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# Progress in *EGFR*-mutant NSCLC: Where are we going?

## Transcript from a touchEXPERT OPINIONS

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# THE EXPERTS

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*Launch date: 07 December 2020*

# INTRODUCTION

Watch leading non-small cell lung cancer (NSCLC) experts discuss the current standard and the latest advancements in epithelial growth factor receptor (EGFR)-targeted therapy.

## LEARNING OBJECTIVES

**After watching this touchEXPERT OPINIONS, you should be better able to:**

- Describe the rationale for and clinical trial data associated with combination therapy in first-line *EGFR*-mutant NSCLC
- Describe the mechanisms of resistance to third-generation EGFR-TKIs and strategies to manage drug resistance in the
- second-line setting
- Recall data on emerging therapeutic strategies for early-stage *EGFR*-mutant NSCLC and how this may impact the metastatic treatment landscape

## TOPICS DISCUSSED

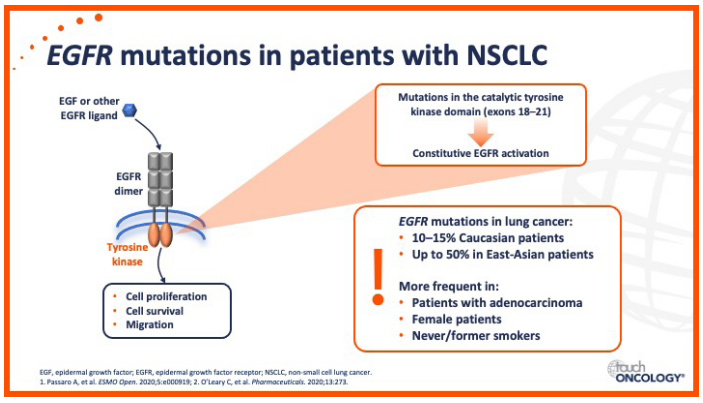
- Are combination strategies the way forward for *EGFR*-mutant NSCLC?
- How will acquired resistance drive treatment choices in *EGFR*-mutant NSCLC?
- How do recent data in early-stage NSCLC impact the current treatment pathway for *EGFR*-mutant NSCLC?

## ARE COMBINATION STRATEGIES THE WAY FORWARD FOR *EGFR*-MUTANT NSCLC?

**Dr Raffaele Califano:** Hello. My name is Raffaele Califano. I'm a consultant medical oncologist at the Christie Hospital in Manchester, UK.

### Is conventional EGFR-TKI monotherapy the best strategy as first-line treatment for NSCLC?

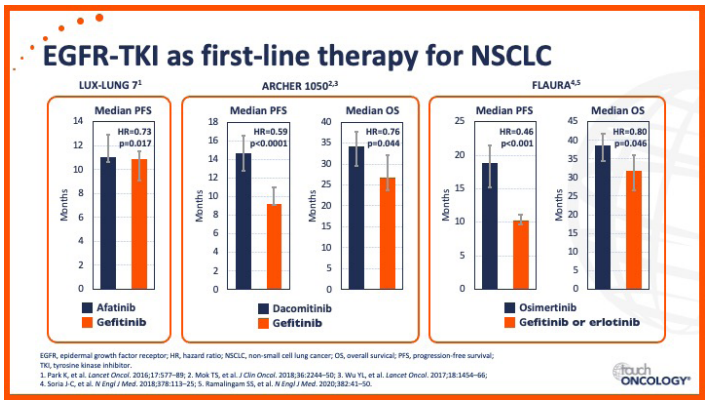
The discovery of epidermal growth factor receptor (*EGFR*)-activating mutations and the use of EGFR tyrosine kinase inhibitors (TKI) has certainly revolutionized the natural history of non-small cell lung cancer (NSCLC) patients. We know that *EGFR* activating mutations happen on the tyrosine kinase domain of the *EGFR* and they are most common on exon 18 to 21. These are present in about 10% of patients with Caucasian ethnicity and up to 50% of patients with East Asian ethnicity. Most commonly these patients are female, have adenocarcinoma histology and are never or light smokers.



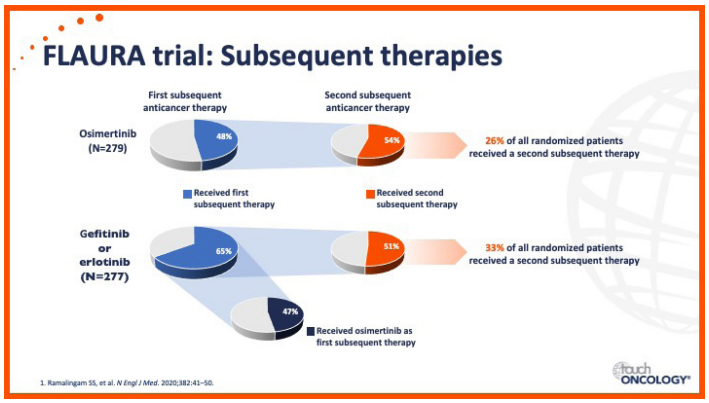

Historically, several trials have compared standard platinum-based chemotherapy versus EGFR-TKIs such as gefitinib, erlotinib and afatinib and they have consistently shown that EGFR-TKIs performed better in terms of response rate, progression-free survival and quality of life, when compared against standard chemotherapy. Later on, a number of clinical trials have evaluated EGFR TKIs head to head. The recently reported trials are, for example, the LUX-LUNG 7 trial, where afatinib was compared against gefitinib and demonstrated a slight advantage in progression-free survival.

More recently, the ARCHER 1050 study evaluated dacomitinib versus gefitinib and demonstrated a longer progression-free survival and also a longer overall survival favouring dacomitinib, and I would like to remind you that the ARCHER 1050 study did not allow patients with brain metastases.

Very recently, the FLAURA study evaluated osimertinib, which is a third-generation EGFR-TKI, versus gefitinib or erlotinib in the first-line setting and demonstrated that osimertinib determined a longer progression-free survival, but also a longer overall survival compared to first-generation EGFR TKIs.



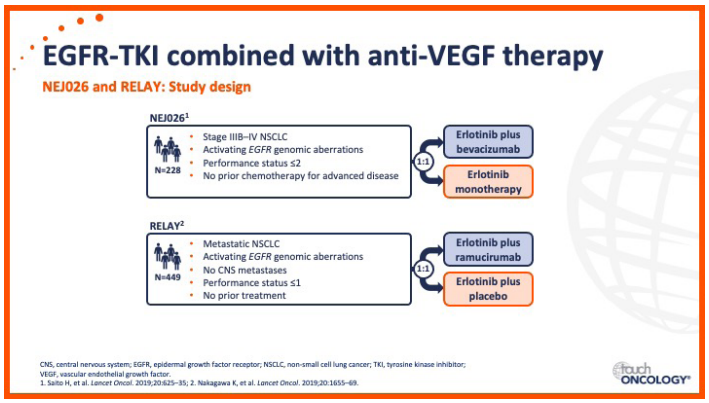

On the basis of this data now, first-line, single-agent EGFR-TKIs represent the standard of care and osimertinib is the most commonly used first-line therapy. Despite the higher response rate and despite the long progression-free survival, all these patients will progress at some point. We know that about 50 or 60% of the patients will be able to receive second-line therapy. For this reason, there is an urgent need to improve the efficacy of first-line therapies. We're going to have a look at different strategies that can maximize the impact of first-line therapies for these patients.




### Can we improve outcomes using combination EGFR-TKI plus VEGF inhibitors?

One of the first strategies that looked at improving the efficacy of first-line treatment for *EGFR*-mutant advanced NSCLC is the combination of an EGFR-TKI with anti-vascular endothelial growth factor (VEGF) therapy and two large phase three clinical trials have been reported so far.

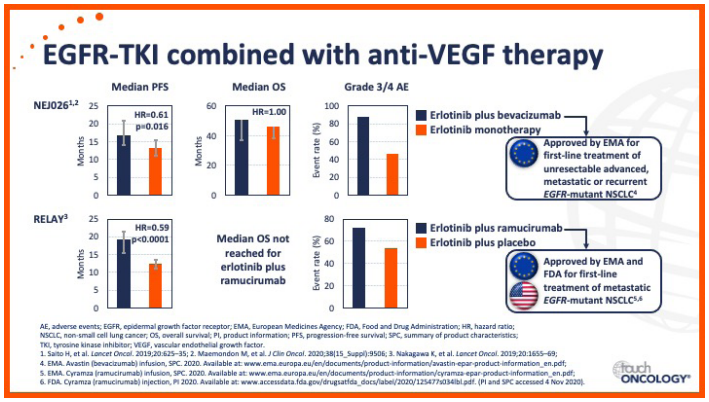
The first trial is the NEJ026, which is an East Asian study where patients were randomized between erlotinib monotherapy and erlotinib plus bevacizumab. Another study is the RELAY trial, which was more recently reported, in which patients were randomized between erlotinib plus placebo or erlotinib plus ramucirumab.




Both trials had progression-free survival as a primary endpoint and both trials showed an improvement in progression-free survival for the combination of EGFR TKI plus anti-angiogenic agents, but there was no improvement in overall survival.

What is important to bear in mind is that the combination of the EGFR-TKI and the anti-VEGF therapy also had an increased incidence of grade 3 or 4 adverse events. In particular, there was an increased incidence of bleeding, hypertension, or liver function test derangement.

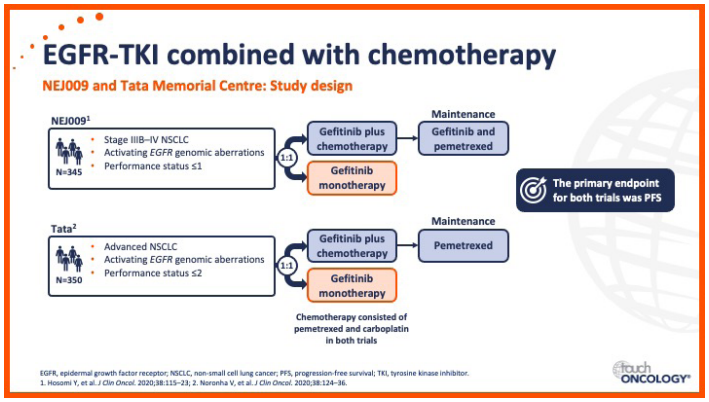
On the basis of the NEJ026 trial and the RELAY trial, the EMA has approved erlotinib plus bevacizumab and erlotinib plus ramucirumab as a first-line strategy for patients with *EGFR*-mutant advanced NSCLC.




## Should chemotherapy be combined upfront with EGFR-TKI?

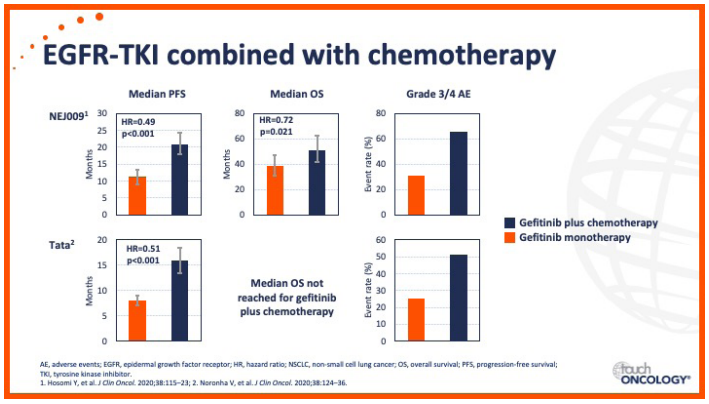
Another fascinating strategy is the combination of platinum-based chemotherapy plus an EGFR-TKI. The rationale is that you can suppress at the same time the tumour clones which are sensitive to EGFR suppression, but also the tumour clones which are not sensitive and therefore they will be addressed by chemotherapy.

Two recent studies have been presented. They are both large phase III randomized clinical trials. The first is the NEJ009, which is an East Asian study. The other one is an Indian study. They had a very similar design but with some differences. They both randomized patients with stage IV NSCLC and common activating mutations to receive gefitinib as monotherapy or the combination of gefitinib plus platinum pemetrexed chemotherapy, with a maintenance option of gefitinib and pemetrexed in the NEJ009 or single-agent pemetrexed in the Indian study. Both studies had progression-free survival as a primary endpoint, but importantly, the Indian study also included patients with a performance status of 2.




What these studies showed is that the combination of chemotherapy and the EGFR TKI increases progression-free survival and also increases overall survival when compared to single agent. This efficacy comes with a cost. In fact, the combination arm in both studies demonstrated an increase in the incidence of grade 3 and 4 toxicity, in particular haematological toxicity and this is due to the addition of chemotherapy.

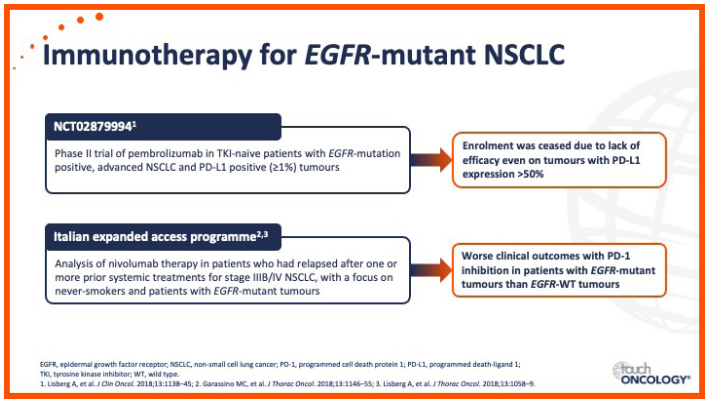
Certainly, the strategy is very interesting at present. The combination of chemotherapy and EGFR-TKI remains investigational, and I think it will be very important to see the results of the FLAURA 2 study, which is an ongoing study evaluating osimertinib plus or minus platinum-based chemotherapy and the study should read out over the next couple of years.




## Is there a role for immune checkpoint inhibitors in the treatment of newly-diagnosed patients with *EGFR*-mutant NSCLC?

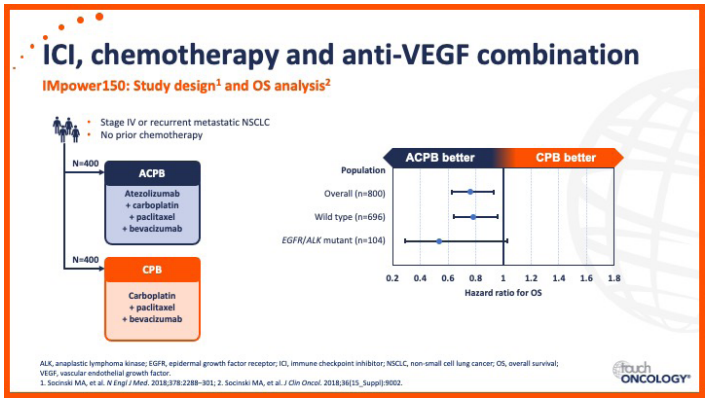
What about the role of immune checkpoint blockade in these patients? Well, we know from retrospective studies, meta-analyses and also

from prospective data that it seems that immune checkpoint blockade is less active in patients with *EGFR* activating mutations when compared to standard chemotherapy. For example, in the Lisburg study, in those patients who were untreated, had a PD-L1 expression of at least 1% and were *EGFR*-mutant and who received pembrolizumab as a first line treatment, there was no response rate and the progression-free survival was very short. We also know from a number of international studies that patients with *EGFR*-mutant advanced NSCLC, when treated with immune checkpoint blockade, they have a poor prognosis and poor outcome when compared to historical controls with standard chemotherapy.




Another worry in the EGFR space with immunotherapy is the potential increased risk of adverse events when you sequence immune checkpoint blockade and a TKI. In particular, there have been reports of increased risk of adverse events such as pneumonitis or other immunotherapy-related toxicities. So at present this strategy remains investigational and is not approved in clinical practice.

The only clinical trial evaluating immune checkpoint blockade in the chemo-naive population is the IMpower150 study, which evaluated patients who were untreated from a chemotherapy perspective, but they also included patients with an *EGFR* activating mutation or anaplastic lymphoma kinase (*ALK*) rearrangement. In the small subgroup of patients with *EGFR* activating mutations who received the quadruplet-carboplatin, paclitaxel, bevacizumab, and atezolizumab, there was a trend towards a longer overall survival favouring the quadruplet over the triplet. This may be a signal of efficacy of combination of chemotherapy, immunotherapy and anti-angiogenic agents in this setting. When you look at the data, this does not reach statistical significance and therefore the data in my opinion remains hypothesis-generating, but this is certainly an approved option in the post-TKI setting for chemo-naive patients.

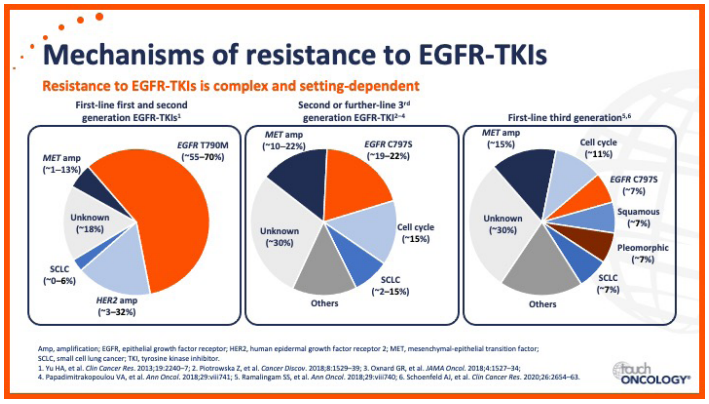



## HOW WILL ACQUIRED RESISTANCE DRIVE TREATMENT CHOICES IN *EGFR*-MUTANT NSCLC

**Dr Lecia Sequist:** Hi. I'm Lecia Sequist from Massachusetts General Hospital Cancer Center in Boston, Massachusetts.

### What are the most common resistance mechanisms following first-line EGFR-TKI therapy?

The pattern of resistance after frontline EGFR-TKI use depends on which EGFR-TKI was given. For many years, the mainstays of our frontline treatment was either a first- or second-generation EGFR-TKI, and the resistance pattern tends to be fairly similar in either case, in that the vast majority of resistance is due to a single mechanism, the T790M point mutation in the gatekeeper location. There were also a minority in the 5% to 10% range of resistance mechanisms in that era that included things like mesenchimal-epithelial transition factor (*MET*) amplification, small cell transformation and other bypass pathways, like human epidermal growth factor receptor (*HER*)2 and B-Raf proto-oncogene (*BRAF*).



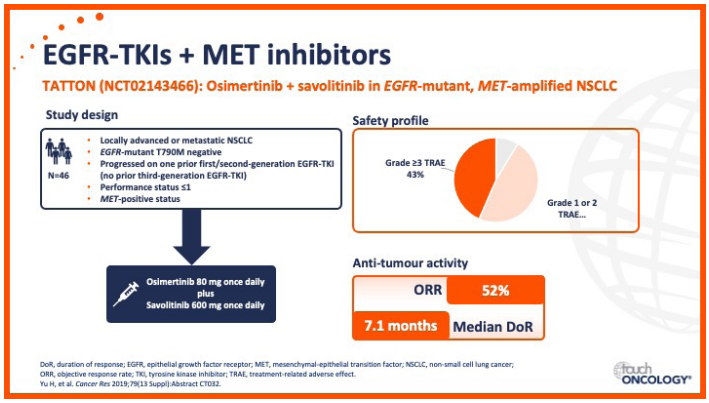

What we've seen in the past couple of years as practice patterns have shifted and now third-generation EGFR-TKIs are being used in the frontline setting, is that resistance after frontline treatment has also shifted, mainly because that dominant, that most common mechanism of resistance in the past, T790M is no longer a type of resistance that comes

up with third-generation drug use. That's because the third-generation drugs like osimertinib and others in that family, block T790M very actively. Therefore, T790M is no longer a resistance mechanism that we see after frontline treatment. Instead, and the data here is still emerging as patients are slowly starting to progress, what we are seeing as a picture after first-line use of drugs like osimertinib is that the resistance mechanisms focus more on the other mechanisms that used to be more rare. We're seeing more *MET* amplification and more small cell lung cancer transformation than we used to see with the older drugs. There's a new mechanism in *EGFR* at the binding site for the third-generation drugs, which is called C797S. We do see that in a small portion of patients as well and we see some bypass tracks like various fusions, *BRAF* mutations, *HER2* amplification. It's a whole smorgasbord. This is part of the reason why biopsying is so important to do.

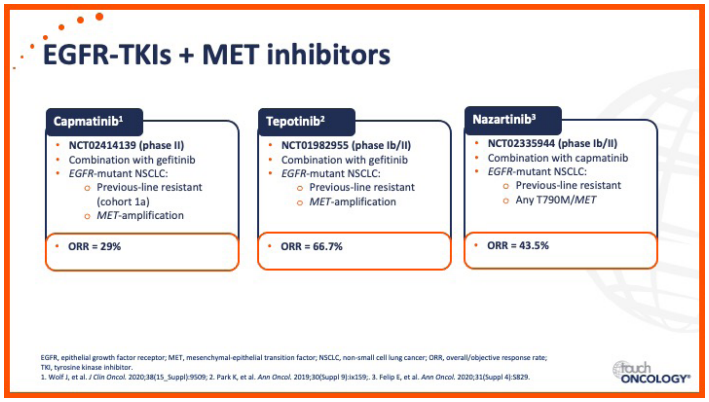
## How do you approach a patient who has a targetable mutation following first-line osimertinib?

I think it's really important to investigate what the mechanism of resistance might be for a patient who is progressing on first-line osimertinib. I typically try to do an invasive tissue biopsy on all patients, rather than a liquid biopsy, because things like small cell transformation cannot be assessed using liquid biopsy.

When you have the results back, I think one of the more actionable resistance mutations that you may find is *MET* amplification. This happens in somewhere between 20 to 30% of patients after first-line osimertinib. *MET* amplification is a bypass pathway, and we've seen, going back over 10 years, there's preclinical evidence that with this mechanism of resistance, if you block both *MET* and *EGFR* simultaneously, the tumours can respond. Now, we've seen that in the clinic as well. The TATTON study which was published earlier this year is really the first definitive proof of this concept, where patients who were resistant because of *MET* amplification and were treated with the MET inhibitor savolitinib and the EGFR inhibitor osimertinib could respond to a combination targeted therapy. To follow up on this data, there are other ongoing studies.



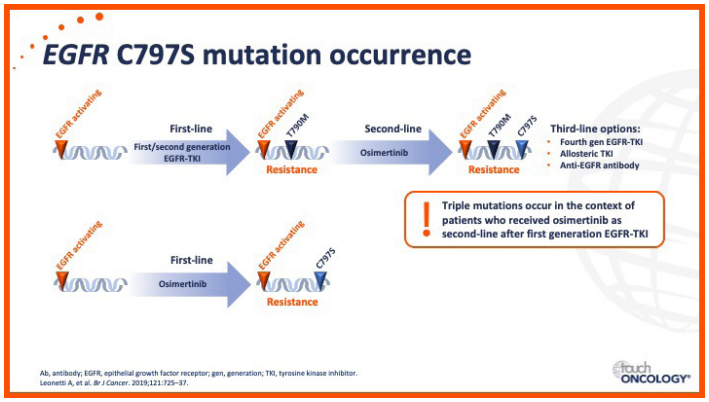

One thing you can do, if you find a patient with *MET* amplification as their resistance mechanism, is try to get them onto an ongoing study. There are studies of the combination of osimertinib and savolitinib that are being done to further characterize this combination. In addition, combinations of EGFR inhibitors with other MET inhibitors are ongoing, such as capmatinib, tepotinib and nazartinib.




## What is the significance of C797S mutation after treatment with osimertinib?

C797S is a very interesting area that I think we're still learning about. The majority of the information we have so far is about patients who were treated with a first-generation EGFR drug then developed T790M, then were treated with osimertinib, a T790M specific third-generation drug, and then developed C797S after that. That situation where patients have both the activating *EGFR* mutation and T790M and C797S, was initially a very hard barrier to overcome.

We have seen some very early data, mostly preclinical data at this point, about so-called fourth-generation EGFR inhibitors, which are just coming out, which may be able to tackle this situation. However, I would note that in the real world nowadays, while we do have some of those legacy patients who receive a first-generation drug, many of them actually are still around who may have this triple mutation. We are also increasingly seeing patients who are treated with first-line osimertinib and maybe developing C797S in that setting where we would expect no T790M to be present.

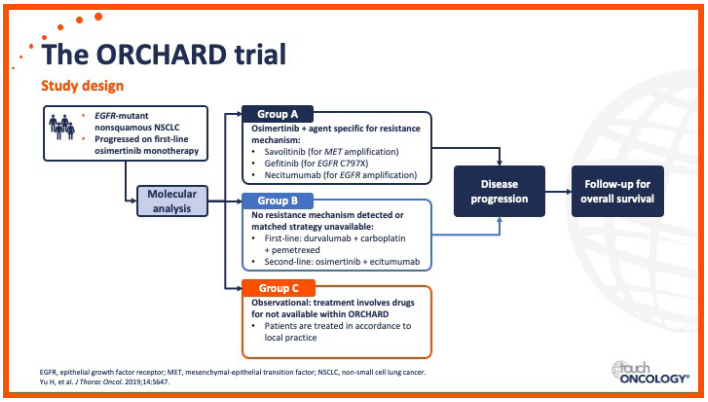


I think as we move forward, there've been several proposed approaches to C797S, including these fourth-generation TKI drugs. Also, allosteric EGFR inhibitors, which do not necessarily bind to the TK domain of EGFR, but another portion of the EGFR protein. Sometimes those are combined with EGFR targeting monoclonal antibodies in order to have maximal effect. As we look at these emerging strategies for C797S, it's going to be important to concentrate on the context in which C797S exists in the various trials and in our patients that we're treating in the clinic.

## What is on the horizon for other rare bypass disorders?

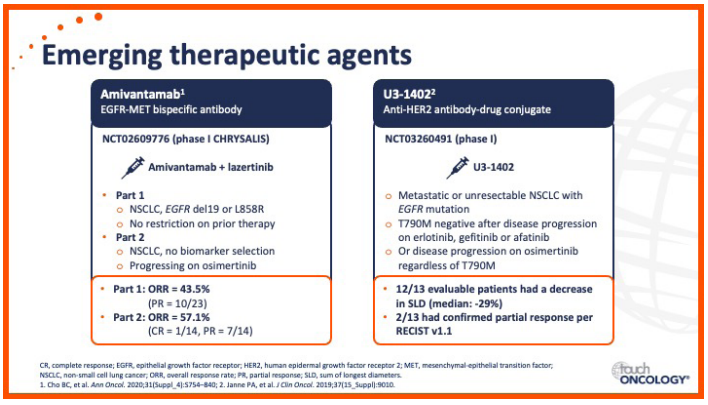
In addition to the larger categories of *MET* amplification, C797S and small cell transformation, what we're seeing after first-line osimertinib use is a number of very small categories, or pieces of the pie, where resistance is driven by another bypass mechanism. A lot of them have been fusions such as acquired rearranged during transfection (*RET*) translocation, acquired *ALK* translocation, acquired *BRAF* translocation. These events we think are relatively rare, but targetable. There have been case reports of small numbers of patients who have had really impressive responses when targeting bypass pathways together with combined ongoing EGFR inhibition. One important question is, can we base our practice on case reports or, phrased another way, how can we gather more substantial evidence about how to treat these patients? Doing a basket trial where there are various arms for various mechanisms of resistance is one way to gain evidence about a number of different subsets, which are individually, each quite rare.

An example of a study like this, which is now up and running, is the ORCHARD study where after first-line osimertinib, patients undergo a biopsy, their tumour is categorized, and the treatment is matched to the resistance mechanism found. If no particular resistance mechanism is found, there are also arms for testing different strategies in a non-matched fashion. I think that biopsies to understand the tumour's mechanism of resistance for the patients sitting in front of you is going to make a lot of sense for osimertinib resistance. It's not going to be one size fits all. We have to really customize our second-line treatment to the biology of the patient's cancer.




## What if the patient doesn't have a targetable mutation?

For patients who don't have a targetable mutation found at the time of acquired resistance to osimertinib, I think some of the important questions are, should you combine a TKI with chemotherapy or drop the TKI and go to chemotherapy alone? How does immunotherapy fit into the setting and what are some emerging compounds in this area? The COMPEL study is a randomized trial that's going to be looking at this issue of whether you should continue osimertinib along with chemotherapy. I think one of the most compelling reasons for the COMPEL study is that we know osimertinib has good central nervous system (CNS) penetration, and so continuing it with chemotherapy could potentially play a role in protecting the CNS Immunotherapy with chemotherapy has certainly become the mainstay of treatment for non-mutation driven cancers. We really have very little information to date about how to apply that data to the *EGFR*-mutation positive patients. We certainly know that there are added toxicities that could be in place. In my opinion, it's important to wait for data before making assumptions about that space.




I'm really excited about some of the emerging compounds being used to look at resistance that's not necessarily driven by a specific mechanism. These are for the most part, antibody-based therapies. We've got amivantamab, which is a bi-specific antibody towards *EGFR* and *MET* in the same compound.

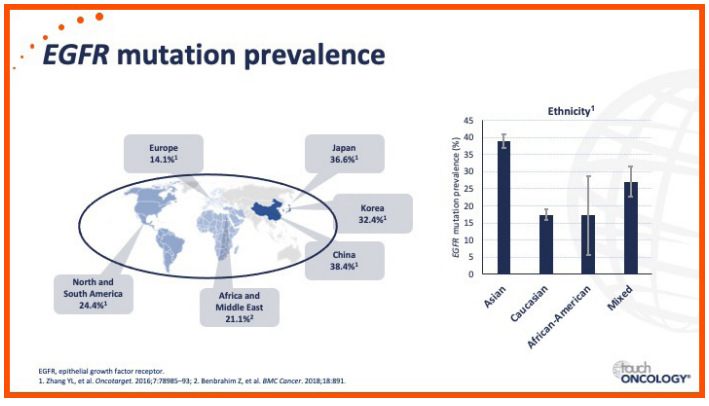
It seems to have good activity in resistant cases, even if the resistance is not driven by *MET* amplification. Stay tuned for more information there, especially on combining that antibody drug with another third-generation TKI, lazertinib. Then separately, the U3-1402 monoclonal antibody, which is actually an ADC, an antibody drug conjugate. We've got a HER3-directed antibody in the front and a chemotherapeutic drug in the back. That compound is showing good activity in osimertinib-resistant patients as well. So, a lot is coming on the horizon in this space.

## HOW DO RECENT DATA IN EARLY-STAGE NSCLC IMPACT THE CURRENT TREATMENT PATHWAY FOR *EGFR*-MUTANT NSCLC?

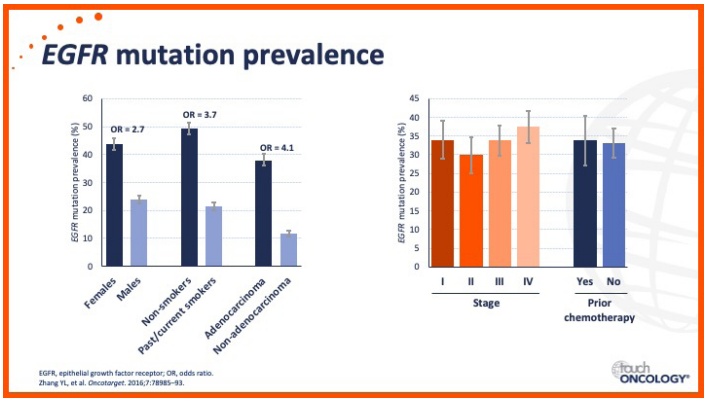
**Prof. Yi-Long Wu:** I am Dr Yi-Long Wu. I am a Thoracic Surgeon and come from Guangdong Lung Cancer Institute at Guangdong Provincial People's Hospital in Guangzhou, in China.

### What are the unmet needs among patients with early-stage NSCLC and how might targeted therapy have a role in patients with an *EGFR*-driver mutation?

The *EGFR* mutation is a very exciting medical advance in the past 20 years. There is a big difference in the *EGFR* mutation prevalence b etween Western and Eastern countries. In North and South America and Europe, *EGFR* mutation prevalence is about 15 to 25%. In Eastern Asian countries, such as Japan, Korea and China, for all NSCLC, the prevalence is about 30%.




For female patients, the prevalence of *EGFR* mutation is higher than 50%, so this is the difference. Also patients with an *EGFR* mutation have clinical characteristics, such as being female, a non-smoker and adenocarcinoma histology. These three categories mean a higher risk for *EGFR* mutation. For stage I to stage IV NSCLC, *EGFR* mutation frequency is almost the same and also with regards to whether patients have had prior chemotherapy, yes or no. So this means for early-stage NSCLC we need to pay more attention to how to use EGFR-TKI in early stage NSCLC. For early-stage disease, the standard of care for adjuvant treatment is chemotherapy, but the little benefit gained from this so-called standard of care means that we need to pay much more attention to these *EGFR*-mutation positive patients with early-stage NSCLC.

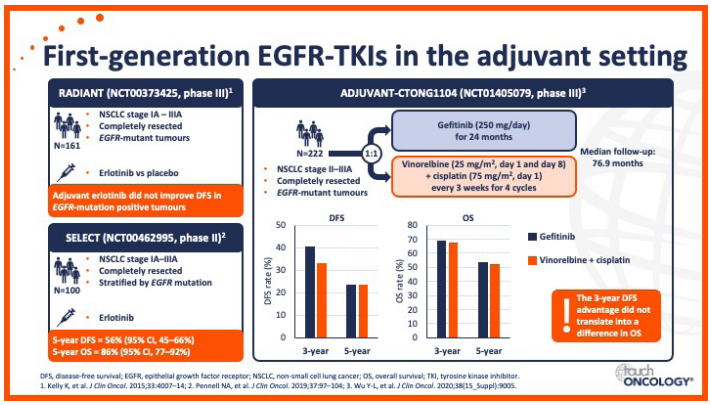



### What has been the experience with first-generation EGFR-TKIs in the adjuvant setting?

In the past 20 years we have had a number of clinical trials for adjuvant treatment of early-stage NSCLC, but most of the focus is on the use of first-generation EGFR-TKIs. Number one is the RADIANT clinical trial. This is a phase III clinical trial for stage IA to stage IIIA, completely-resected *EGFR* mutation patients. This uses a first-generation TKI erlotinib versus placebo. Data showed that adjuvant erlotinib did not improve the disease-free survival (DFS) in patients with *EGFR*-mutation positive NSCLC.

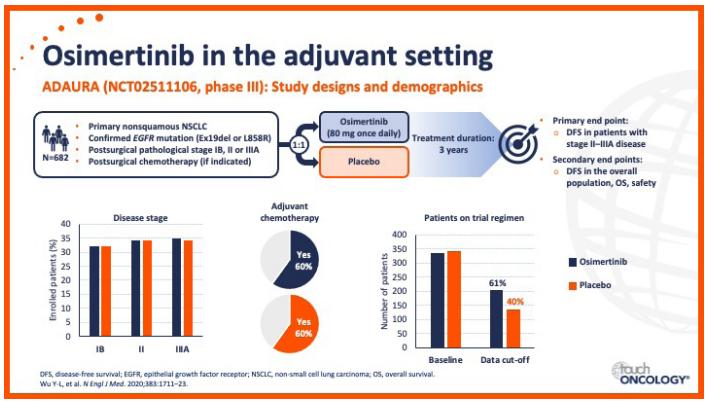
Another important trial was SELECT. This is a phase II monotherapy, single arm trial. The five year DFS was 56% and overall survival was 86%. So this is a very high five year survival. This means improved overall survival trends in adjuvant EGFR-TKI. So this is SELECT, but this is a phase II clinical trial.

In 2017, we reported on the ADJUVANT/CTONG1104 trial. This is the first randomized phase III clinical trial and is different from the RADIANT or the SELECT trials. This is focused on stage II and stage IIIA completely-resected *EGFR*-mutant disease and is also a head to head trial comparing gefitinib versus chemotherapy. The median follow up was almost 80 months. The final results saw the three-year and five-year DFS in favour of adjuvant gefitinib compared with adjuvant chemotherapy. However, the three-year DFS advantage did not translate into a difference in the overall survival. So I think this means we could improve the DFS using first-generation EGFR-TKI, but this advantage did not translate to overall survival. So this is why we need to explore the newer generation EGFR-TKIs in a clinical trial.



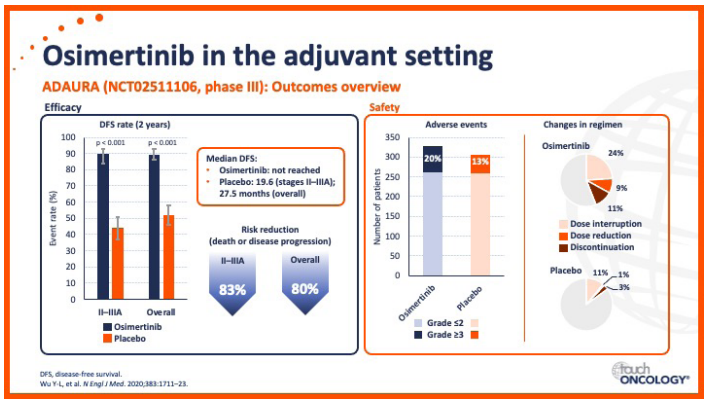

## How does the recent study evaluating the use of a third-generation EGFR-TKI in the adjuvant setting compare with the studies with first-generation EGFR-TKIs?

Osimertinib in the adjuvant setting was evaluated in a clinical trial , the so-called ADAURA trial. This is a phase III clinical trial. This was designed with a primary endpoint of DFS in patients with stage II to stage IIIA disease. The secondary endpoint was DFS in the overall population (this means including the stage IB patients), and overall survival and safety. So in this trial they included stage IB, stage II, and stage IIIA. This is very balanced. The stage IB patients accounted for  30 to 32%. So this is an important point because we know that for  stage IB, most patients did not receive adjuvant chemotherapy. Therefore we need a control group for this clinical trial as this is only 30% of patients.




Also in the adjuvant setting, the DFS rate at two years for the stage II or the IIIA patient increased, as well as for the overall population, including stage IB. The median DFS for osimertinib was not reached, but in the placebo arm it was almost 20 months for stage II or stage IIIA patients and 27.5 months for the overall population. The risk reduction was very, very exciting and promising.

Regarding safety, the incidence of grade 3 adverse events for osimertinib was only 20%, but for the placebo arm, it was 13%.

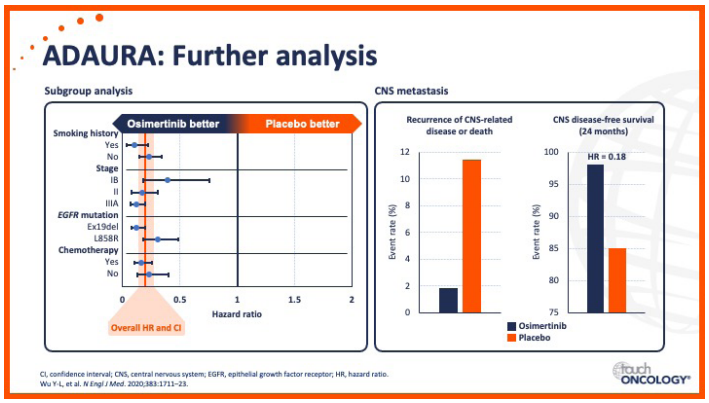



These results show that adjuvant osimertinib in stage II, stage III, even in stage IB reduced the disease relapse, which is very exciting. This is an exciting result, which was early and unplanned; so this result is exciting.

## Are there particular patients with *EGFR*-mutant early stage NSCLC who are likely to benefit most from targeted therapy?

This is a good question because we have the stratification from the clinical trial, including the smoking history, stage, *EGFR*-mutation subtype or whether the patient received chemotherapy, yes or no. So, for this subgroup analysis, the patients were stratified by their smoking history, yes or no, both subgroups were in favour of adjuvant osimertinib. For the stage, the hazard ratio for stage IB was below 0.50. For stage II the hazard ratio was below 0.20 and the stage IIIA was 0.12. So this means that any of the different stages were also in favour of adjuvant osimertinib. For the *EGFR* mutation subtype, either exon 19 or exon 21, both were  in favour of adjuvant osimertinib. About the adjuvant chemotherapy, yes or no, this was also in favour of adjuvant chemotherapy with osimertinib. So this is a very, very good result for the different subgroups analyzed, which were all in favour of adjuvant osimertinib.

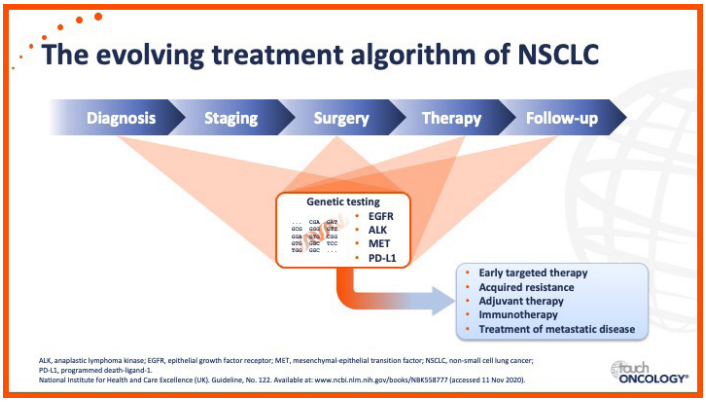
So there are also very important issues about brain metastases. Brain metastases are an important worse prognosis filter for early-stage NSCLC. If the patient has brain metastases, it means that he is likely to be stage IV and the patient is at the limit of life. For adjuvant osimertinib in regards to CNS-related disease rate, recurrence is lower, but for adjuvant placebo, there is a much higher recurrence of brain metastases. So this means that osimertinib could prevent or reduce brain metastases. So for the CNS disease-free survival at 24 month the hazard ratio was 0.18, so this means that we reduce brain metastases by about 82%. These data show that for all the patients with NSCLC, adjuvant osimertinib could give the patient a much greater benefit.




## How might recent data impact the management of patients with early stage disease and how might this change treatment choices for patients with *EGFR*-mutant NSCLC?

So because of all our clinical trials that we have done, and with the the results presented at the ASCO meeting and the ESMO meeting and published in the *New England Journal of Medicine*, I think, in the near future, if the FDA or the regulatory department in the different countries approve osimertinib with an adjuvant treatment indication, this is a great change to our clinical practice. This means for early-stage NSCLC, adjuvant EGFR-TKI, especially for osimertinib, this will become our standard of care. This is the first point. The second point is important as we need to test for *EGFR* in the early-stage. In the past, we only tested for *EGFR* mutations in advanced disease. Now we need to test for *EGFR* in early-stage. So this means that treatment of NSCLC is evolving. For the diagnosis, we have changed our clinical practice; we need to test the so-called driver gene mutation. For the staging, we give the patient an EGFR-TKI in early stage or in the later stage.

Also important in terms of therapy, we have the very exciting bonus, we've explored early targeted therapy and we also know the acquired resistance for the EGFR-TKI, and also we will now explore the neoadjuvant or adjuvant immunotherapy. So this has become a revolution for NSCLC, and this is why the five-year survival rate for NSCLC will increase in the recent and the near future.

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