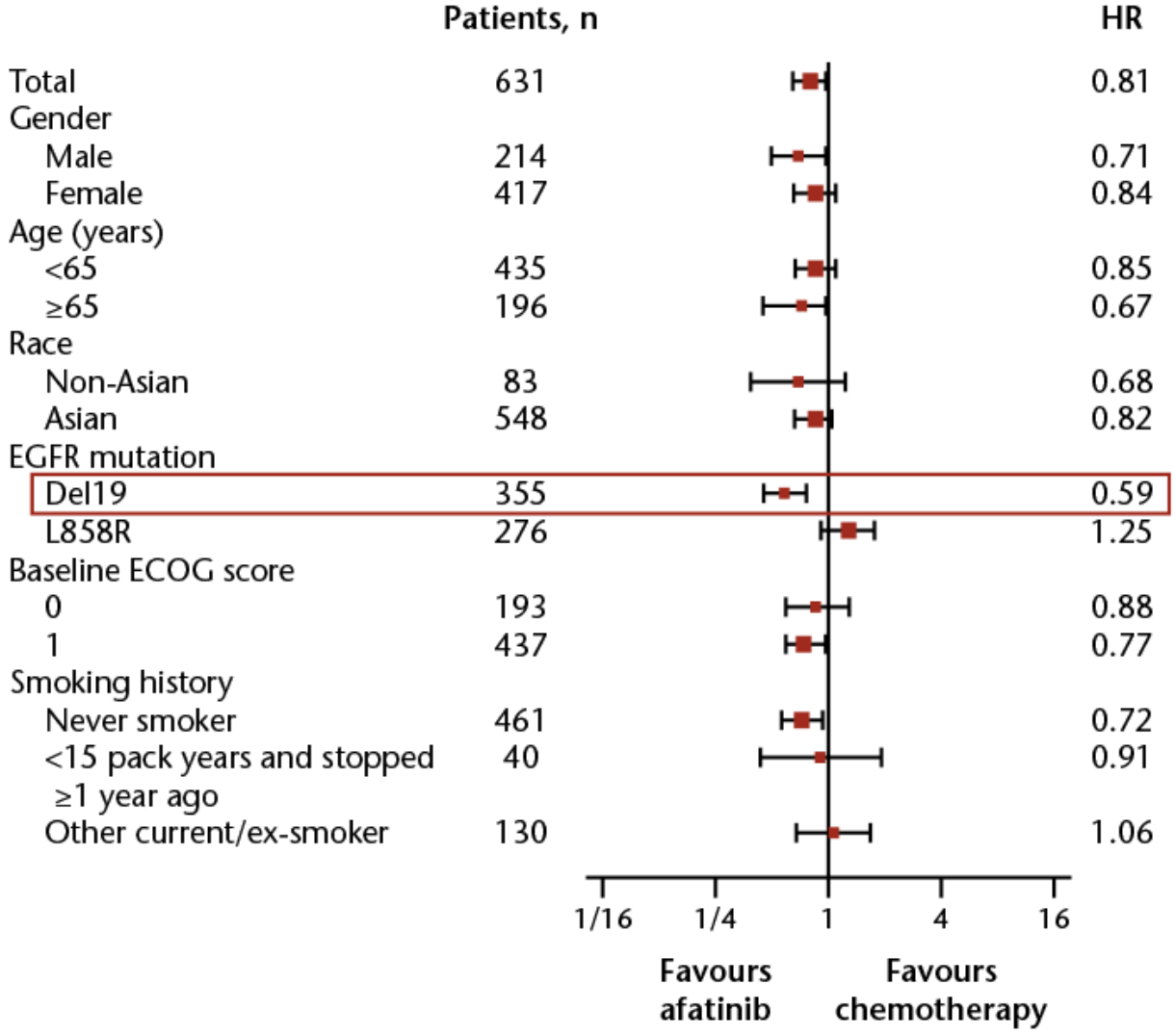
DCR = disease control rate; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PRO = patient-reported outcomes; PS = performance status

Figure 3. Overall survival of patients with common EGFR mutations — pooled data (n = 631)



CI = confidence interval; HR = hazard ratio; OS = overall survival

Figure 4. Overall survival subgroup analysis of patients with common EGFR mutations — pooled data



ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; HR = hazard ratio

Your based on your assessment of the patient, the pathology, and the data presented, what treatment option would you recommend for MK:

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Afatinib therapy

Chjef scientific officer at Sarah Cannon

David Spigel on predictive assays & targeted therapies in lung cancer

The treatment of advanced non–small-cell lung cancer has really changed over the last few years. Really for about 20 years, the standard approach to somebody with stage IV lung cancer was to give them chemotherapy, and it was kind of a "one size fits all" approach to care. That has all really changed in the last few years with the development of some novel oral agents, specifically some agents we call EGFR TKIs.

Now, it is not a "one size fits all." It's more of an individualized or personalized approach to cancer care. In the case of EGFR TKIs, we are looking for something specific in the lung cancer. I tell patients this is a "switch" and, when turned on, it makes the cancer cells aggressive and behave the way we don't want them to behave.

This is what we mean by finding biomarkers on lung cancer: trying to discover does the patient's lung cancer harbour these switches, these mutations, or gene rearrangements? If we discover those, then we know that up-front therapy with one of these oral agents can be quite remarkable for those patients.

Back to the real world now. What does NICE have to say on the matter. Will we be allowed to prescribe afatinib therapy?

NICE National Institute for Health and Care Excellence

Afatinib for treating epidermal growth factor receptor mutation-positive locally advanced or metastatic non-small-cell lung cancer
NICE technology appraisal guidance [TA310] Published date: 23 April 2014

Afatinib is recommended as a possible treatment for adults with locally advanced or metastatic non-small-cell lung cancer if:

- their cancer tests positive for the epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation and
- they have not had a type of drug called an EGFR-TK inhibitor before.

The NHS list price, provided by the manufacturer, is £2023.28 per pack of 28 tablets (20 mg, 30 mg, 40 mg or 50 mg). The manufacturer stated that the NHS list price per course of treatment is expected to be around **£22,000 per patient**, based on a progression-free survival of 11 months. The manufacturer of afatinib has agreed a patient access scheme with the Department of Health in which a confidential discount is applied at the point of purchase or invoice. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

Learning review

- We have differential diagnosis and initial management for a patient with a red flag symptom
- We have undertaken staging investigations and co-factoring for a lung cancer patient
- We have considered use of biomarkers and their use as predictive assays that guide therapy in non-small cell lung cancer