Cambridge Oncology

Module 2 e-learning case 1
Cancer biology and targeted therapies

David Favara, NIHR academic clinical fellow in medical oncology
October 2020

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.

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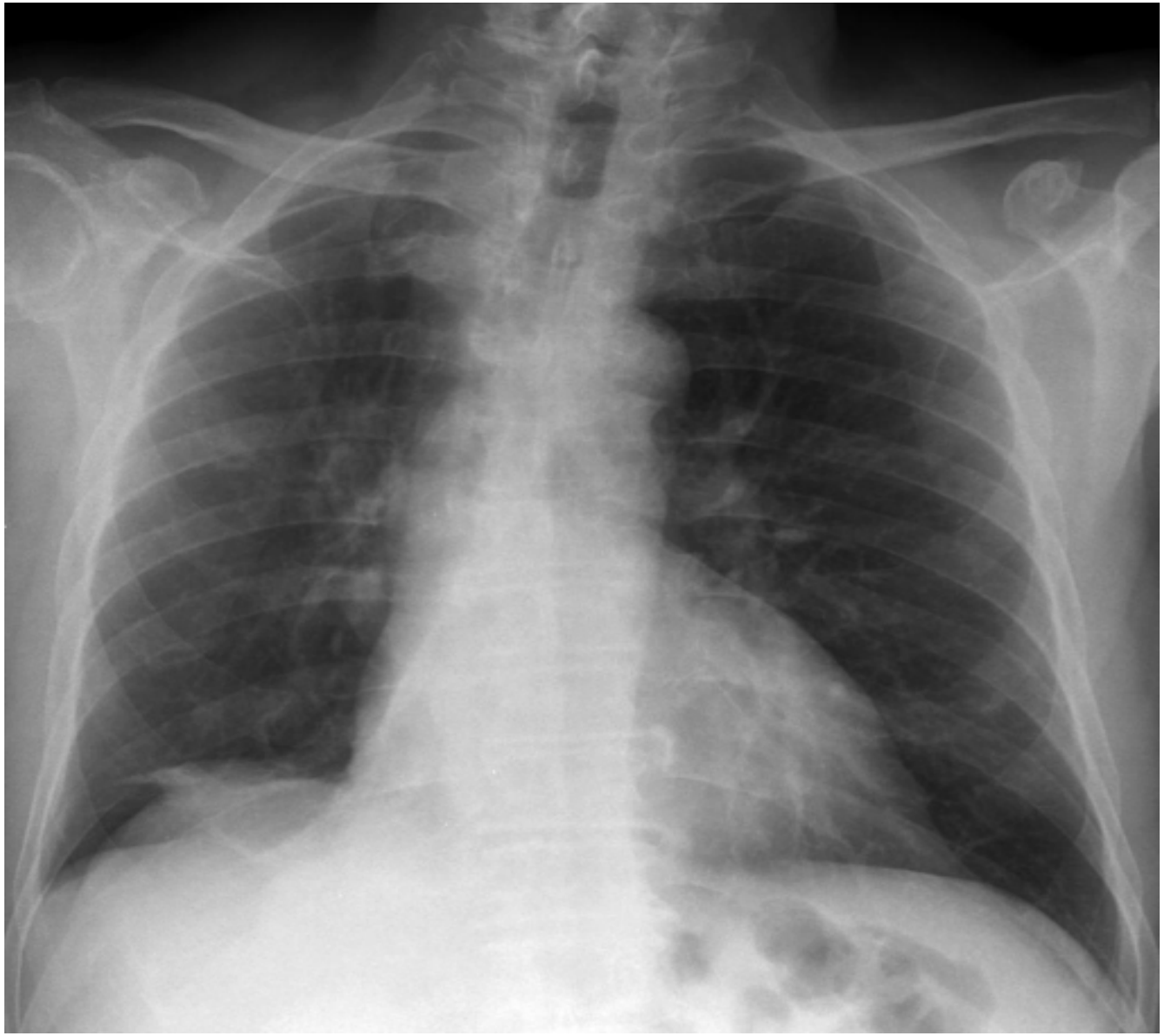
The GP sees her and comes up with a differential diagnosis. What would you consider on your differential?

- TB
- Pneumonia
- COPD
- Cardiac failure
- 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?

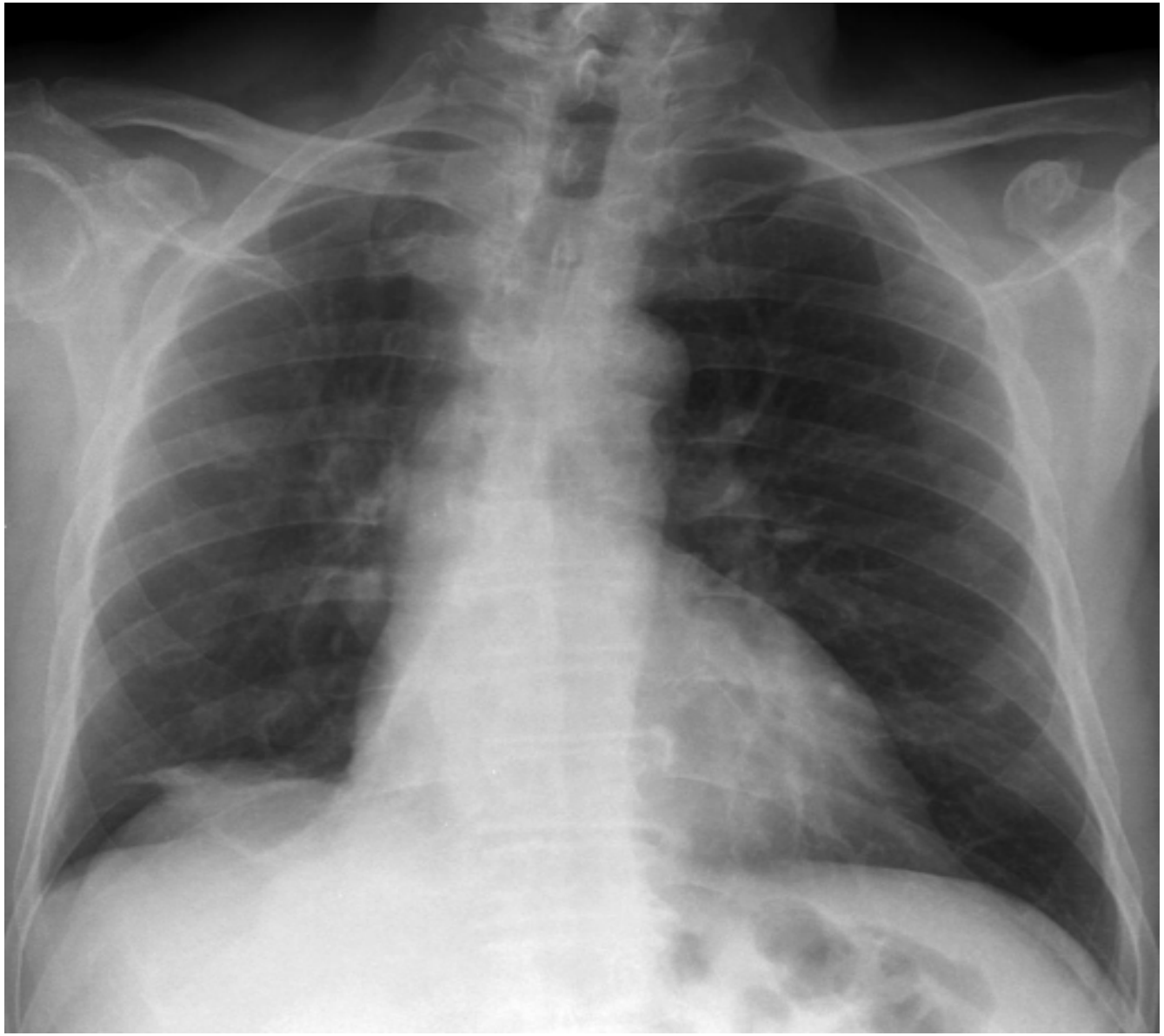


She is sent for a chest radiograph later the same day.

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 also 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

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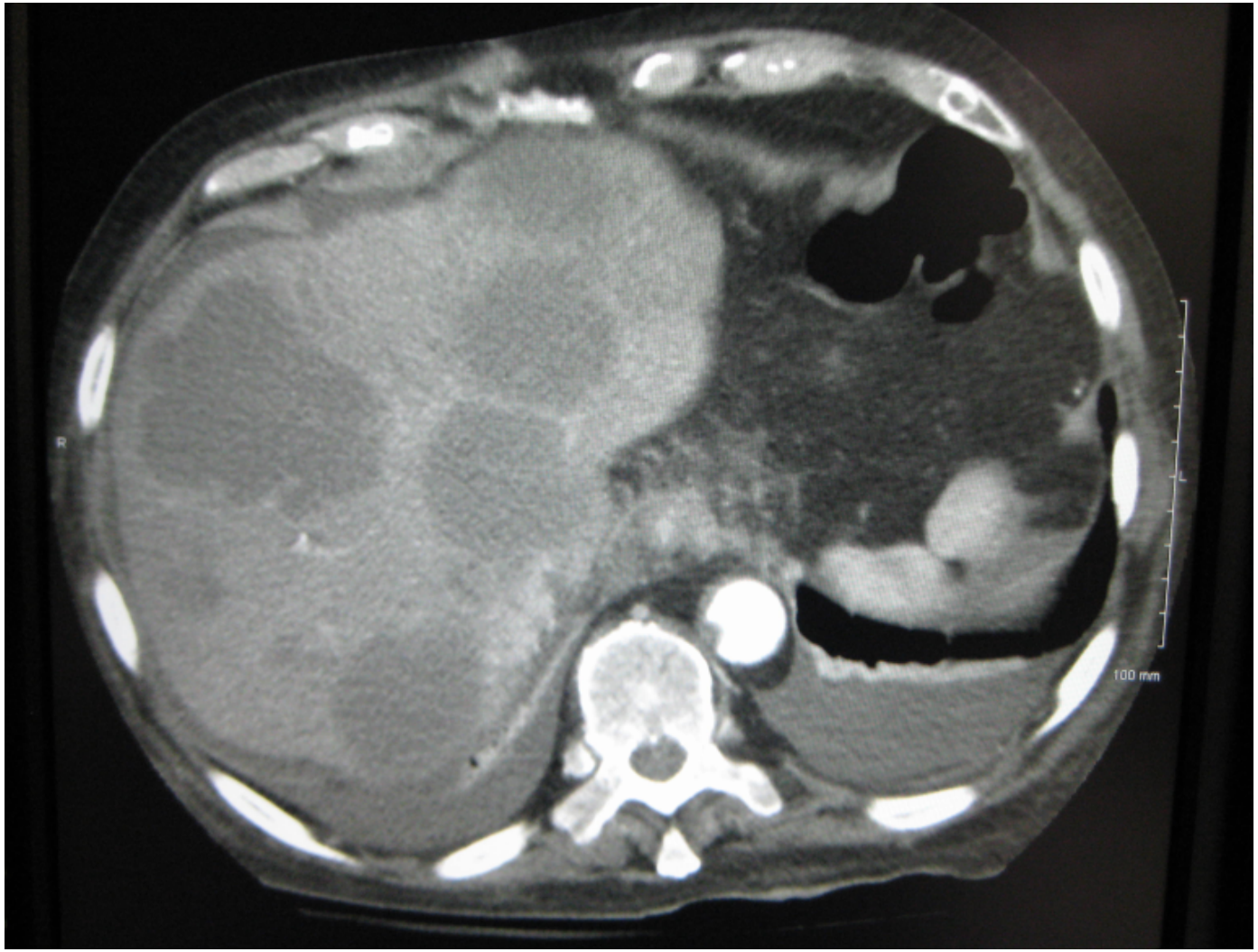
This is the CT scan of her liver…



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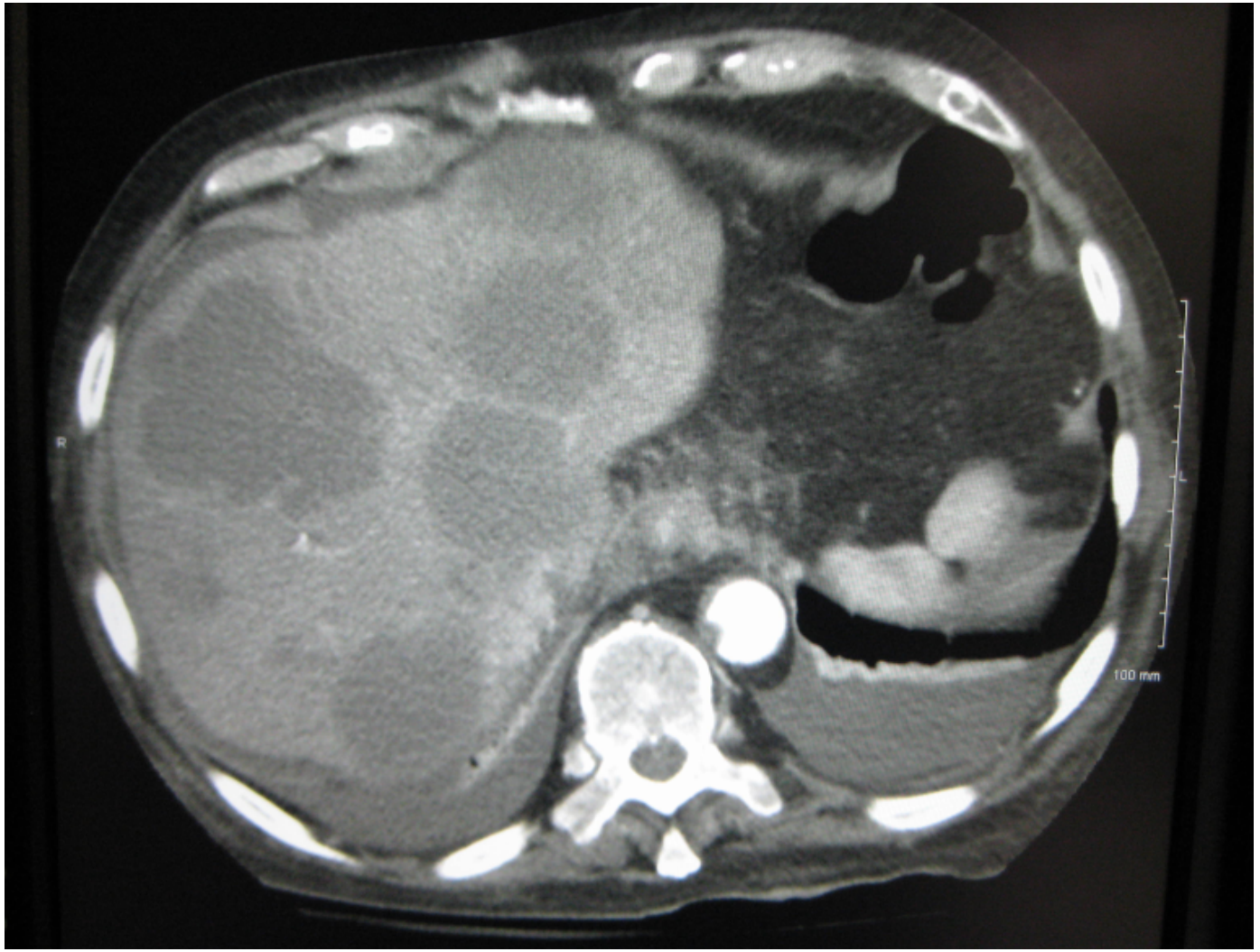
This is the CT scan of her liver…

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.

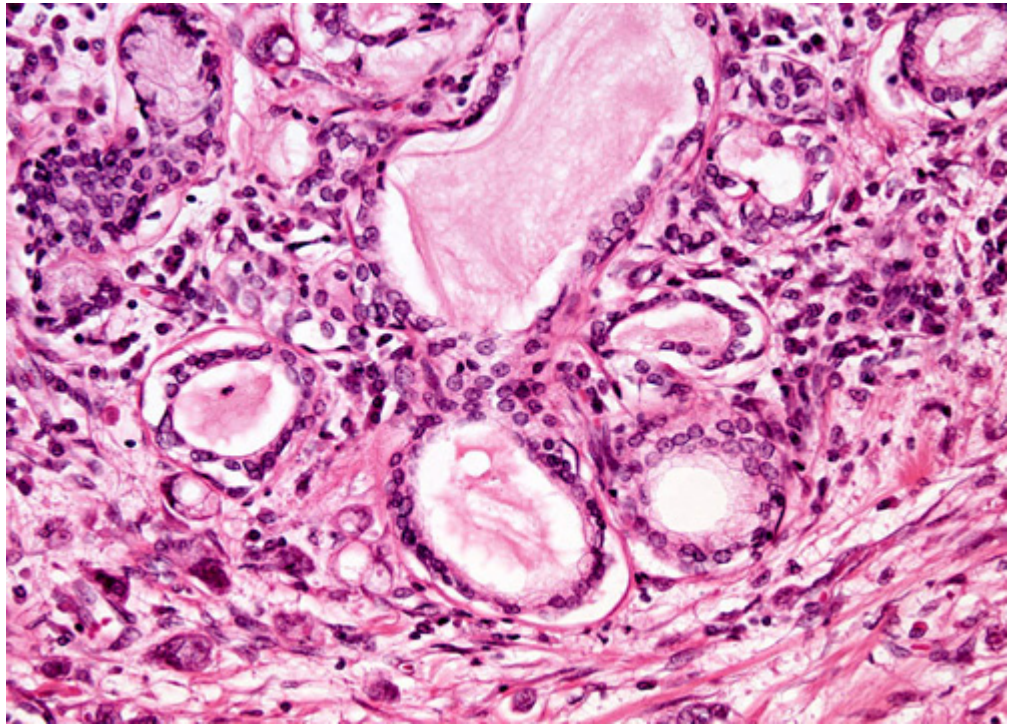
Immunohistochemistry showed the following

CK7 positive

CK20 negative

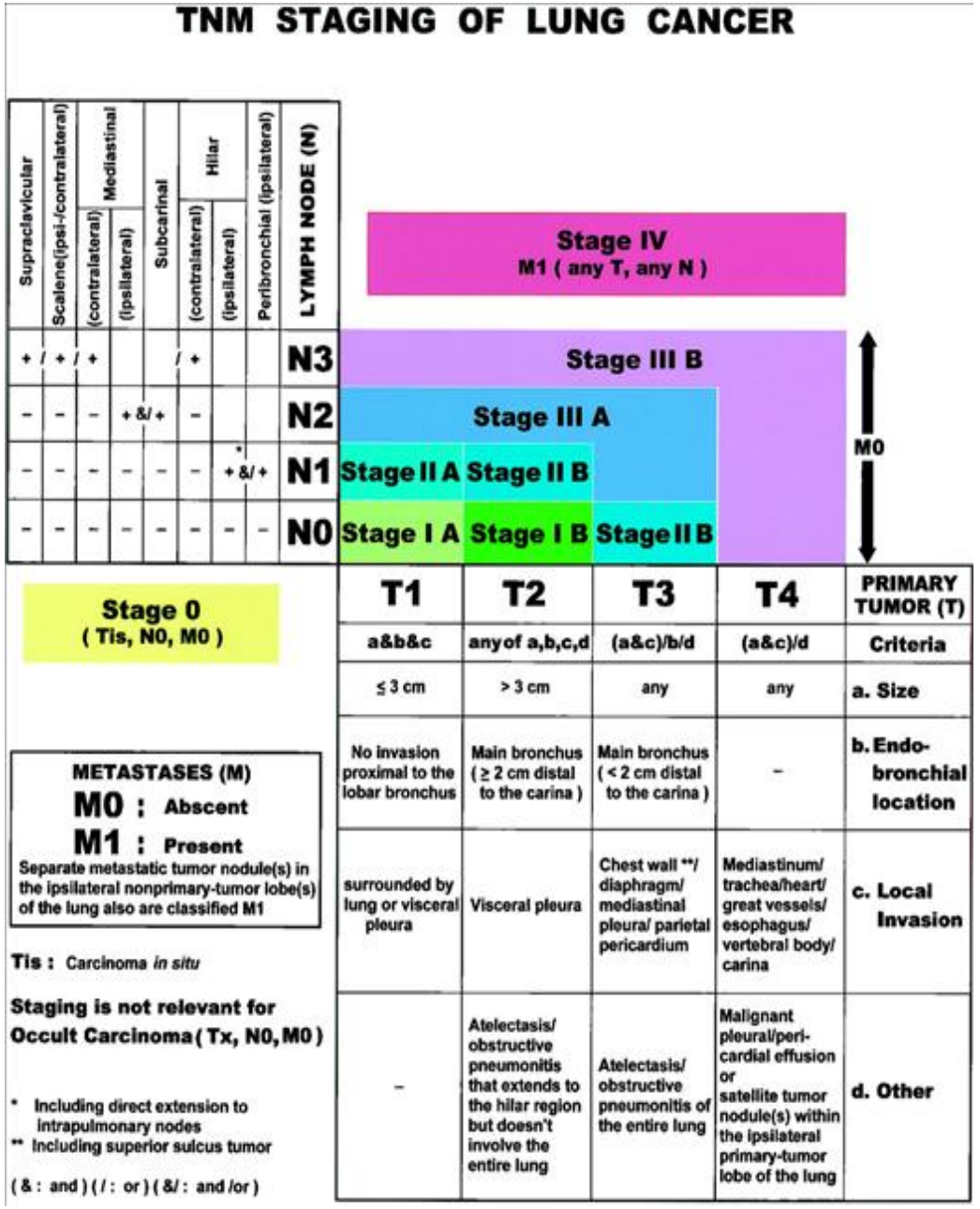
TTF1 positive

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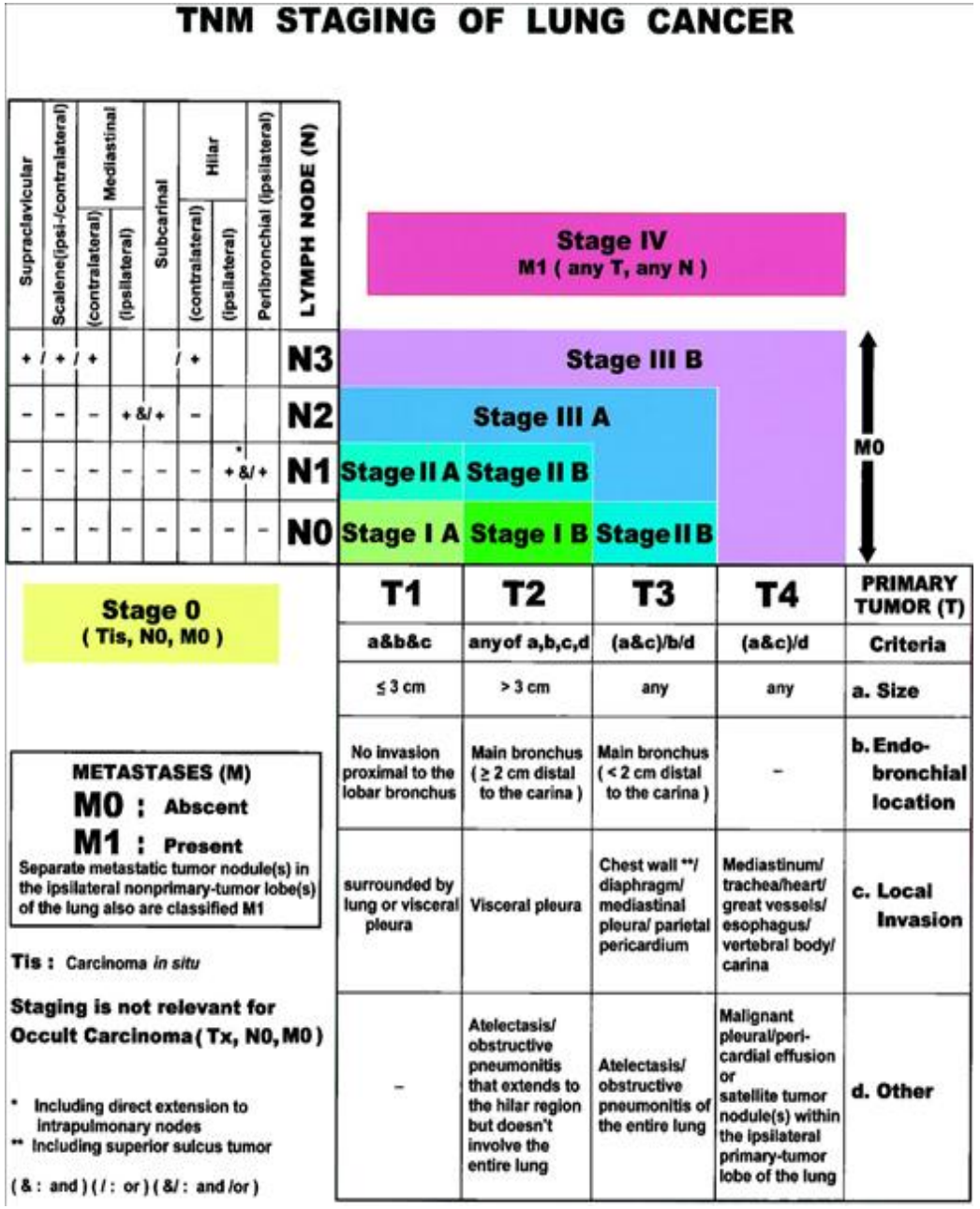
Is it consistent with non-small cell lung cancer (adenocarcinoma)

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

Staging is **pT1 N3 M1**, which is stage 4 lung cancer

The summary we have so far tells us about the clinical stage of the cancer.

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



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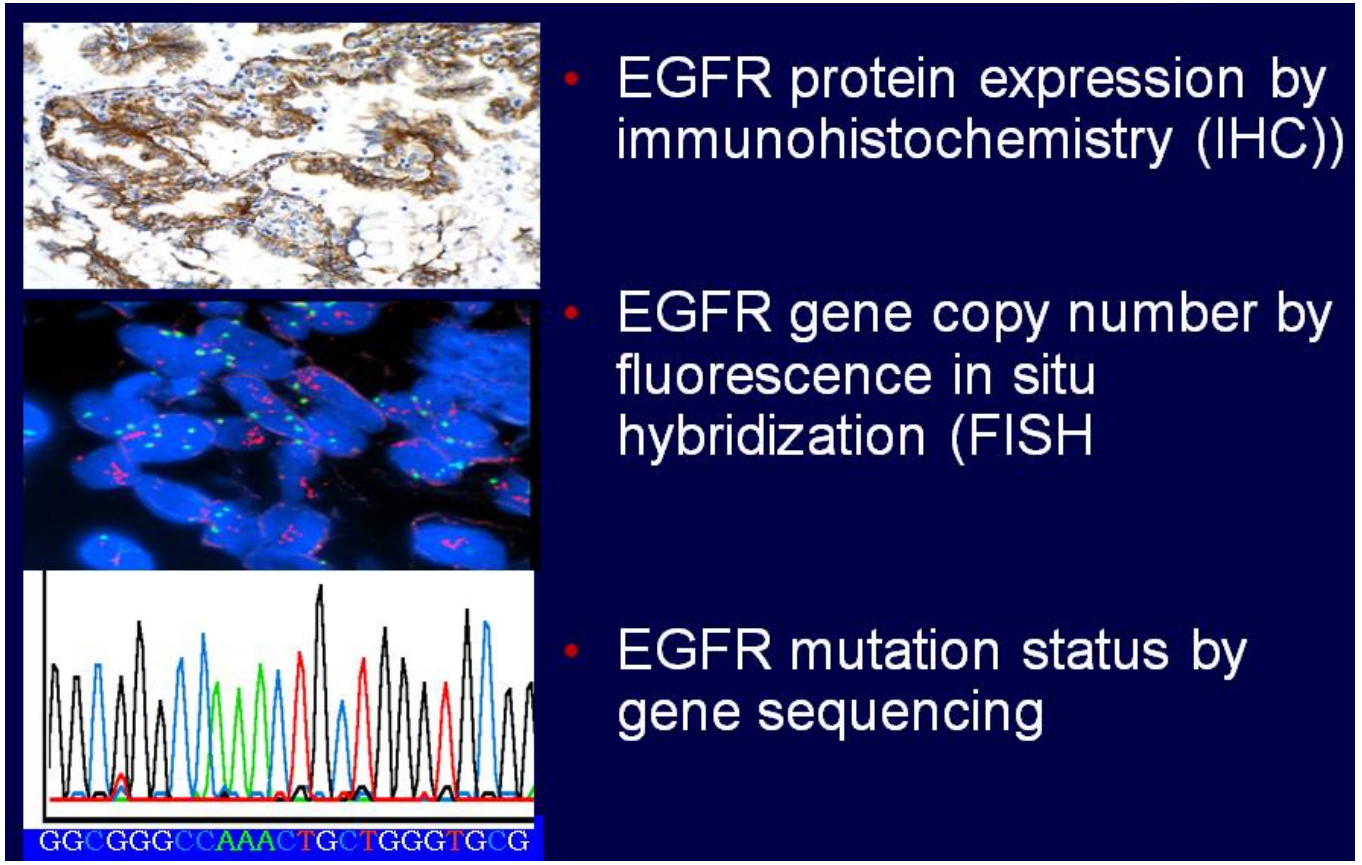
Molecular profiling of the tumour:

- Done in order to detect mutations that can guide therapy (ie EGFR and ALK)

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

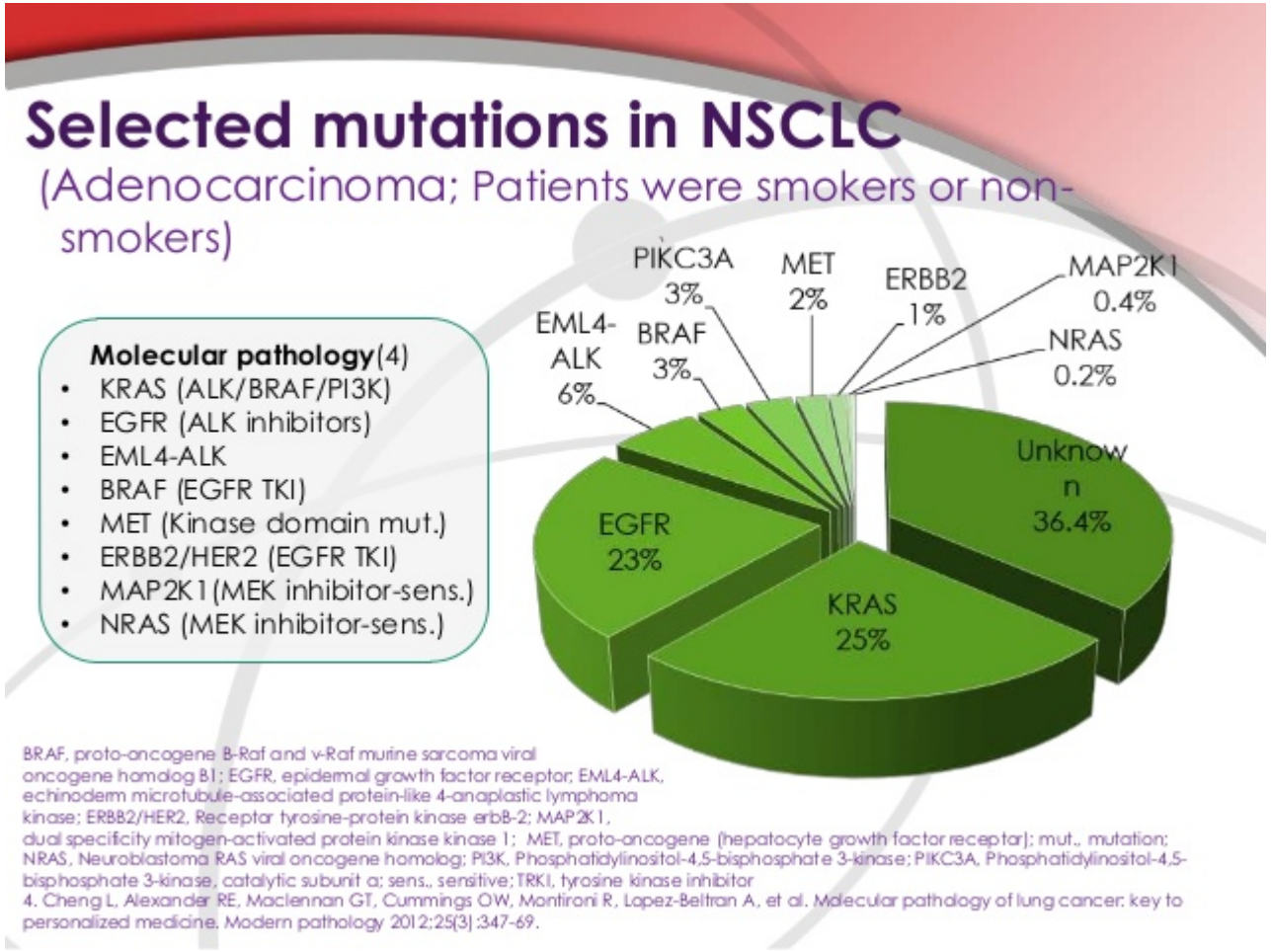


She has to stay in hospital for a few days after her biopsy due to bleeding complications but makes a full recovery.

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

Tumour is positive for EGFR point mutation **L858R**

What are her treatment options?



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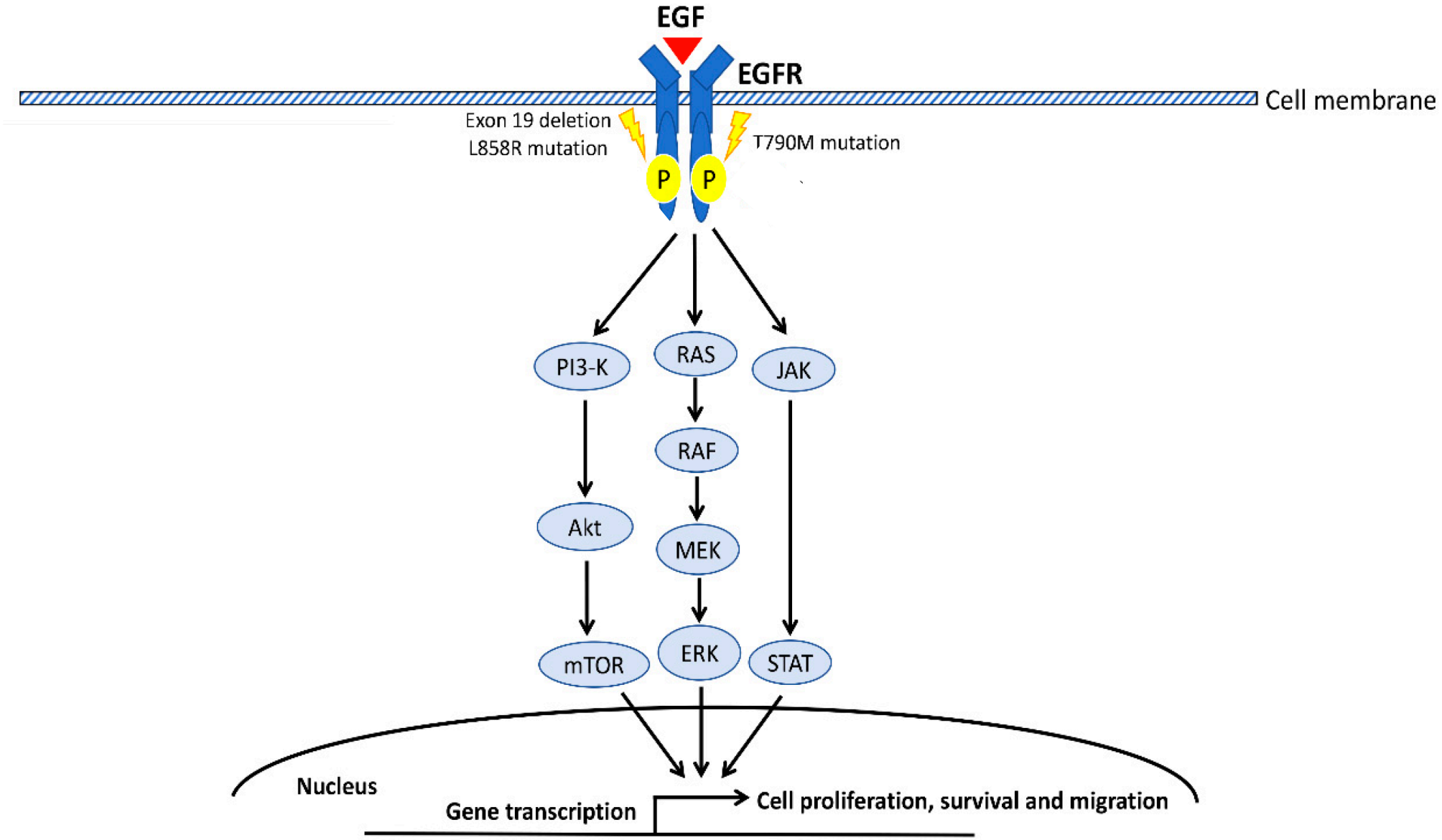

Modified from *Hsu et al. Int. J. Mol. Sci. 2019, 20(15), 3821*

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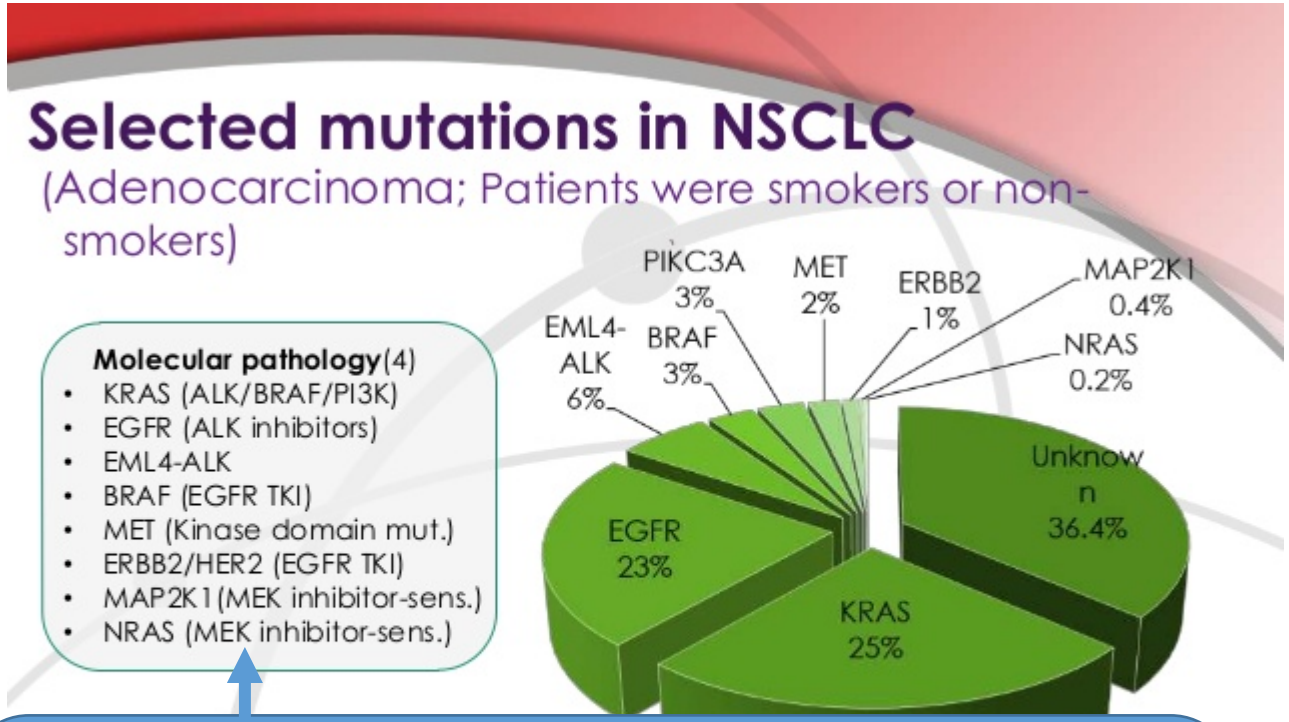
What are her treatment options?

- Conventional chemotherapy?
- Targeted therapy with an EGFR inhibitor?
- Immunotherapy?
- Best supportive care?

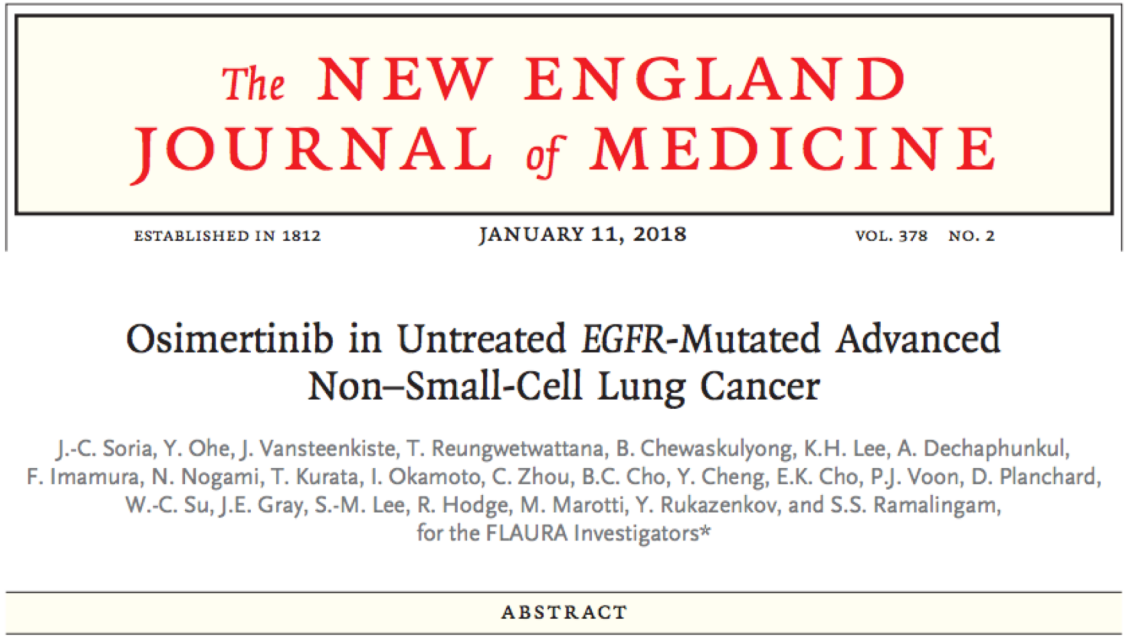


Predictive assays : These molecular pathology tests are looking for mutations in targetable cancer pathways, and are predictive of response to a specific therapy.

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

The consultant is away on leave and you are asked to see the patient.

You do a few searches using Pubmed and Google and find the following NEJM paper (11/01/2018):



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 11, 2018 VOL. 378 NO. 2

Osimertinib in Untreated *EGFR*-Mutated Advanced Non–Small-Cell Lung Cancer

J.-C. Soria, Y. Ohe, J. Vansteenkiste, T. Reungwetwattana, B. Chewaskulyong, K.H. Lee, A. Dechaphunkul, F. Imamura, N. Nogami, T. Kurata, I. Okamoto, C. Zhou, B.C. Cho, Y. Cheng, E.K. Cho, P.J. Voon, D. Planchard, W.-C. Su, J.E. Gray, S.-M. Lee, R. Hodge, M. Marotti, Y. Rukazenkov, and S.S. Ramalingam, for the FLAURA Investigators*

ABSTRACT

Soria et al. N Engl J Med . 2018 Jan 11;378(2):113-125.

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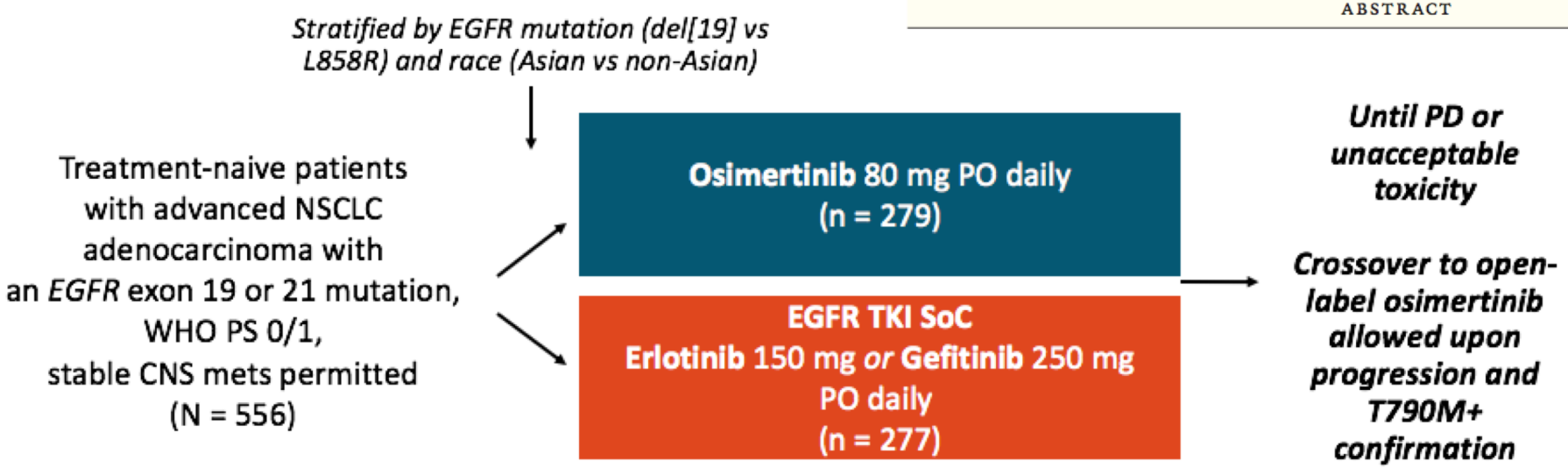
ABSTRACT

- Double-blind phase III study



- Primary endpoint: investigator-assessed PFS (RECIST v1.1)
- Secondary endpoints including ORR, DoR, DCR, depth of response, OS, PRO, safety

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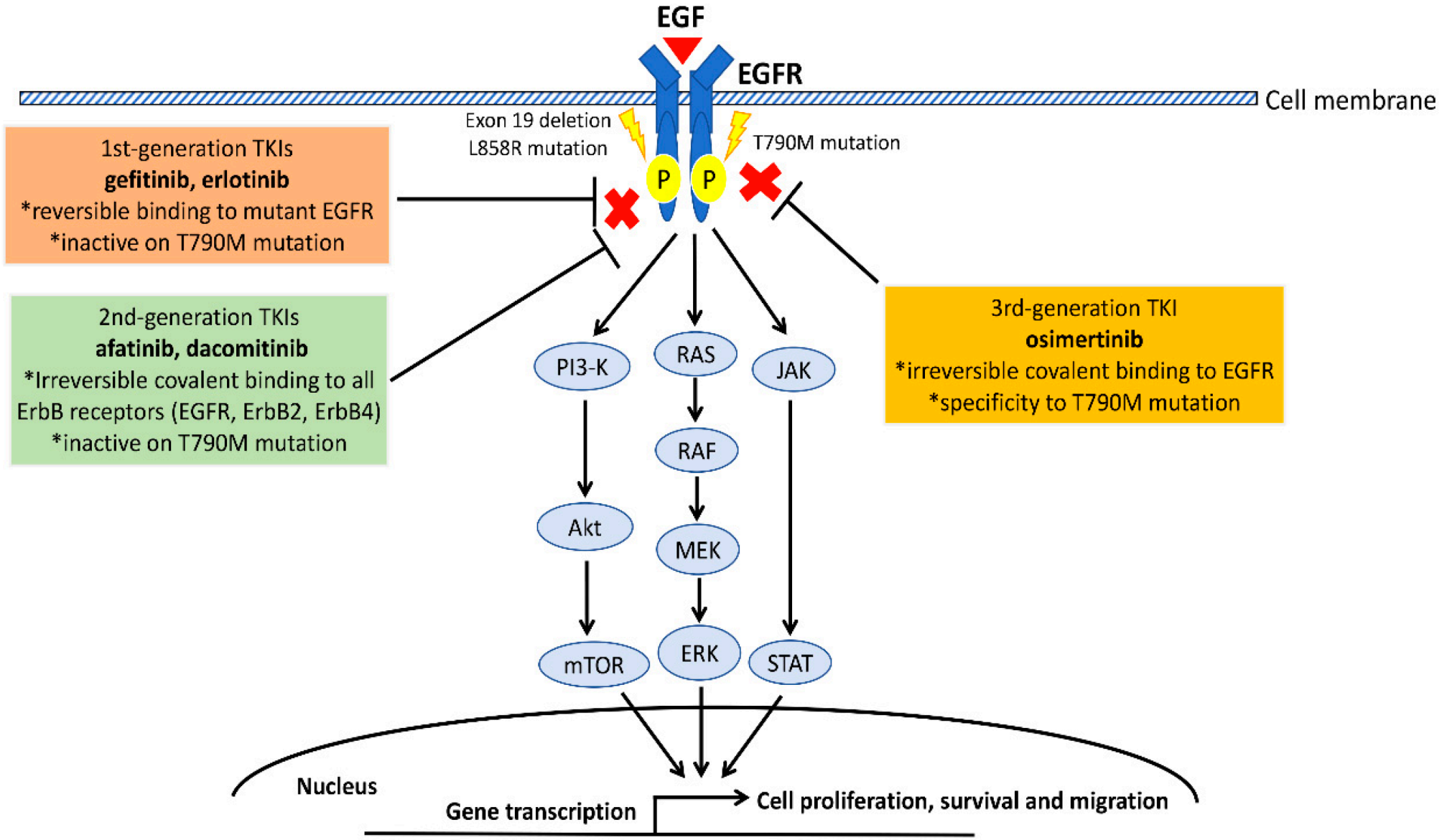

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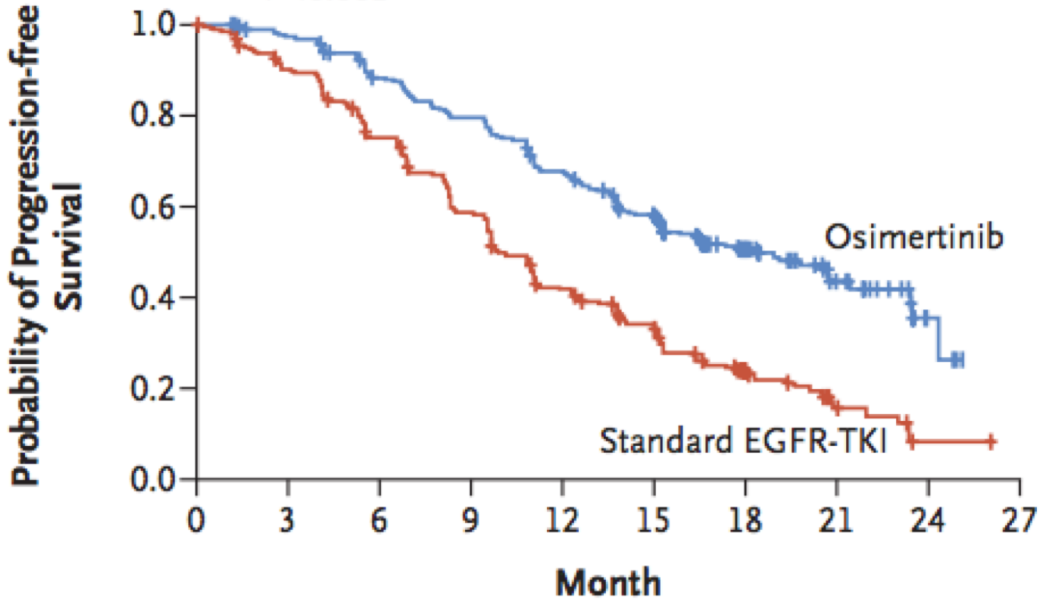
A Progression-free Survival in Full Analysis Set

	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Osimertinib	279	18.9 (15.2–21.4)
Standard EGFR-TKI	277	10.2 (9.6–11.1)

Hazard ratio for disease progression or death, 0.46 (95% CI, 0.37–0.57)
P<0.001



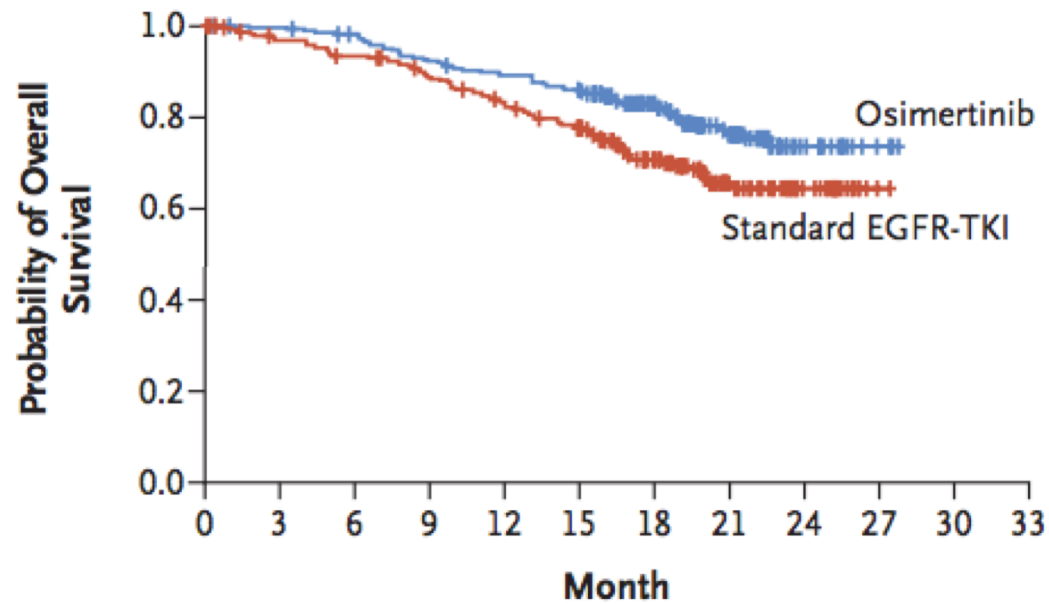
No. at Risk

Osimertinib	279	262	233	210	178	139	71	26	4	0
Standard EGFR-TKI	277	239	197	152	107	78	37	10	2	0

D Overall Survival

	No. of Patients	Median Overall Survival (95% CI)
		mo
Osimertinib	279	NC (NC–NC)
Standard EGFR-TKI	277	NC (NC–NC)

Hazard ratio for death, 0.63 (95% CI, 0.45–0.88)
P=0.007



No. at Risk

Osimertinib	279	276	269	253	243	232	154	87	29	4	0	0
Standard EGFR-TKI	277	263	252	237	218	200	126	64	24	1	0	0

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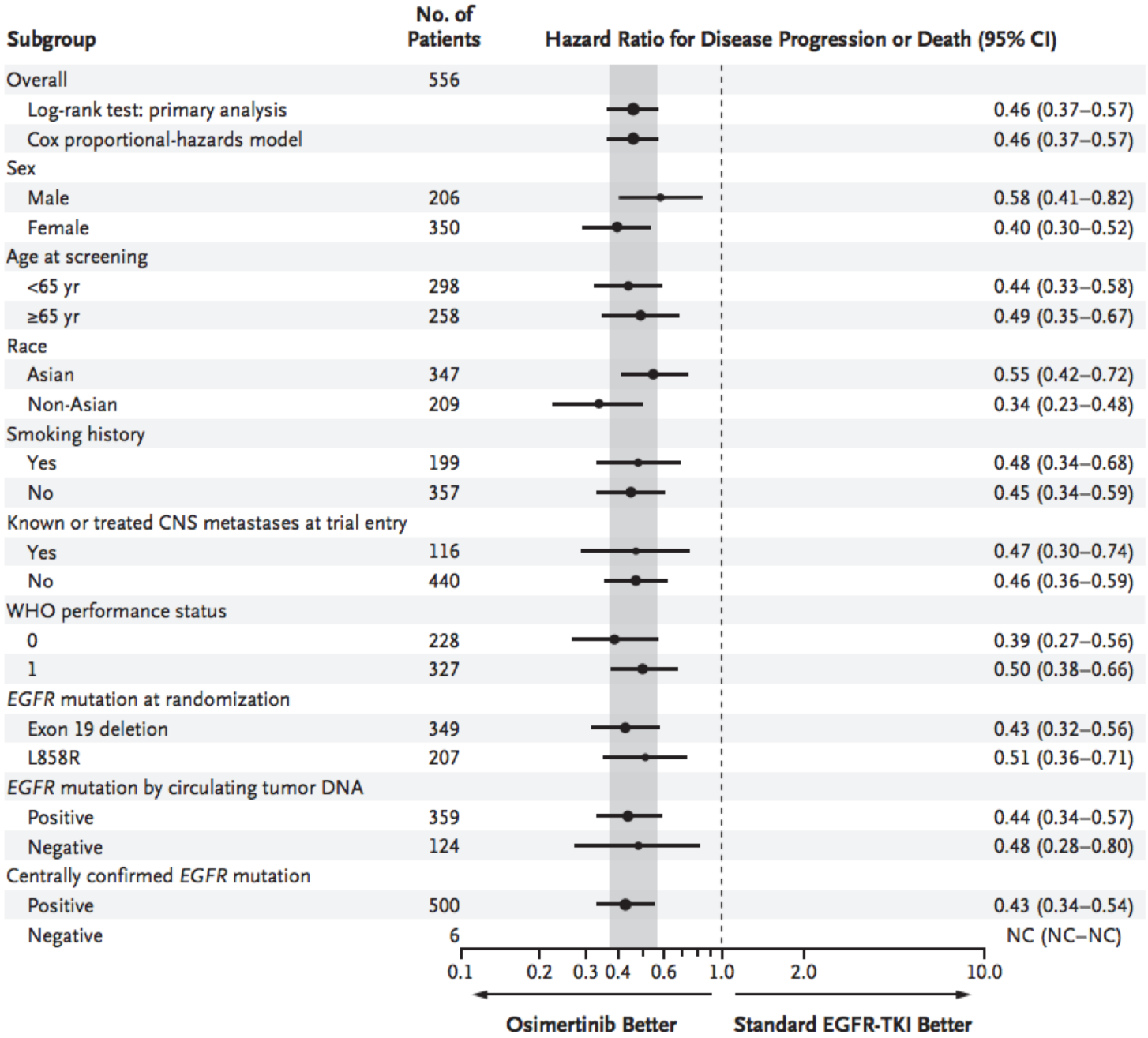

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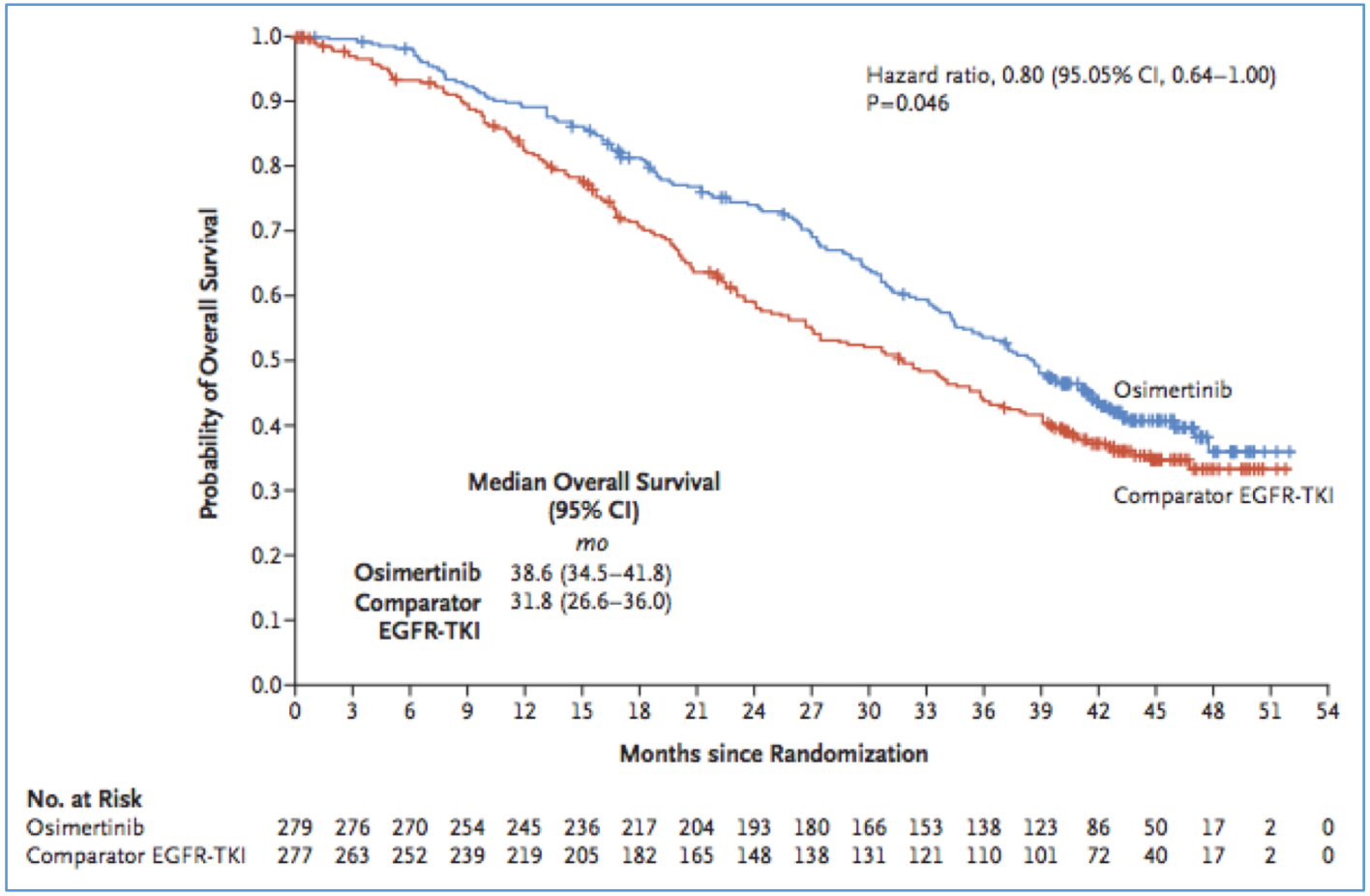
Some more searching leads you to a more recent NEJM paper from the same study: (02/01/2020)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Overall Survival with Osimertinib in Untreated, *EGFR*-Mutated Advanced NSCLC

S.S. Ramalingam, J. Vansteenkiste, D. Planchard, B.C. Cho, J.E. Gray, Y. Ohe, C. Zhou, T. Reungwetwattana, Y. Cheng, B. Chewaskulyong, R. Shah, M. Cobo, K.H. Lee, P. Cheema, M. Tiseo, T. John, M.-C. Lin, F. Imamura, T. Kurata, A. Todd, R. Hodge, M. Saggese, Y. Rukazenkov, and J.-C. Soria, for the FLAURA Investigators*



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

NICE National Institute for Health and Care Excellence

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Osimertinib for untreated EGFR mutation-positive non-small-cell lung cancer

Technology appraisal guidance [TA654] Published date: 14 October 2020

Osimertinib is recommended, within its marketing authorisation, as an option for untreated locally advanced or metastatic EGFR mutation-positive NSCLC in adults. It is recommended only if the company provides osimertinib according to the commercial arrangement.

Price

The price is £5,770 for 80 mg and 40 mg osimertinib (pack of 30 tablets, excluding VAT; BNF online, accessed August 2020). The company has a commercial arrangement that makes osimertinib available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

Chief Scientific Officer; Director, Lung Cancer Research Program, Sarah Cannon Research Institute

David Spigel MD 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.

Learning review

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